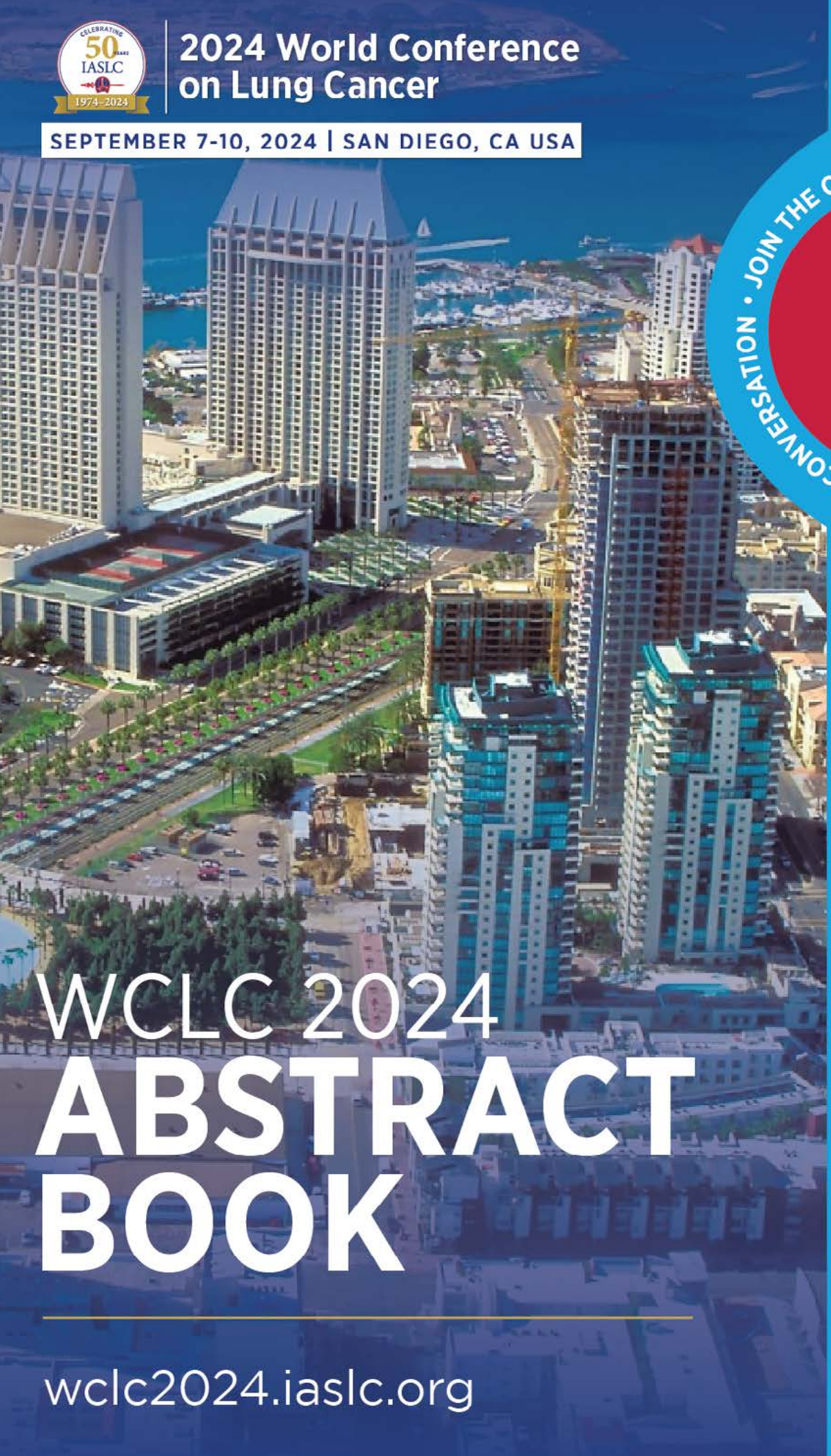

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X. Le[1], Y. Yu[2], Y. Zhao[3], D. Planchard[4], Y. Cheng[5], X. Li[6], S. Gadgeel[7], J. Zhang[8], A. Spira[9], H. Hayashi[10], J. Riess[11], S. Kitazono[12], N. Leighl[13], B. Gao[14], O. Juan-Vidal[15], A.J. de Langen[16], J. Mazieres[17], M. Pérol[18], Y. Jiang[19], T. Hu[20], J. Huang[20], N. Baio[20], L. Musib[20], M. Kowanetz[20], S. Wang[20], W. Leung[20], S. Yea[20], J. Hsu[20], J. Wang[21], [1]University of Texas MD Anderson Cancer Center, Houston/TX/USA ,[2]Harbin Medical University Cancer Hospital, Harbin/CN ,[3]Henan Cancer Hospital, Zhengzhou/CN ,[4]Gustave Roussy, Villejuif/FR ,[5]Jilin Cancer Hospital, Changchun/CN ,[6]The First Affiliated Hospital of Zhengzhou University, Zhengzhou/CN ,[7]Henry Ford Cancer Institute, Detroit/MI/USA ,[8]Anhui Provincial Hospital, Hefei/CN ,[9]Virginia Cancer Specialists Research Institute and Next Oncology, Fairfax/VA/USA ,[10]Kindai University Hospital, Osaka/JP ,[11]UC Davis Comprehensive Cancer Center, Sacramento/CA/USA ,[12]Cancer Institute Hospital of JFCR, Tokyo/JP ,[13]University Health Network – Princess Margaret Hospital, Toronto/ON/CA ,[14]Blacktown Cancer and Haematology Centre, Blacktown/AU ,[15]La Fe University and Polytechnic Hospital, Valencia/ES ,[16]Netherlands Cancer Institute, Amsterdam/NL ,[17]Cancer Universitary Institute, Toulouse/FR ,[18]Léon Bérard Center, Lyon/FR ,[19]Shanghai Allist Pharmaceuticals Co, Shanghai/CN ,[20]ArriVent Biopharma, Burlingame/CA/USA ,[21]Cancer Hospital Chinese Academy of Medical Sciences, Beijing/CN

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J. Yang[1], A. Li[1], W.N. Feng[2], J. Li[3], H.H. Yan[1], B.F. Xu[1], J. Zhao[4], Y. Jia[5], K.J. Tang[6], Y.S. Li[7], C.Z. Zhou[8], Y. Fan[9], C.R. Xu[1], Y.L. Sun[1], H.J. Chen[1] , [1]Guangdong Lung Cancer Institute, Guangdong Provincial People's Hospital (Guangdong Academy of Medical Sciences), Southern Medical University, Guangzhou/CN ,[2]The First People's Hospital Foshan, Guangzhou/CN ,[3]Sichuan Cancer Hospital & Institute, Sichuan Cancer Center, Affiliate Cancer Hospital of University of Electronic Science and Technology of China, Chengdu/CN ,[4]Beijing Cancer Hospital, Beijing/CN ,[5]Dongguan People `s Hospital, Dongguan/CN ,[6]The First Affiliated Hospital, Sun Yat-sen University, Guangzhou/CN ,[7]Chongqing University Cancer Hospital, Chongqing/CN ,[8]The First Affiliated Hospital of Guangzhou Medical University, Guangzhou/CN ,[9]Zhejiang Cancer Hospital, Hangzhou/CN

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J. Yu[1], X. Meng[1], H. Ge[2], Q. Liu[3], F. Ning[4], Y. Cheng[5], J. Wang[6], X. Zhang[7], G. Wu[8], J. Chen[9], Y. Xu[10], X. Zhao[11], K. Lu[11], O. Jiang[12], D. Lv[13], C. Xie[14], X. Li[15], Y. Yao[16], X. Dong[17], B. Liu[18], J. Fang[19], K. Yang[20], B. Zhu[21], Q. Lin[22], J. Shi[23], S. Ye[24], A. Shi[25], S. Cang[26], J. Li[27], B. Xu[28], H. Li[29], Z. Zhang[30], J. Yin[31], G. Wang[32], C. Liu[33], [1]Shandong Cancer Hospital and Institute, Shandong First Medical University, Jinan/CN ,[2]Henan Cancer Hospital, Affiliated Cancer Hospital of Zhengzhou University, Zhengzhou/CN ,[3]Fudan University Shanghai Cancer Center, Shanghai/CN ,[4]Binzhou Medical University Hospital, Binzhou/CN ,[5]Qilu Hospital of Shangdong University, Jinan/CN ,[6]The Fourth Hospital of Hebei Medical University, Shijiazhuang/CN ,[7]Qingdao Central Hospital, Qingdao/CN ,[8]Meizhou People's Hospital, Meizhou/CN ,[9]Hunan Cancer Hospital, Changsha/CN ,[10]Shanghai Pulmonary Hospital, Shanghai/CN ,[11]Jiangsu Province Hospital, Nanjing/CN ,[12]Neijiang Second People's Hospital, Neijiang/CN ,[13]Taizhou Hospital of Zhejiang Province, Taizhou/CN ,[14]Zhongnan Hospital of Wuhan University, Wuhan/CN ,[15]The First Affiliated Hospital of Zhengzhou University, Zhengzhou/CN ,[16]Renmin Hospital of Wuhan University, Wuhan/CN ,[17]Union Hospital, Tongji Medical University, Wuhan/CN ,[18]Affiliated Tumor Hospital of Harbin Medical University, Harbin/CN ,[19]Peking University Cancer Hospital, Beijing/CN ,[20]Weifang Respiratory Disease Hospital, Weifang NO.[2] people's Hospital, Weifang/CN ,[21]Second Affiliated Hospital of Army Medical University, Chongqing/CN ,[22]First Affiliated Hospital of Xiamen University, Xiamen/CN ,[23]Linyi Cancer Hospital, Linyi/CN ,[24]Affiliated Hospital of Jining Medical University, Jining/CN ,[25]Beijing Cancer Hospital, Beijing/CN ,[26]Henan Provincial People's Hospital, Zhengzhou/CN ,[27]Fujian Provincial Cancer Hospital, Fuzhou/CN ,[28]Union Hospital Affiliated to Fujian Medical University, Fuzhou/CN ,[29]Linfen People's Hospital, Linfen/CN ,[30]Anhui Cancer Hospital, Hefei/CN ,[31]Nanjing General Hospital of Nanjing Military Region, Nanjing/CN ,[32]The First Affiliated Hospital of Bengbu Medical College, Bengbu/CN ,[33]Xinjiang Medical University Affiliated Cancer Hospital, Urumqi/CN

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ORAL ABSTRACT SESSIONS

OA01 PERIOPERATIVE STRATEGIES 1
SUNDAY, SEPTEMBER 8, 2024 - 10:45 - 12:00

OA01.03 Association of Pathologic Regression with EFS in the KEYNOTE-671 Study of Perioperative Pembrolizumab for Early-Stage NSCLC

D.R. Jones[1], H. Wakelee[2], J.D. Spicer[3], M. Liberman[4], T. Kato[5], M. Tsuboi[6], S-H. Lee[7], W. Wang[8], H. Chen[9], C. Dooms[10], M. Majem[11], E. Eigendorff[12], G.L. Martinengo[13], O. Bylicki[14], H-C. Huang[15], S. Novello[16], E. Jensen[17], S.M. Keller[17], A. Samkari[17], N. Kalhor[1], [1]Department of Surgery, Memorial Sloan Kettering Cancer Center, New York/NY/USA ,[2]Stanford University School of Medicine/Stanford Cancer Institute, Stanford/CA/USA ,[3]McGill University Health Centre, Montréal/QC/CA ,[4]Centre Hospitalier de Universite to Montréal (CHUM), Montréal/QC/CA ,[5]Kanagawa Cancer Center, Yokohama/JP ,[6]National Cancer Center Hospital East, Kashiwa/JP ,[7]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul/KR ,[8]The Affiliated Cancer Hospital of Xiangya School of Medicine, Hunan Cancer Hospital, Central South University, Changsha/CN ,[9]Fudan University Shanghai Cancer Hospital, Shanghai/CN ,[10]University Hospitals Leuven, Leuven/BE ,[11]Hospital de la Santa Creu i Sant Pau, Barcelona/ES ,[12]Zentralklinik Bad Berka, Bad Berka/DE ,[13]Sanatorio Parque, Córdoba/AR ,[14]HIA Sainte-Anne, Toulon/FR ,[15]Taipei Veterans General Hospital and National Yang Ming Chiao Tung University, Taipei/TW ,[16]Department of Oncology, University of Turin, A.O.U. San Luigi Gonzaga di Orbassano, Turin/IT ,[17]Merck & Co., Inc., Rahway/NJ/USA ,[18]The University of Texas MD Anderson Cancer Center, Houston/TX/USA

Introduction: Neoadjuvant pembrolizumab plus chemotherapy, surgery, and adjuvant pembrolizumab significantly improved OS (HR, 0.72; 95% CI, 0.56-0.93; P = 0.00517) versus neoadjuvant placebo plus chemotherapy, surgery, and adjuvant placebo and had manageable safety in early-stage NSCLC in KEYNOTE-671 (NCT03425643). In addition, event-free survival (EFS; HR, 0.58; 95% CI, 0.46–0.72; P <0.001), major pathologic response (mPR; 30.2% vs 11.0%; P <0.0001), and pathologic complete response (pCR; 18.1% vs 4.0%; P <0.0001) were also significantly improved in the pembrolizumab arm. We present a post hoc analysis of EFS based on the degree of pathologic regression, defined as percent residual viable tumor (%RVT), following resection.

Methods: Patients aged ≥18 years with previously untreated resectable stage II, IIIA, or IIIB (N2) NSCLC per AJCC 8th edition were randomized to pembrolizumab 200 mg IV Q3W or placebo with cisplatin-based chemotherapy for 4 cycles, then surgery and pembrolizumab 200 mg IV Q3W or placebo for ≤13 cycles. EFS and OS were dual primary endpoints; mPR and pCR per blinded independent pathology review were key secondary endpoints. Patients who underwent surgery and had tissue evaluable for blinded independent pathology review were categorized by %RVT in the primary lung tumor and sampled lymph nodes. The data cutoff date was July 10, 2023.

Results: 320 (80.6%) of 397 patients in the pembrolizumab arm and 300 (75.0%) of 400 in the placebo arm had pathologically evaluable tumors. Median (interquartile range [IQR]) %RVT was 29.5% (1.0%–56.0%) in the pembrolizumab arm and 52.0% (29.0%–68.0%) in the placebo arm. For the pembrolizumab arm versus the placebo arm, 31.9% versus 12.3% of patients had %RVT of >0%–5%, 19.1% versus 14.7% had %RVT of >5%–30%, 31.6% versus 38.0% had % RVT of >30%-60%, and 17.5% versus 35.0% had % RVT of >60%. Lower %RVT was associated with longer EFS in both arms. EFS was numerically improved in the pembrolizumab vs placebo arm in nearly every %RVT group (Table).

Conclusions: In this post hoc analysis, neoadjuvant pembrolizumab plus chemotherapy were associated with greater pathological regression based on %RVT than neoadjuvant placebo plus chemotherapy. There was a clinically meaningful EFS benefit for perioperative pembrolizumab across different %RVT. These data support the benefit of a perioperative regimen of neoadjuvant pembrolizumab plus chemotherapy and adjuvant pembrolizumab for early-stage NSCLC.

Table. Relationship Between %RVT and EFS

%RVT	Pembrolizumab Arm n = 320	Placebo Arm n = 300
0%–5%	n = 102	n = 37
Median EFS (95% CI), mo	NR (NR–NR)	NR (38.2-NR)
36-mo EFS rate (95% CI), %	83.0 (72.4–89.8)	75.9 (57.2–87.3)
HR (95% CI)	0.58 (0.27–1.23)	
>5%–30%	n = 61	n = 44
Median EFS (95% CI), mo	NR (34.1–NR)	39.1 (19.6–NR)
36-mo EFS rate (95% CI), %	61.8 (47.2–73.4)	59.0 (41.5–72.9)
HR (95% CI)	0.73 (0.38–1.38)	
>30%–60%	n = 101	n = 114
Median EFS (95% CI), mo	39.2 (26.0–NR)	22.1 (14.9–33.0)
36-mo EFS rate (95% CI), %	54.7 (43.6–64.4)	38.0 (28.2–47.7)
HR (95% CI)	0.65 (0.45–0.94)	
>60%	n = 56	n = 105
Median EFS (95% CI), mo	15.0 (13.1–NR)	18.5 (13.6–22.1)
36-mo EFS rate (95% CI), %	37.7 (24.6–50.7)	29.1 (20.0–38.9)
HR (95% CI)	0.90 (0.60–1.36)	

NR, not reached.

Keywords: Residual viable tumor, pembrolizumab, EFS

OA01 PERIOPERATIVE STRATEGIES 1
SUNDAY, SEPTEMBER 8, 2024 - 10:45 - 12:00

OA01.04 IMpower010 5-y Subgroup Analysis and Relapse Patterns: Phase 3 Study of Atezolizumab vs BSC in Stage II-IIIA NSCLC

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Introduction: IMpower010 (NCT02486718) met its primary endpoint of significant disease-free survival (DFS) improvement with adjuvant atezolizumab vs best supportive care (BSC) in the stage II-IIIA PD-L1 tumor cell (TC)≥1% and all-randomized stage II-IIIA populations, but not in the ITT population, in patients with resected NSCLC post-chemotherapy. Enhanced benefit was also observed in the population with TC≥50% (Felip Lancet 2021). In the recent DFS final analysis and overall survival (OS) second interim analysis, with ≥5 y of follow-up, the significance boundary for DFS in the ITT population was not crossed and OS was similar between arms. The atezolizumab DFS benefit continued to translate into positive OS trends vs BSC in the PD-L1 TC≥1% and TC≥50% stage II-IIIA populations (Wakelee ASCO 2024). We present outcomes by disease and regional lymph node status, and descriptive analyses of sites of relapse and post-relapse treatments in the stage II-IIIA PD-L1 TC≥1% and TC≥50% populations at ≥5 y of follow-up.

Methods: The study design has been reported (Felip Lancet 2021). Briefly, 1005 patients received 1-4 21-day chemotherapy cycles post-surgery and were randomized 1:1 to receive 16 cycles of atezolizumab 1200 mg Q3W or BSC. Clinical cutoff date for this analysis was January 26, 2024.

Results: In the stage II-IIIA TC≥1% and TC≥50% populations, the DFS unstratified HRs (95% CI) were 0.77 (0.52-1.13) and 0.57 (0.32-1.02) for stage II disease; 0.66 (0.47-0.93) and 0.42 (0.24-0.75) for stage IIIA disease; 0.82 (0.45-1.52) and 0.89 (0.37-2.16) for regional lymph node (pN) status N0; 0.65 (0.42-0.99) and 0.40 (0.20-0.81) for pN1; and 0.74 (0.51-1.07) and 0.42 (0.22-0.77) for pN2. Similar patterns were seen for OS, and for DFS and OS when patients with EGFR or ALK alterations were excluded from the TC≥50% population. Overall recurrence, patterns of relapse and post-relapse therapies are shown in the Table.

	Stage II-IIIA PD-L1 TC≥1%		Stage II-IIIA PD-L1 TC≥50%	
Patients, n (%)	**Atezolizumab (n=248)**	**BSC (n=228)**	**Atezolizumab (n=115)**	**BSC (n=114)**
Overall recurrence	91 (36.7)	115 (50.4)	32 (27.8)	54 (47.4)
Relapse sites[a]				
Locoregional only[b]	43 (47.3)	48 (41.7)	18 (56.3)	19 (35.2)
Distant only[c,d]	33 (36.3)	45 (39.1)	9 (28.1)	23 (42.6)
Central nervous system only[e]	9 (9.9)	12 (10.4)	2 (6.3)	7 (13.0)
Locoregional + distant	12 (13.2)	18 (15.7)	4 (12.5)	8 (14.8)
Second primary lung only	2 (2.2)	3 (2.6)	1 (3.1)	3 (5.6)
Post-relapse treatments[a,f]				
Any systemic anticancer therapy[g]	63 (69.2)	78 (67.8)	24 (75.0)	32 (59.3)
Cancer immunotherapy	16 (17.6)	41 (35.7)	5 (15.6)	20 (37.0)
Radiotherapy	43 (47.3)	51 (44.3)	14 (43.8)	26 (48.1)
Surgery	14 (15.4)	14 (12.2)	4 (12.5)	9 (16.7)

[a] The denominators for relapse sites and post-relapse treatments are based on the number of patients with relapse. [b] Patients who had "local recurrence" or "regional recurrence" checked on the "Disease status" case report form were included. One patient with locoregional + second primary lung is included due to no biopsy confirmation. [c] Two patients with distant + second primary non-lung are included due to lack of biopsy confirmation or because "second primary" was diagnosed on the same day as distant recurrence with no clear differentiation. [d] A patient could have more than one distant site. [e] Patients who had central nervous system distant site-only recurrence were included. [f] Multiple uses of a specific medication for a patient were counted once in frequency for the medication. Likewise, multiple uses within a specific medication class for patients were counted once in frequency for the medication class. [g] Systemic anticancer therapy includes chemotherapy, cancer immunotherapy, targeted tyrosine kinase inhibitor therapy, monoclonal antibody therapy, bisphosphonate therapy, corticosteroid therapy, hormonal therapy, somatostatin therapy, and unknown therapy. Clinical data cutoff date: January 26, 2024.

Conclusions: After ≥5 y of follow-up, patients in the atezolizumab arm had greater DFS and OS improvements than those in the BSC arm, regardless of disease stage or pN status (favoring N1/N2). Overall recurrence rates were lower in the atezolizumab arm than in the BSC arm, irrespective of PD-L1 TC≥1% and TC≥50% status. Although patient numbers were small, distant and central nervous system relapse rates were higher in the BSC arm than in the atezolizumab arm in the TC≥50% population. Post-relapse cancer immunotherapy use was higher in the BSC arm.

Keywords: Atezolizumab, early NSCLC, PD-L1

OA01 PERIOPERATIVE STRATEGIES 1
SUNDAY, SEPTEMBER 8, 2024 - 10:45 - 12:00

OA01.05 Neoadjuvant Nivolumab with or without Relatlimab in Resectable NSCLC: Additional Analysis and Extended Follow-up

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Introduction: In patients with resectable NSCLC at high risk of recurrence, immune checkpoint inhibition (ICI) has become a cornerstone in the curative multimodality treatment. The multicentric, non-comparative phase II study NEOpredict-Lung (NCT04205552) confirmed the primary endpoint of feasibility of dual PD-1 and LAG-3 inhibition prior to surgery [Schuler et al. Nature Medicine 2024]. MPR occurred in 30% of patients treated in the combination arm.

Methods: Patients with NSCLC (stages IB, II and selected IIIA) eligible for surgery were randomized (30 per arm) to receive two preoperative doses (q14d) of nivolumab (240 mg, arm A), or nivolumab plus relatlimab (80 mg, arm B). Extended survival outcomes, stage and nodal evolution analysis, recurrence patterns and subsequent therapy were analyzed as of March 1st, 2024. Study design does not allow for formal comparison of treatment arms.Three patients (arm B) were excluded due to stage IV disease which had been undetected at baseline staging. Sixteen (28.1%) patients had cN1 or cN2 disease [7 (23.3%) in arm A; 9 (33.3%) in arm B], confirmed at randomization by EBUS (13), mediastinoscopy (1) or both (2).

Results: Survival: Median follow-up was 29.8 months. In total, 13 patients experienced disease recurrence, and 6 patients died [1 tumor progression, 1 pulmonary embolism, 1 acute liver failure and 3 unknown/lost to follow-up). The 2-year OS and DFS-rates were 92.3% and 75.3% in arm A and 88.6% and 69.1% in arm B. Patients achieving MPR trended towards better DFS (HR 0.41; 95%CI, 0.09-1.78), compared to non-MPR patients.

Stage and nodal evolution: In total, 16 (53.3%) patients treated in arm A and 18 (66.7%) in arm B experienced TNM-downstaging postoperatively. Upstaging occurred in 8 (26.7%) and 6 (22.2%) patients respectively. Nodal downstaging occurred in 2 (28.6%) patients in arm A and in 6 (66.7%) in arm B (all ypN0). A total of 10 (17.5%) patients experienced nodal upstaging [5 (16.7%) arm A; 5 (18.5%) arm B].

Patterns of recurrence and subsequent therapy: Thirteen (22.8%) patients experienced disease recurrence [6 (20.0%) arm A; 7 (25.9%) arm B]. Three patients had a locoregional recurrence, and 10 distant relapse (5 multisite and 5 oligorecurrences). The most prevalent site of recurrence was the contralateral lung (6). Two patients developed adrenal metastasis and 2 brain metastases. All patients with disease-recurrence underwent therapy [locally ablative (5) or systemic treatment (5)]. All locoregional relapses (3) were treated with chemoradiotherapy (+/- consolidation ICI). Of 17 patients with MPR, 2 experienced an oligorecurrence in the contralateral lung, treated with stereotactic radiotherapy. No new safety signals were noted after subsequent therapies.

Conclusions: Updated analyses of the first study on short-course PD-1 and LAG-3 inhibition, NEOpredict-Lung, shows encouraging 2-year OS- and DFS-rates in both treatment arms. In the dual inhibition arm, TNM-downstaging, in particular nodal clearance, appears more pronounced. The majority of recurrences were at distant sites. All relapsed patients received subsequent therapy without new safety signals.

Keywords: neoadjuvant, LAG-3, relatlimab

OA01 PERIOPERATIVE STRATEGIES 1
SUNDAY, SEPTEMBER 8, 2024 - 10:45 - 12:00

OA01.06 A Phase II Study of Perioperative Ivonescimab Alone or Combined with Chemotherapy in Resectable Non-Small Cell Lung Cancer

C. Wang[1], X. Zhao[1], L. Zhang[1], D. Yue[1], Z. Zhang[1], M. Wang[1], Z. Tian[2], S. Wang[1], C. Pang[1], B. Zhang[1], Q. Zhang[1], W. Wei[1], Y. Zhang[1], X. Wang[1], Y. Li[1], H. Lv[2], Y. Xia[3], B. Li[3], Z.M. Wang[3], W. Li[3], [1]Tianjin Medical University Cancer Institute & Hospital, Tianjin/CN ,[2]The Fourth Hospital of Hebei Medical University, Shijiazhuang/CN ,[3]Akeso, Inc., Zhongshan/CN

Introduction: Ivonescimab (AK112/SMT112) is a first-in-class anti-PD-1/VEGF bispecific antibody. Previous clinical studies have indicated that ivonescimab showed potential efficacy in patients (pts) with advanced non-small cell lung cancer (NSCLC) and ivonescimab is currently being investigated in four phase 3 clinical trials in NSCLC. This study aimed to evaluate the efficacy and safety of ivonescimab monotherapy or in combination with chemotherapy in the neoadjuvant/adjuvant treatment of resectable NSCLC.

Methods: This was an open-label, multi-center phase II study, pts diagnosed with resectable stage II, IIIA or IIIB (N2) NSCLC per AJCC 8th edition were enrolled into two cohorts. Pts received neoadjuvant ivonescimab (20 mg/kg) monotherapy in cohort 1 or ivonescimab (20 mg/kg or 30 mg/kg) plus cisplatin/carboplatin and paclitaxel in cohort 2 once every 3 weeks for 3-4 cycles, followed by surgery and adjuvant ivonescimab once every 3 weeks for up to 16 cycles. Primary endpoints were safety and major pathological response (MPR).

Results: A total of 60 pts were enrolled from Mar 09, 2022 to Jul 31, 2023 (11 pts in cohort 1 and 49 pts in cohort 2, 24 pts received ivonescimab 20 mg/kg plus chemotherapy, 25 pts received ivonescimab 30 mg/kg plus chemotherapy). Of these pts, the median age at baseline was 64 [range: 31-74] years, 85% were male, 75% with squamous carcinoma, 78% with stage III, and 90% with lymph node metastasis. As of Jan 08, 2024, in cohort 1, 10 pts completed surgery, the rate of MPR was 60% and the rate of pathological complete response (pCR) was 30%. In cohort 2, 39 pts completed surgery, the rate of MPR was 71.8% and the rate of pCR was 43.6%. The pathological response was better in 30 pts with squamous carcinoma: the rate of MPR and pCR were 83.3% and 53.3%, respectively. MPR and pCR occurred in 70% and 40% of pts with ivonescimab 20 mg/kg plus chemotherapy, 73.7% and 47.4% of pts with ivonescimab 30 mg/kg plus chemotherapy, respectively. Median event-free survival and overall survival were not reached with the median follow-up duration of 10.1 months. The treatment was well tolerated during the perioperative period. There were no treatment related adverse events (TRAEs) that led to cancelled or delayed surgery or wound healing complications. The most common TRAEs (incidence ≥5%) of grade 3 or higher were decreased neutrophil count and decreased white blood cell count. The safety profiles were similar in the two groups of ivonescimab 20 mg/kg and 30 mg/kg in cohort 2.

Conclusions: Ivonescimab alone or plus chemotherapy showed a promising MPR and pCR in pts with resectable NSCLC. Higher rates of MPR and pCR were seen with ivonescimab plus chemotherapy than with ivonescimab alone, with ivonescimab 30 mg/kg plus chemotherapy than 20 mg/kg plus chemotherapy, and with squamous NSCLC than non-squamous NSCLC. The safety profile was manageable, and no TRAEs impeded the surgery.

Keywords: Ivonescimab, Immunotherapy, NSCLC

OA02 REDEFINING FIRST-LINE EGFR THERAPY
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OA02.03 Amivantamab Plus Lazertinib vs Osimertinib in First-line EGFR-mutant Advanced NSCLC: Longer Follow-up of the MARIPOSA Study

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Introduction: Amivantamab is an EGFR-MET bispecific antibody with immune cell-directing activity. Lazertinib is a central nervous system-penetrant 3rd-generation EGFR TKI. In the primary analysis of the phase 3 MARIPOSA study (NCT04487080), at a median follow-up of 22.0 months, amivantamab plus lazertinib significantly improved progression-free survival (PFS) by blinded independent central review vs osimertinib in patients with treatment-naïve, EGFR-mutated advanced NSCLC (HR, 0.70; 95% CI, 0.58-0.85; P<0.001). Early interim overall survival (OS) analysis showed a favorable trend for amivantamab-lazertinib over osimertinib (HR, 0.80; 95% CI, 0.61-1.05; P=0.11). Here, we present updated results with longer follow-up from MARIPOSA.

Methods: MARIPOSA randomized 1074 patients with treatment-naïve, EGFR-mutated (Exon 19 deletions or Exon 21 L858R substitutions) locally advanced or metastatic NSCLC 2:2:1 to open-label amivantamab-lazertinib (n=429), blinded osimertinib (n=429), or blinded lazertinib (n=216; included to assess contribution of components). This updated analysis, requested by health authorities, compares amivantamab-lazertinib with osimertinib.

Results: As of May 13, 2024 (median follow-up, 31.1 months), 44% (185/421) and 34% (145/428) of patients were still receiving treatment in the amivantamab-lazertinib and osimertinib arms, respectively. In total, 155 patients in the amivantamab-lazertinib arm and 233 in the osimertinib arm had investigator-assessed progressive disease and discontinued treatment. Among those, 72% (111/155) and 74% (173/233) initiated subsequent therapy, respectively, with carboplatin-pemetrexed being the most common first subsequent therapy across arms (amivantamab-lazertinib, 26% [29/111]; osimertinib, 28% [48/173]). PFS after first subsequent therapy (PFS2) favored amivantamab-lazertinib (HR, 0.73; 95% CI, 0.59-0.91; nominal P=0.004). Patients receiving amivantamab-lazertinib demonstrated significantly longer median time to treatment discontinuation and time to subsequent therapy vs osimertinib (Table). Intracranial PFS showed a favorable trend for amivantamab-lazertinib vs osimertinib (Table). While not formally tested for significance, median OS was not estimable for amivantamab-lazertinib vs 37.3 months for osimertinib (HR, 0.77; 95% CI, 0.61-0.96; nominal P=0.019). At 24 months, 75% and 70% of patients were alive in the amivantamab-lazertinib and osimertinib arms, respectively; corresponding values at 36 months were 61% and 53%.

Conclusions: Amivantamab-lazertinib continues to show a trend towards improved OS while also improving post-progression outcomes vs osimertinib, reaffirming amivantamab-lazertinib as a first-line standard-of-care for EGFR-mutated advanced NSCLC.

Keywords: amivantamab, lazertinib, NSCLC mutations

Table: Key Endpoints from Longer-term Follow Up of MARIPOSA

Endpoint, median months (95% CI)	Amivantamab -lazertinib (n=429)	Osimertinib (n=429)	Treatment effect (95% CI)	Nominal *P*-value
OS	NE (NE-NE)	37.3 (32.5-NE)	HR, 0.77 (0.61-0.96)	0.019
At 24 months, % (95% CI)	75 (71-79)	70 (65-74)		
At 36 months, % (95% CI)	61 (56-67)	53 (47-59)		
TTD	26.3 (22.3-30.4)	22.6 (20.3-24.5)	HR, 0.80 (0.68-0.96)	0.014
TTST	30.0 (26.3-36.0)	24.0 (22.5-26.2)	HR, 0.77 (0.65-0.93)	0.005
PFS2	NE (36.0-NE)	32.4 (29.3-NE)	HR, 0.73 (0.59-0.91)	0.004
Intracranial PFS[a]	24.9 (20.1-34.7)	22.2 (18.4-26.1)	HR, 0.82 (0.62-1.09)	0.165
At 24 months, % (95% CI)	51 (43-58)	48 (40-56)		
At 36 months, % (95% CI)	38 (28-47)	18 (11-28)		

[a]By BICR based on RECIST v1.1 among patients with a history of brain metastases.
BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; PFS2, progression-free survival after first subsequent therapy; RECIST, Response evaluation criteria in solid tumors; TTD, time to treatment discontinuation; TTST, time to subsequent therapy.

OA02 REDEFINING FIRST-LINE EGFR THERAPY
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OA02.04 A Phase III Study of Rilertinib Versus Gefitinib as First-Line Therapy for Patients with Locally Advanced or Metastatic EGFR-Mutated NSCLC

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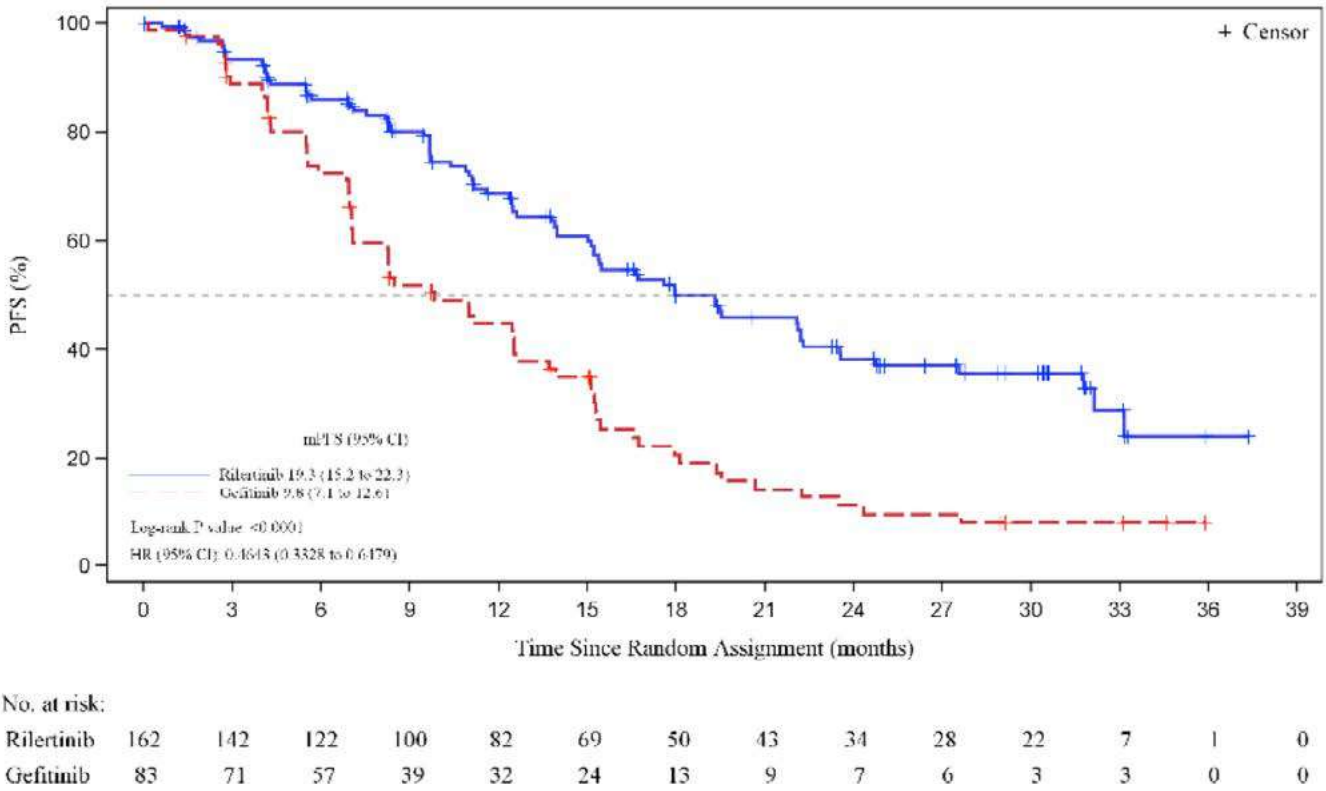
Introduction: Rilertinib (formerly Oritinib, SH-1028) is a novel, selective oral third-generation epidermal growth factor receptor tyrosine kinase inhibitor developed by Nanjing Sanhome Pharmaceutical Co., Ltd,. This trial evaluated the efficacy and safety of rilertinib compared with gefitinib as a first-line treatment for locally advanced or metastatic EGFR mutation-positive non-small-cell lung cancer (NSCLC; ClinicalTrials.gov identifier: NCT04239833).

Methods: This study was a multicentre, double-blind, randomised phase 3 study at 31 sites in China. Patients were randomly assigned 2:1 to receive either rilertinib (200 mg) or gefitinib (250 mg) once daily in 21-day cycles until disease progression or withdrawal criteria were met. The primary end point was progression-free survival (PFS) per independent review committee (IRC) assessment.

Results: Between Apr 10, 2020, and Apr 30, 2021, 420 patients were screened, of whom 246 were enrolled. 245 patients had received at least one dose of study drug were randomly assigned to rilertinib (n=162) or gefitinib (n=83) group and were included in the full analysis set. IRC-assessed PFS was significantly longer with rilertinib compared with gefitinib (hazard ratio, 0.46; 95% CI, 0.33 to 0.65; P < 0.0001). The median PFS with rilertinib was 19.3 months (95% CI, 15.2 to 22.3) versus 9.8 months with gefitinib (95% CI, 7.1 to 12.6). Objective response rate (ORR) and disease control rate (DCR) were similar in the rilertinib and gefitinib groups, the ORR with rilertinib was 72.8% (95% CI, 65.3 to 79.5) versus 78.3% with gefitinib (95% CI, 67.9 to 86.6); the DCR with rilertinib was 93.8% (95% CI, 88.9 to 97.0) versus 97.6% with gefitinib (95% CI, 91.6 to 99.7). The median duration of response was 20.7 months (95% CI, 14.1 to 23.4) with rilertinib versus 11.1 months (95% CI, 6.9 to 12.6) with gefitinib. Treatment-related adverse events of grade ≥ 3 severity were observed in 17.3% and 22.9% of patients in the rilertinib and gefitinib groups, respectively. Treatment-related serious adverse events were reported in 6.2% patients in the rilertinib group and in 9.6% patients in the gefitinib group. No patient in either group died due to treatment-related adverse events judged by the investigators.

Conclusions: Rilertinib is a well-tolerated third-generation EGFR-TKI that demonstrated superior efficacy compared with gefitinib in first-line treatment for patients with EGFR mutation-positive NSCLC, along with an acceptable safety profile without new signals. Rilertinib could serve as a new treatment option for this population.



Keywords: Rilertinib (SH-1028), First-line therapy, EGFR-mutated NSCLC

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SUNDAY, SEPTEMBER 8, 2024 - 10:45 - 12:00

OA02.05 Lazertinib vs Osimertinib in 1L EGFR-Mutant Advanced NSCLC: A Randomized, Double-Blind, Exploratory Analysis from MARIPOSA

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Introduction: Lazertinib is an oral, central nervous system-penetrant, 3rd-generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) that significantly improved progression-free survival (PFS) versus gefitinib in patients with treatment-naïve, EGFR-mutant advanced non-small cell lung cancer (NSCLC; Cho JCO 2023). In the phase 3 MARIPOSA study (NCT04487080), lazertinib combined with amivantamab, an EGFR-MET bispecific antibody with immune cell-directing activity, significantly improved PFS versus osimertinib in the same patient population (HR, 0.70; 95% CI, 0.58-0.85; P<0.001; Cho Ann Oncol 2023). The MARIPOSA study included a lazertinib monotherapy arm to assess contribution of components in the combination. This is the first trial to prospectively evaluate two 3rd-generation EGFR-TKIs in a randomized, double-blind fashion. Herein, we report results from an exploratory analysis of lazertinib versus osimertinib.

Methods: In MARIPOSA, 1074 patients were randomized 2:2:1 to receive amivantamab plus lazertinib, osimertinib monotherapy, or lazertinib monotherapy. These exploratory analyses focus on the 216 patients randomized to receive lazertinib (240-mg daily) and the 429 patients randomized to osimertinib (80-mg daily) in a double-blinded fashion. Serial brain imaging with MRI was required for all patients. Efficacy endpoints included PFS (by blinded independent central review [BICR] per RECIST v1.1), overall response rate (ORR), duration of response (DoR), overall survival (OS), and safety.

Results: At a median follow-up of 22.0 months, median PFS by BICR was 18.5 months (95% CI, 14.8-20.1) for lazertinib versus 16.6 months (95% CI, 14.8-18.5) for osimertinib (HR, 0.98; 95% CI, 0.79-1.22). ORR was 83% (95% CI, 77-88 for lazertinib versus 85% (95% CI, 81-88) for osimertinib, with median DoR of 16.6 months (95% CI, 14.8-20.2) versus 16.8 months (95% CI, 14.8-18.5), respectively, among confirmed responders. At interim survival analysis, median OS was not estimable for both arms (HR, 1.00; 95% CI, 0.73-1.38).

Additionally, we evaluated PFS of lazertinib versus osimertinib in subgroups of high-risk disease. Median PFS for patients with a history of brain metastases was 16.4 months (95% CI, 12.9-19.4) for lazertinib versus 13.0 months (95% CI, 12.2-16.4) for osimertinib (HR, 0.90; 95% CI, 0.65-1.25). Median PFS for patients with detectable circulating tumor DNA at baseline was 18.4 months (95% CI, 14.6-20.1) for lazertinib versus 14.8 months (95% CI, 12.9-16.6) for osimertinib (HR, 0.88; 95% CI 0.66-1.17). Median PFS for patients with TP53 co-mutations was 14.6 months (95% CI, 11.0-19.4) for lazertinib versus 12.9 months (95% CI, 11.1-14.7) for osimertinib (HR, 0.85; 95% CI 0.58-1.23).

The safety profiles of lazertinib and osimertinib were similar, with EGFR-related adverse events (AEs) being the most common. Most individual AEs were grade 1-2. Higher rates of diarrhea, thrombocytopenia, leukopenia, and QT interval prolongation were observed with osimertinib versus higher rates of rash and paresthesia with lazertinib. Treatment-related AEs leading to discontinuations were similar between arms.

Conclusions: Efficacy and safety were similar for lazertinib and osimertinib. Patients with EGFR-mutant advanced NSCLC, including those with high-risk features, may benefit from lazertinib as an important new treatment option.

Keywords: EGFR TKI, Lazertinib, NSCLC

OA03 PREDICTING THE FUTURE: NOVEL PATHOLOGY ASSESSMENTS AND IMAGING BIOMARKERS
SUNDAY, SEPTEMBER 8, 2024 - 10:45 - 12:00

OA03.03 The 2024 International Association for the Study of Lung Cancer (IASLC) Global Survey on Biomarker Testing

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OA03 PREDICTING THE FUTURE: NOVEL PATHOLOGY ASSESSMENTS AND IMAGING BIOMARKERS, SUNDAY, SEPTEMBER 8, 2024 - 10:45 - 12:00

OA03.04 Predicting Disease Progression to Upfront Pembrolizumab Monotherapy in Advanced NSCLC with Machine Learning and CT Radiomics

I. Janzen[1,2], Q. Ye[2], J. Li[2], C. Ho[1], B. Melosky[1], S. Lam[1], C. MacAulay[1], R. Yuan[1], [1]BC Cancer, Vancouver/BC/CA ,[2]University of British Columbia, Vancouver/BC/CA

Introduction: Health Canada approved pembrolizumab in the first line setting for advanced Non-Small-Cell Lung Cancer with PD-L1≥50% and no EGFR/ALK aberration. The Keynote 024 trial showed 55% of such patients progress on pembrolizumab monotherapy. Thus the clinical question: Can we distinguish the sub-cohort of PDL1≥50% patients that are best treated with pembrolizumab alone or require pembrolizumab + platinum doublet chemotherapy? We propose that a Machine Learning model using baseline CT radiomics features can predict disease progression for patients receiving upfront pembrolizumab monotherapy for advanced non-small-cell lung cancer, prior to the initiation the treatment.

Methods: This study included two retrospective cohorts of patients with advanced NSCLC, a discovery training cohort (Tr-set; N=97, 56F:41M, 73±6yo) and an external validation cohort (X-set; N=17, 9F:8M, 65±10yo). All patients had CT at baseline and additional follow-up CTs 9-12 weeks after receiving 1st-line pembrolizumab. Response was assessed using RECIST v1.1 standard definitions: “disease control, DC” vs “progressive disease, PD” (Tr-set: 60 DC vs. 37 PD X-set: 9 DC vs 8 PD). A radiomic feature extraction pipeline was used to extract 2D radiomic shape, texture, and intensity features from axial CT images of lung tumor lesion(s). A five-fold cross validated ML model (Logisitic Regression; LR) was trained on a combination of patients baseline demographic, clinical, and CT radiomic features to classify DC vs. PD patients. The best-fit LR model was used to calculate the predicted “risk of PD” for each patient and separate patients into “high- vs. “low-risk of PD” groups by comparing the calculated “risk-of-PD” to the Youden cut-off, and Kaplan-Meier plot were used to compare survivals (OS and PFS) and between the two groups.

Results: ROC analysis showed a good performance for the best-fit LR model that integrates a combination of baseline variables in predicting PD (in Tr-set: AUC=0.91±0.06, in X-set: AUC=0.88, CI 95%: 0.72-0.99). The Kaplan-Meier plots suggested that the “predicted high-risk of PD” group had statistically worse OS compared to the “predicted low-risk of PD” group in both Tr- and X-sets (Tr-set: log rank $p<0.0001$; X-set: log rank $p<0.01$ [NB: only X-set shown in Figure 1C and 1D]).

Conclusions: This pilot study suggests that a ML model integrating baseline CT radiomic features can identify patients who may progress on pembrolizumab monotherapy hence can potentially facilitate decision-making for the optimal first line treatment in high PD-L1 cohorts of advanced NSCLC patients.

Keywords: Radiomics, Machine Learning, Treatment Response

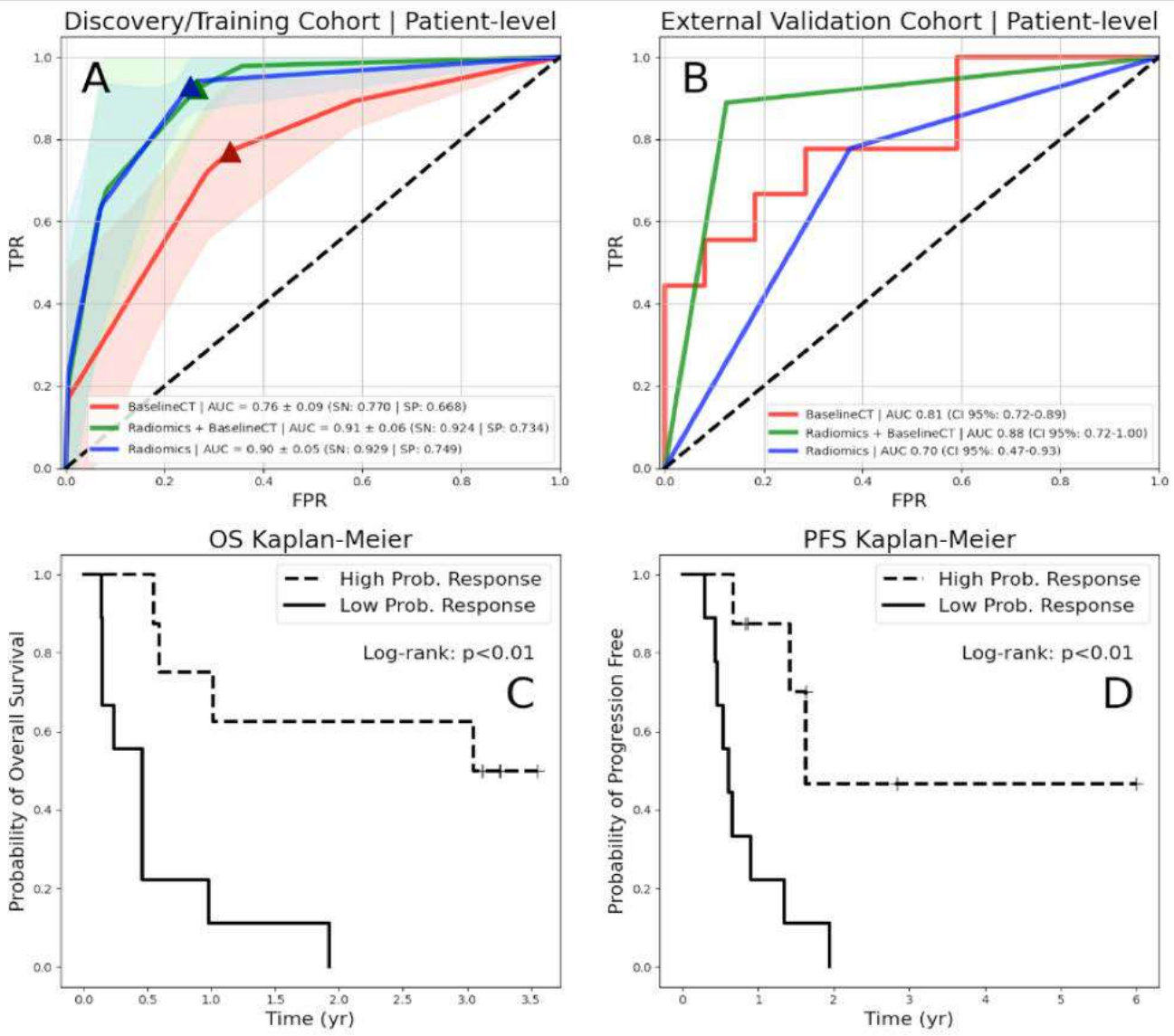

Figure 1: (Color) 5-fold cross validated LR models performance trained with 3 discrete feature sets (up-to 8 features): clinical and demographic features (red), radiomic CT features (blue), and a combination of clinical and demographic features (green). A: ROC curve showing cross validation performance on the Discovery/Training cohort of patients. Optimal prediction thresholds are determined to be the Youden-J threshold (triangle marker) with sensitivities and specificities (SN; SP) are indicated at the optimal threshold in the plot legend. B: ROC curve showing LR model prediction performance on an external validation cohort of patients. One can observe that the addition of clinical/demographic features to complimentary radiomic features increased model generalizability on an external cohort. C and D: Overall survival Kaplan-Meier plot indicating the LR model separation between high and low probability of response for both Overall Survival (OS) and Progression Free Survival (PFS) for the external validation cohort as predicted by the combination LR model (green) in subplot B.

OA03 PREDICTING THE FUTURE: NOVEL PATHOLOGY ASSESSMENTS AND IMAGING BIOMARKERS, SUNDAY, SEPTEMBER 8, 2024 - 10:45 - 12:00

OA03.05 Deep Muitiple Instance Learning-Enabled Gene Mutation Prediction of Lung Cancer from Histopathology Images

S. Xiong[1], Y. Zhao[2], Q. Ren[2], M. Li[3], L. Yang[4], D. Wu[4], K. Tang[5], X. Pan[6], F. Chen[7], W. Wang[8], S. Jin[9], X. Liu[10], G. Lin[11], W. Yao[12], L. Cai[13], Y. Yang[14], J. Liu[15], J. Wu[16], W. Fu[17], K. Sun[2], F. Li[1], B. Cheng[1], S. Zhan[1], H. Wang[1], Z. Yu[1], X. Liu[1], R. Zhong[1], H. Wang[1], P. He[18], Y. Zheng[1], P. Liang[1], L. Chen[19], T. Hou[19], B. He[2], J. Song[20], L. Wu[8], C. Hu[3], J. He[1], J. Yao[2], W. Liang[1], [1]China State Key Laboratory of Respiratory Disease & National Clinical Research Center for Respiratory Disease, the First Affiliated Hospital of Guangzhou Medical University, Guangzhou/CN ,[2]AI Lab, Tencent, Shenzhen/CN ,[3]National Key Clinical Specialty, Branch of National Clinical Research Center for Respiratory Disease, Xiangya Hospital, Central South University, Changsha/CN ,[4]Shenzhen People's Hospital, [2]nd Clinical Medical College of Jinan University, Shenzhen/CN ,[5]The First Affiliated Hospital of Sun Yat-sen University, Guangzhou/CN ,[6]Shengli Clinical Medical College of Fujian Medical University, Fujian Provincial Hospital, Fuzhou/CN ,[7]Hainan General Hospital, Haikou/CN ,[8]Hunan Cancer Hospital and The Affiliated Cancer Hospital of Xiangya School of Medicine, Central South University, Changsha/CN ,[9]National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital & Shenzhen Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Shenzhen/CN ,[10]The Second XiangYa Hospital of Central South University, Changsha/CN ,[11]Clinical Oncology School of Fujian Medical University, Fujian Cancer Hospital, Fujian Key Laboratory of Advanced Technology for Cancer Screening and Early Diagnosis, Fuzhou/CN ,[12]University of Electronic Science and Technology of China, Sichuan Cancer Hospital and Institute & Cancer, The Second People's Hospital of Sichuan Province, Chengdu/CN ,[13]Guangdong Sanjiu Brain Hospital, Guangzhou/CN ,[14]Chengdu Third People's Hospital, the Affiliated Hospital of Southwest Jiaotong University, Chengdu/CN ,[15]Peking University Shenzhen Hospital, Shenzhen Peking University-The Hong Kong University of Science and Technology Medical Center, Shenzhen/CN ,[16]The First Affiliated Hospital of Xiamen University, Xiamen/CN ,[17]Affiliated Cancer Hospital & Institute of Guangzhou Medical University, Guangzhou/CN ,[18]The First Affiliated Hospital of Guangzhou Medical University, Guangzhou/CN ,[19]Burning Rock Biotech, Guangzhou/CN ,[20]Monash University, Melbourne/AU

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OA03 PREDICTING THE FUTURE: NOVEL PATHOLOGY ASSESSMENTS AND IMAGING BIOMARKERS, SUNDAY, SEPTEMBER 8, 2024 - 10:45 - 12:00

OA03.06 Deciphering Single-Cell Resolved Tumour Microenvironment Profiles Using Spatial Metabolic Mapping

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OA04 ANTIBODY DRUG CONJUGATES IN SCLC
SUNDAY, SEPTEMBER 8, 2024 - 14:00 - 15:15

OA04.03 Ifinatamab Deruxtecan (I-DXd) in Extensive-Stage Small Cell Lung Cancer (ES-SCLC): Interim Analysis of Ideate-lung01

C.M. Rudin[1], M-J. Ahn[2], M. Johnson[3], C.L. Hann[4], N. Girard[5], M. Nishio[6], Y. Cheng[7], H. Hayashi[8], Y. Jung Kim[9], A. Navarro[10], Y. Chen[11], T. Sakai[12], M. Qian[13], J. Godard[14], M. Tang[13], J. Singh[13], L. Paz-Ares[15], [1]Memorial Sloan Kettering Cancer Center, New York/NY/USA ,[2]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul/KR ,[3]Sarah Cannon Research Institute, Nashville/TN/USA ,[4]Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore/MD/USA ,[5]Institute Curie, Paris/FR ,[6]The Cancer Institute Hospital of the Japanese Foundation for Cancer Research, Tokyo/JP ,[7]Jilin Cancer Hospital, Changchun/CN ,[8]Department of Medical Oncology, Kindai University, Osaka/JP ,[9]Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seongnam/KR ,[10]Vall d'Hebron University Hospital and Vall d'Hebron Institute of Oncology, Barcelona/ES ,[11]Cancer and Hematology Centers, Grand Rapids/MI/USA ,[12]National Cancer Center Hospital East, Kashiwa/JP ,[13]Daiichi Sankyo, Inc., Basking Ridge/NJ/USA ,[14]Daiichi Sankyo, SAS, Paris/FR ,[15]Hospital Universitario [12] de Octubre, Madrid/ES

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OA04 ANTIBODY DRUG CONJUGATES IN SCLC
SUNDAY, SEPTEMBER 8, 2024 - 14:00 - 15:15

OA04.04 Sacituzumab Govitecan as Second-Line Treatment in Patients with Extensive Stage Small Cell Lung Cancer

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Introduction: Treatment options are limited for patients with extensive stage small cell lung cancer (ES-SCLC) that progresses after platinum-based chemotherapy (chemo) and anti-programmed death ligand 1 (PD-L1) therapy. Sacituzumab govitecan (SG), a Trop-2-directed antibody-drug conjugate, is being evaluated in patients with metastatic or locally advanced solid tumors in TROPiCS-03 (NCT03964727), an open-label, multicohort, phase 2 trial. In a preliminary analysis of the ES-SCLC cohort (N=30), SG demonstrated promising antitumor activity and manageable safety (Dowlati et al, ESMO 2023). Here, we report updated results with additional patients and longer follow-up from the ES-SCLC cohort.

Methods: Adult patients with ES-SCLC that progressed after no more than 1 prior line of platinum-based chemo and anti-PD-(L)1 therapy received SG 10 mg/kg on days 1 and 8 of a 21-day cycle. The primary endpoint was objective response rate (ORR) by investigator assessment per RECIST v1.1. Secondary endpoints included clinical benefit rate (CBR), duration of response (DOR), progression-free survival (PFS), overall survival (OS), and safety.

Results: As of March 8, 2024, 43 patients were enrolled, and the median follow-up was 12.3 months (range, 8.1-20.1). Median age was 67 years (range, 48-83) and 81.4% of patients had an ECOG performance status of 1. Of the 43 patients, 20 (46.5%) patients had platinum-resistant disease (chemo-free interval <90 days). Treatment was ongoing for 7 (16.3%) patients. In the efficacy analysis (n=43), ORR was 41.9% and CBR was 48.8% (Table). The median DOR was 4.73 months (95% CI, 3.52-6.70), median PFS was 4.40 months (95% CI, 3.81-6.11), and median OS was 13.60 months (95% CI, 6.57-14.78). ORRs were 35.0% and 47.8% in platinum-resistant and -sensitive patients, respectively. In the safety analysis (n=43), any-grade treatment-emergent, treatment-related adverse events (TE TRAEs) occurred in 97.7% (grade ≥3, 60.5%) of patients. There were no TE TRAEs leading to discontinuation of study treatment. There was 1 TE TRAE that led to death (neutropenic sepsis).

Conclusions: SG as second-line treatment for ES-SCLC demonstrated promising antitumor activity in the fully enrolled ES-SCLC cohort. This activity was seen in patients with both platinum-resistant and -sensitive disease. Safety was manageable and consistent with that observed in other SG studies.

Keywords: second-line, small cell lung cancer, Trop-2–directed antibody–drug conjugate

Table

Efficacy[a]	All patients N=43	Chemotherapy-free <90 days N=20	Chemotherapy-free ≥90 days N=23
ORR (95% CI), %	41.9 (27.0-57.9)	35.0 (15.4-59.2)	47.8 (26.8-69.4)
BOR, n (%)			
Confirmed PR	18 (41.9)	7 (35.0)	11 (47.8)
SD	18 (41.9)	7 (35.0)	11 (47.8)
PD	4 (9.3)	4 (20.0)	0
Not assessed[b]	3 (7.0)	2 (10.0)	1 (4.3)
DCR (95% CI),[c] %	83.7 (69.3-93.2)	70.0 (45.7-88.1)	95.7 (78.1-99.9)
CBR (95% CI),[d] %	48.8 (33.3-64.5)	40.0 (19.1-63.9)	56.5 (34.5-76.8)
Median DOR (95% CI),[e] months	4.73 (3.52-6.70)	6.31 (1.54-6.87)	4.44 (3.02-NR)
Median PFS (95% CI),[e] months	4.40 (3.81-6.11)	3.81 (1.38-7.56)	4.98 (4.07-7.43)
Median OS (95% CI),[e] months	13.60 (6.57-14.78)	6.57 (4.73-17.71)	14.72 (7.72-NR)

[a]By investigator assessment. [b]Patients without any post-baseline assessments. [c]Patients with confirmed PR + SD. [d]Patients with confirmed PR + SD for ≥ 6 months. [e]Based on Kaplan-Meier estimates. BOR, best overall response; CI, confidence interval; DCR, disease control rate; NR, not reached; PD, progressive disease; PR, partial response; SD, stable disease.

OA04 ANTIBODY DRUG CONJUGATES IN SCLC
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OA04.05 SHR-A1921, A TROP-2 Targeted Antibody-Drug Conjugate (ADC), In Patients (pts) with Advanced Small-Cell Lung Cancer (SCLC)

J. Wang[1], L. Wu[2], X. Li[3], N. Xing[4], S. Zhang[5], Z. Song[6], L. Chen[7], Q. Dang[7], C. Liu[8], Y. Li[9], H. XU[10], J. Zhong[1], Y. Wu[11], Z. Lin[11], Z. Zhang[11], S. Wang[11], [1]National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences Peking Union Medical College, Beijing/CN ,[2]Hunan Cancer Hospital/The Affiliated Cancer Hospital of Xiangya School of Medicine, Central South University, Changsha/CN ,[3]The First Affiliated Hospital of Zhengzhou University, Zhengzhou/CN ,[4]Shanxi Provincial Cancer Hospital, Taiyuan/CN ,[5]Sichuan Cancer Hospiital, Chengdu/CN ,[6]Zhejiang Cancer Hospital, Hangzhou/CN ,[7]Shandong Cancer Hospital, Jinan/CN ,[8]Shengjing Hospital of China Medical University, Shenyang/CN ,[9]The First Affiliated Hospital of Nanchang University/The First Affiliated Hospital of Nanchang University, Nanchang/CN ,[10]Hubei Cancer Hospital, Wuhan/CN ,[11]Jiangsu Hengrui Pharmaceuticals Co., Ltd, Shanghai/CN

Introduction: SHR-A1921 is a novel ADC composed of a humanized anti-TROP-2 IgG1 monoclonal antibody attached to a DNA topoisomerase I inhibitor via a tetrapeptide-based cleavable linker. Here, we report the clinical activity and safety of SHR-A1921 in pts with pretreated extensive-stage SCLC, a condition with a poor prognosis and limited therapeutic options.

Methods: This was a first-in-human, dose-escalation, dose-expansion, and efficacy-expansion phase 1 study (NCT05154604). In SCLC expansion cohort, pts with extensive-stage disease who had relapsed to/refractory from platinum-based chemotherapy, regardless of TROP-2 expression level, were enrolled to receive SHR-A1921 at selected dose of 3.0 mg/kg every 3 weeks until disease progression or unacceptable toxicity.

Results: As of Feb 19, 2024, 17 pts were enrolled, among whom, 6 (35.3%) were still on treatment. At the study entry, 52.9% of pts had received ≥2 prior lines of therapy. 64.7% of pts had been treated with anti-PD-1/PD-L1 antibodies and 11.8% had been treated with DNA topoisomerase I inhibitors. TROP-2 expression was detectable in 16 pts, and all showed a low level with an H-Score of 0-50. Median follow-up was 5.3 months (range 1.3-9.4). Among the 15 pts evaluable for tumor response, ORR was 33.3% (95% CI 15.2-58.3), DCR was 66.7% (95% CI 41.7-84.8), and median DoR was 4.4 months (95% CI 2.3-not reached [NR]). Among all pts, median PFS was 3.8 months (95% CI 1.4-NR), and median OS was not reached. All pts experienced treatment-related adverse events (TRAEs), and the most common TRAEs included stomatitis (58.8%), nausea (35.3%), vomiting (23.5%), decreased appetite (23.5%), and anemia (23.5%). 6 pts (35.3%) experienced grade ≥3 TRAEs, with the most common being stomatitis (11.8%). No treatment-related interstitial lung disease/pneumonitis occurred. No TRAEs led to treatment discontinuation or death.

Conclusions: SHR-A1921 showed promising clinical efficacy and a manageable safety profile in pts with heavily pretreated extensive-stage SCLC, even with low TROP-2 expression.

Keywords: SCLC, TROP-2, SHR-A1921

OA04 ANTIBODY DRUG CONJUGATES IN SCLC
SUNDAY, SEPTEMBER 8, 2024 - 14:00 - 15:15

OA04.06 Efficacy and Safety of HS-20093 in Extensive Stage Small Cell Lung Cancer in a Multicenter, Phase 1 Study (ARTEMIS-001)

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Introduction: ARTEMIS-001 study is a multicenter, open-label phase 1 study investigating the safety and efficacy of HS-20093 (GSK5764227), an antibody-drug conjugate targeting B7-H3, in advanced solid tumors (NCT05276609). Promising antitumor activity was observed across multiple tumor types, particularly in extensive stage small cell lung cancer (ES-SCLC) during the dose-escalation phase of the study (Jie Wang et al., JCO, 2023). Here, we present the latest efficacy and safety results of HS-20093 in ES-SCLC patients (pts) from both the dose-escalation and dose-expansion phases.

Methods: The study is currently at the dose-expansion phase and included 4 cohorts of pts with diverse advanced solid tumors. Within ES-SCLC cohort, pts received HS-20093 at 8.0 mg/kg or 10.0 mg/kg dose every 3 weeks until disease progression. All pts had previously undergone platinum-based standard therapy. Efficacy endpoints were objective response rate (ORR), disease control rate (DCR), duration of response (DoR), progression free survival (PFS) and overall survival (OS). B7-H3 expression in tumor tissue was analyzed retrospectively.

Results: Fifty-six pts received ≥1 dose of HS-20093 at 8.0 mg/kg (N = 31) or 10.0 mg/kg (N = 25). All pts received platinum plus etoposide, 73.2% received immunotherapy (IO), and 23.2% received topoisomerase 1 inhibitor (TOPO1i). Out of 56 pts, 53 pts were evaluable for efficacy (8.0 mg/kg: 31 pts; 10.0 mg/kg: 22 pts). The median follow-up duration was 9.0 and 11.1 months for pts at 8.0 and 10.0 mg/kg dose, respectively (as of 30 Jun 2024). HS-20093 showed encouraging efficacy in ES-SCLC. ORR was 61.3% for pts at 8.0 mg/kg dose and 50.0% for pts at 10.0 mg/kg dose. DCR, median DoR, median PFS for pts at 8.0 and 10.0 mg/kg dose were 80.6% and 95.5%, 6.4 and 8.9 months, 5.9 and 7.3 months, respectively. Median OS was 9.8 months for pts at 8.0 mg/kg dose and not reached for pts at 10.0 mg/kg dose. The ORR in 32 pts who were previously exposed to IO plus platinum but were TOP1i naive was 75.0% and 66.7% at 8.0 and 10.0 mg/kg dose, respectively. No correlation was observed between B7-H3 expression level and tumor objective response to treatment; however, the pts with B7-H3 IHC expression (≥1%) demonstrated a trendency toward prolonged median PFS. Safety profile was consistent with previous reports. Grade ≥3 treatment-related adverse events (with incidence ≥10%) were neutrophil count decreased (39.3%), white blood cell count decreased (33.9%), lymphocyte count decreased (25.0%), platelet count decreased (17.9%), and anaemia (16.1%).

Conclusions: HS-20093 demonstrated encouraging antitumor activity and manageable safety in pts with previously-treated ES-SCLC. A phase 3 study is currently ongoing in China to compare the efficacy and safety of HS-20093 with standard-of-care chemotherapy in pts with relapsed SCLC (NCT06498479). The clinical development program of HS-20093 is planned to be expanded into US, EU, and rest of the world.

Keywords: HS-20093, ES-SCLC, ORR

OA05 LOCAL CONSOLIDATIVE THERAPY FOR METASTATIC NSCLC
SUNDAY, SEPTEMBER 8, 2024 - 14:00 - 15:15

OA05.03 Ablation to Oligo-Residual Sites Plus ICIs Improved Survival of Patients with Advanced NSCLC: Preliminary Results of a Prospective Phase II Trial

S. Yang, B. Chen, J. Yu, X. Liu, T. Jiang, F. Wu, A. Li, G. Gao, X. Chen, S. Ren, Tongji University Affiliated Shanghai Pulmonary Hospital, Shanghai/CN

Introduction: Local ablative treatments have been validated to prolong the survival benefit of TKIs in patients with oncogenic mutations. Whether ablation improves the survival benefit of ICIs remains unclear. Herein, we initiated a controlled randomized phase II trial to evaluate the impact of ablation to oligo-residual disease on the survival benefit of ICIs in patients with advanced NSCLC.

Methods: Patients achieved oligo-residual disease on ICIs those met inclusion criteria were recruited and randomized to two cohorts with ratio as 2:1, either with ablation (Arm A) or without ablation (Arm B) both with continued ICIs. Survival benefit of ICIs and adverse effects were captured and analyzed (ChiCTR2000032479).

Results: From August 1st 2020 to March 15th 2024, 152 out of 618 patients received ICIs (with or without chemotherapy) as first line treatment achieved oligo-residual disease were screened. Finally, 62 patients met inclusion criteria but not exclusion criteria were enrolled for analyses. Among them, 42 patients were randomized to Arm A, and 20 patients randomized to Arm B with 8 patients received ablation after progressed on ICIs. Clinicopathological characteristics were comparable in two cohorts (Table 1). Patients received ablation showed significantly improved median PFS (26.7 vs. 11.7 months, p<0.001) and OS of ICIs (NA vs. 32.8 months, p=0.012) than patients without ablation (Figure B, C). Multivariate cox regression analysis further demonstrated that ablation significantly associated with improved PFS (HR=0.161, 95%CI 0.07-0.39, p<0.001) (Figure A) and OS (HR=0.215, 95%CI 0.05-11.74, p=0.033). Subgroup analysis unveiled that cryoablation (n=13) plus ICIs yielded prolonged PFS than those with thermal ablation (n=29) (34.9 vs. 22.4 months, p=0.048) and with a trend towards prolonged OS (p=0.241).

Conclusions: Ablation significantly improved the survival benefit of ICIs in patients with advanced NSCLC. Subgroup analysis further demonstrated cryoablation combined with ICIs associated with superior benefit to thermal ablation with ICIs.

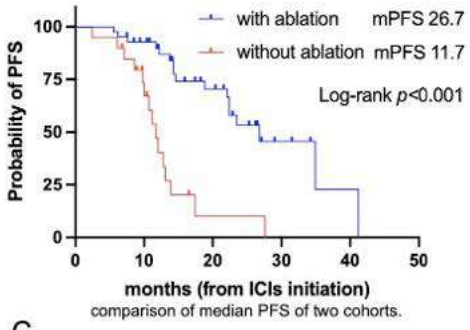
Keywords: ablation, immunotherapy, nsclc

A

Multivariate cox regression analyses of PFS.

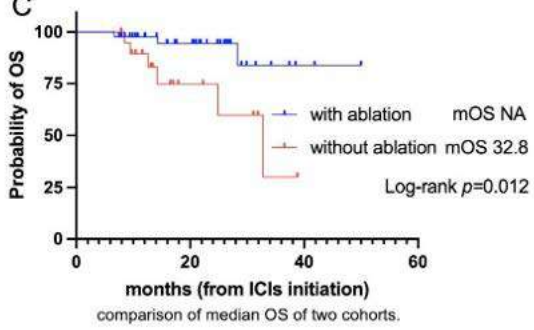
	Univariate analysis			Multivariate analysis		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Gender						
male	1		0.002	1		<0.001
female	4.165	1.72-10.08		5.821	2.11-16.08	
Age						
<65	1		0.181			
≥65	0.589	0.27-1.28				
ECOG-PS						
0	1		0.326			
1	1.486	0.67-3.27				
Histology						
adenocarcinoma	1		0.790			
squamous carcinoma	0.725	0.29-1.83				
nsclc and other	0.872	0.26-2.96				
Treatments						
Camrelizumab	1		0.251			
Tislelizumab	1.995	0.73-5.41				
Pembrolizumab	0.618	0.18-2.11				
PD-L1 expression						
unknown	1		0.008	1		
negative	2.293	0.92--5.70		3.081	1.10-8.60	0.032
1-50%	0.434	0.13-1.41		0.555	0.17-1.84	0.335
≥50%	0.511	0.17-1.55		1.121	0.38-3.34	0.837
Disease extent						
intrathoracic	1		0.044	1		0.028
extrathoracic	2.134	1.02-4.46		2.505	1.10-5.68	
Oncogenic mutation						
unknown	1		0.155			
wild type	1.882	0.74-4.81				
KRAS	0.767	0.21-2.81				
others	3.765	0.75-18.90				
Ablation						
without ablation	1		<0.001	1		<0.001
with ablation	0.192	0.41		0.161	0.07-0.39	

B



comparison of median PFS of two cohorts.

C



comparison of median OS of two cohorts.

Table 1. Clinicopathological characteristics of patients treated with immunotherapy with and without ablation of lung lesions.

	Total (n=62)	with ablation (n=42)	without ablation (n=20)	p value
Gender, No (%)				
male	55 (88.7)	36 (85.7)	19 (95.0)	0.412
female	7 (11.3)	6 (14.3)	1 (5.0)	
Age, yr, No (%)				
<65	33 (53.2)	22 (52.4)	11 (55.0)	1.000
⩾65	29 (46.8)	20 (47.8)	9 (45.0)	
ECOG, No (%)				
0	20 (32.3)	14 (33.3)	6 (30.0)	1.000
1	40 (67.7)	28 (66.7)	14 (70.0)	
Histology, No (%)				
adenocarcinoma	38 (61.3)	25 (59.5)	13 (65.0)	0.621
squamous carcinoma	17 (27.4)	11 (26.2)	6 (30.0)	
nsclc and other	7 (11.3)	6 (14.3)	1 (5.0)	
PD-L1 expression, N (%)				
unknown	18 (29.0)	12 (28.6)	6 (30.0)	0.316
negative	16 (25.8)	8 (19.0)	8 (40.0)	
1-50%	15 (24.2)	12 (28.6)	3 (15.0)	
⩾50%	13 (21.0)	10 (23.8)	3 (15.0)	
Oncogenic mutation, N (%)				
unknown	18 (29.0)	12 (28.6)	6 (30.0)	0.377
wild type	29 (46.8)	19 (45.2)	10 (50.0)	
KRAS	12 (19.4)	10 (23.8)	2 (10.0)	
others#	3 (4.8)	1 (2.4)	2 (10.0)	
Disease extent, N (%)				
intrathoracic	34 (54.8)	26 (61.9)	8 (40.0)	0.172
extrathoracic	28 (45.2)	16 (38.1)	12 (60.0)	
ICIs, No (%)				
Camrelizumab	44 (71.0)	32 (76.2)	12 (60.0)	0.327
Tislelizumab	10 (16.1)	5 (11.9)	5 (25.0)	
Pembrolizumab	8 (12.9)	5 (11.9)	5 (25.0)	
Diamter of lung lesions received ablation, N (%) *				
⩽1cm	8 (16.0)	7 (16.7)	1 (12.5)	0.659
⩽3cm	30 (60.0)	26 (61.9)	4 (50.0)	
>3cm	12 (24.0)	9 (21.4)	3 (37.5)	
mPFS, months (95%CI)	22.3 (15.3, 29.4)	26.7 (19.2, 34.3)	11.7 (10.1, 13.2)	<0.001
mOS, months (95%CI)	NA	NA	32.8 (21.1, 44.5)	0.012

Abbreviations: ECOG, Eastern Cooperative Oncology Group; PS, performance status; PFS, progression free survival; OS, overall survival. * 8 patients of cohort without ablation received ablation of lung lesions after progression on ICIs. # one with HER2 mutation, one with MET amplification and one with RET fusion.

OA05 LOCAL CONSOLIDATIVE THERAPY FOR METASTATIC NSCLC
SUNDAY, SEPTEMBER 8, 2024 - 14:00 - 15:15

OA05.04 Radiotherapy Improves Survival in Non-Small Cell Lung Cancer Following Oligoprogression on Immunotherapy: A Cohort Study

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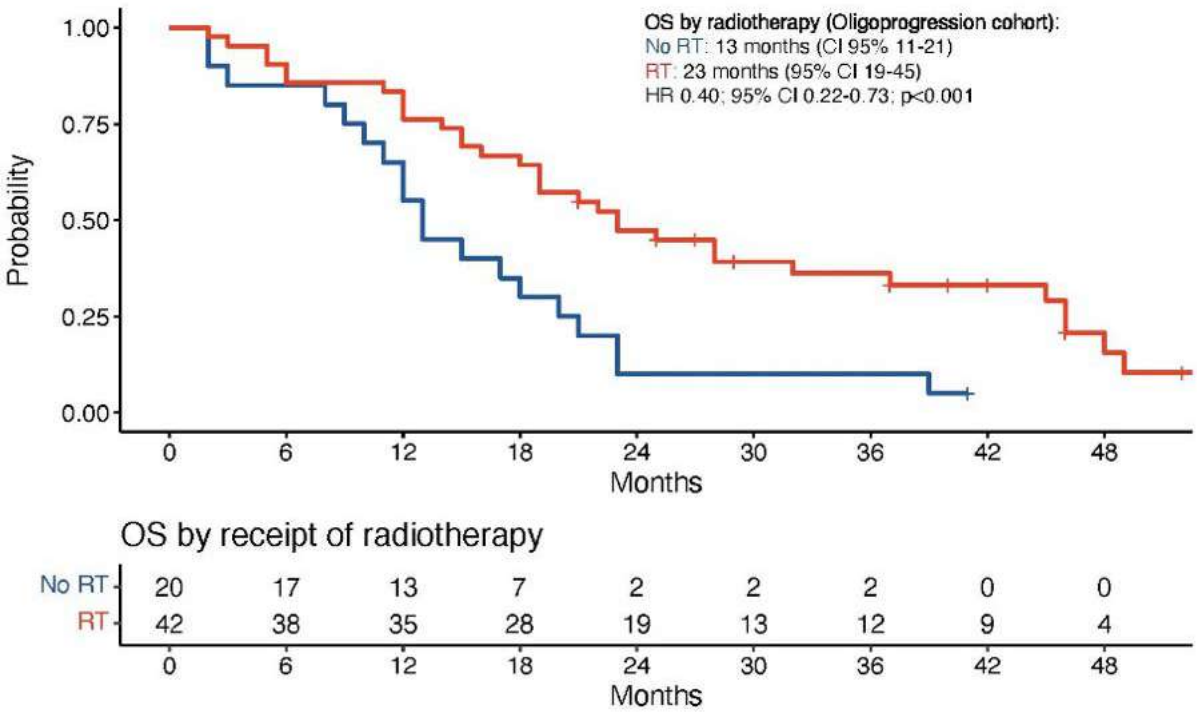
Introduction: The patterns of oligoprogression following first-line immune checkpoint inhibitors (ICI's) for metastatic NSCLC are yet to be well established. There is increasing data to suggest directed radiotherapy improves survival outcomes.

Methods: A retrospective cohort study of patients with metastatic NSCLC who had progressed following first-line PD-(L)1 inhibitors +/- chemotherapy at two high-volume cancer centres was performed. We sought to characterise the frequency and location of oligoprogression and determine the overall survival (OS) following radiotherapy in this population.

Results: One-hundred and fifty-nine patients were included in the study. At first progression, 62 (39.0%) were classified as oligoprogression. Multivariate analysis confirmed the presence of brain metastases was associated with increased likelihood of oligoprogression (OR 2.44; p=0.04) and the presence of liver metastases was associated with decreased likelihood of oligoprogression (OR 0.17; p<0.01). For patients with oligoprogression, those who received radiotherapy had a longer median PFS2 (17 vs. 11.5 months; HR 0.51; p=0.02) and a longer median OS (23 vs. 13 months; HR 0.40; p<0.001) compared to those who did not receive radiotherapy.

Conclusions: In patients with oligoprogressive metastatic NSCLC following treatment with first-line ICI's, radiotherapy significantly improves OS and PFS2 outcomes. Patients with baseline brain metastases are more likely to experience oligoprogression. Further prospective studies in directed, less heterogenous populations of patients with metastatic NSCLC will be fundamental to optimise management.

Keywords: oligoprogression, immunotherapy, radiotherapy



OA05 LOCAL CONSOLIDATIVE THERAPY FOR METASTATIC NSCLC
SUNDAY, SEPTEMBER 8, 2024 - 14:00 - 15:15

OA05.05 Pre-Local Consolidative Therapy Circulating Circulating Tumor DNA Defines Molecular Oligometastatic Non-Small Cell Lung Cancer

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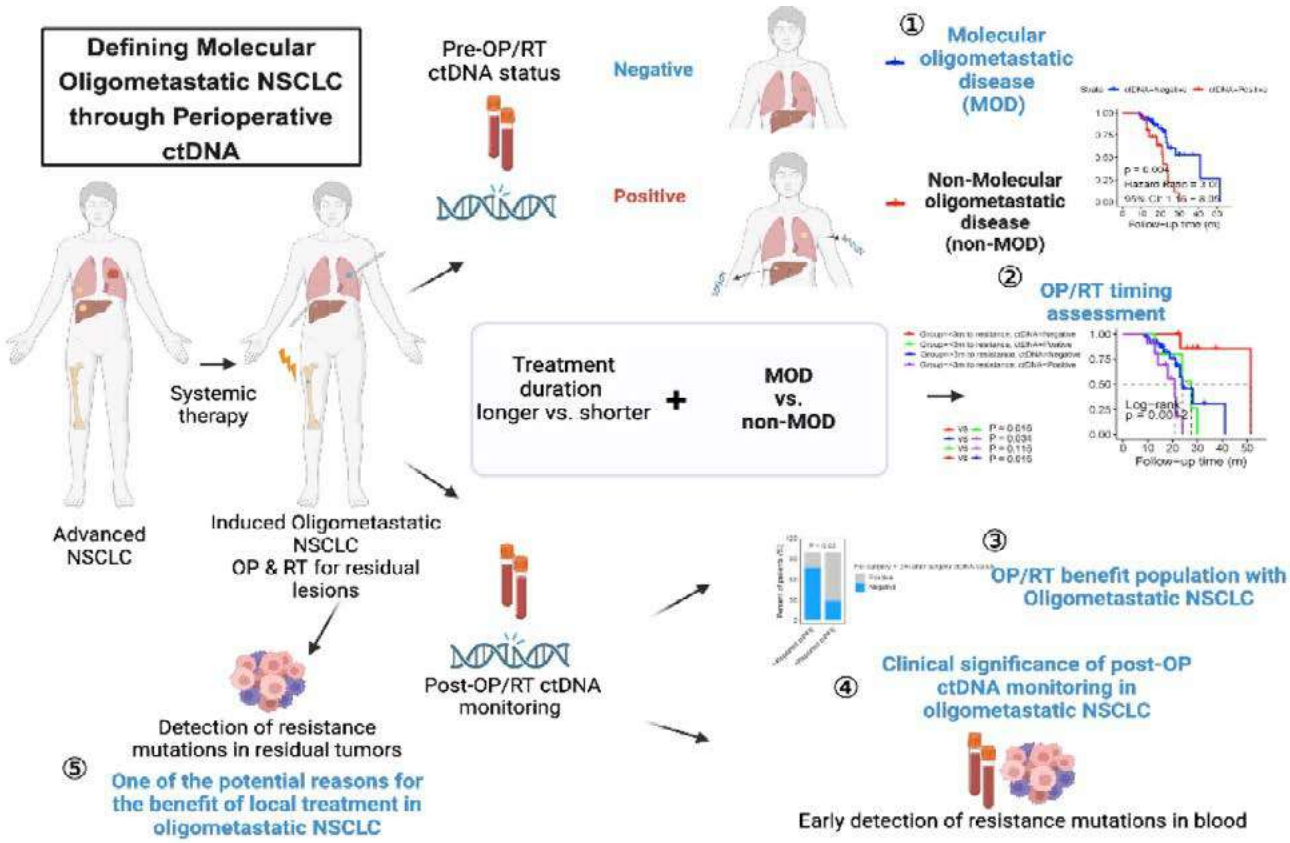
Introduction: Previous studies have proven that local consolidative therapy (LCT) could prolong survival in induced oligometastatic NSCLC, however, the clinical benefit varies widely and the therapeutic window for LCT remains unclear. We propose that ctDNA can molecularly redefine populations with induced oligometastatic disease and guide LCT timing selection.

Methods: In this observational study, we enrolled patients with advanced NSCLC who developed oligometastatic disease following systemic therapy (referred to as induced oligometastatic NSCLC). Oligometastasis was diagnosed based on radiological findings, following the guidelines of the ESRO consensus1 and pan-European multidisciplinary consensus2. Patients underwent resection and radiotherapy targeting residual lesions after multidisciplinary team discussion. Comprehensive ctDNA monitoring was conducted perioperatively using a highly sensitive panel assay targeting 338 lung cancer-related genes.

Results: A total of 339 plasma samples from 68 eligible patients were analyzed, predominantly with adenocarcinoma (n=63, 92.6%) and oligopersistence (n=58, 85.3%). We propose that patients who meet radiological oligometastatic criteria and have negative plasma ctDNA before LCT should be defined as Molecular Oligometastatic (MO) NSCLC, whereas those with positive ctDNA before LCT should be defined as non-Molecular Oligometastatic (non-MO) NSCLC. Patients with MO NSCLC had better progression-free survival (PFS) compared to those with non-MO disease (p=0.004, HR=3.05, 95% CI=1.16-8.05). Furthermore, regarding the timing of LCT, a longer duration of systemic therapy was associated with better PFS (p<0.05), and among patients with the same duration of drug treatment, patients with MO had longer PFS compared to those with non-MO (p<0.05). We also found that patients who maintained or transitioned to negative ctDNA 1 month after LCT had a higher proportion achieving PFS greater than the median PFS reported in corresponding phase III trials of the respective drugs when compared to those who maintained or transitioned to positive (p<0.05). Of note, resistance mutations were found in the post-LCT ctDNA of 11 patients, 10 of whom experienced disease progression. Moreover, post-LCT ctDNA monitoring revealed potential drug resistance mechanisms up to 14.9 months before radiological progression, with a median lead time of 5.0 months. It allows for immediate modification of treatment regimens based on ctDNA results when there is radiological progression.

Conclusions: Undetectable pre-LCT ctDNA may be truly induced oligometastatic disease, which we define as Molecular Oligometastatic NSCLC. The combination of pre-LCT ctDNA and the duration of systemic therapy assists in the early prediction of clinical outcomes and the determination of the LCT window in induced oligometastatic NSCLC.

Keywords: oligometastatic non-small cell lung cancer, ctDNA, local consolidative therapy



OA05 LOCAL CONSOLIDATIVE THERAPY FOR METASTATIC NSCLC
SUNDAY, SEPTEMBER 8, 2024 - 14:00 - 15:15

OA05.06 Radiotherapy Combined with Enhanced Immunotherapy for NSCLC

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Introduction: Patients with driver gene-negative advanced non-small cell lung cancer (NSCLC) commonly face issues of treatment resistance after first-line therapies, making the exploration of strategies to improve the survival quality of these patients of significant clinical importance. This study aims to evaluate the efficacy and safety of pulsed high-dose fractionated radiotherapy combined with granulocyte-macrophage colony-stimulating factor (GM-CSF) and tislelizumab in treating patients with driver gene-negative Stage IV NSCLC.

Methods: This is a single-arm, single-center, prospective Phase II clinical study. From March 2022 to December 2023, patients with histologically or cytologically confirmed Stage IV NSCLC (excluding those with driver mutations) after treatment were screened and enrolled. The treatment regimen included localized radiotherapy (5-6Gy × 3-10 fractions), tislelizumab (200 mg, starting within a week after radiotherapy, then every 3 weeks), and GM-CSF (starting the second day after radiotherapy, subcutaneous injection of 200ug per dose, for 14 consecutive days). The primary endpoints were to assess the Objective Response Rate (ORR) and Disease Control Rate (DCR), with secondary endpoints including Progression-Free Survival (PFS), Overall Survival (OS), safety, and tolerability.

Results: As of December 1, 2023, 15 patients with treated advanced NSCLC were enrolled, including 8 cases of adenocarcinoma and 7 of squamous cell carcinoma. The observed local ORR was 80.0% (95% Confidence Interval: 54.8%-92.9%), and DCR reached 100.0% (95% Confidence Interval: 79.6%-100.0%), showing statistically significant differences compared to historical data of second-line treatments. Median PFS and OS have not yet been reached. Regarding safety, no Grade 3 or higher treatment-related adverse events (TRAEs) or immune-related adverse events were observed.

Conclusions: The results of this study demonstrate that for patients with driver gene-negative Stage IV NSCLC, pulsed high-dose fractionated radiotherapy combined with GM-CSF and tislelizumab as a second-line treatment regimen showed promising efficacy and controllable safety. This finding highlights the potential value of this treatment strategy and lays the groundwork for further research.

Keywords: NSCLC, Tislelizumab, Radiotherapy

OA06 NOVEL IMMUNOTHERAPY STRATEGIES AND COMBINATIONS
SUNDAY, SEPTEMBER 8, 2024 - 15:30 - 16:45

OA06.03 SAFFRON-301: Tislelizumab Plus Sitravatinib in Advanced/Metastatic NSCLC Progressing on/after Chemotherapy and Anti-PD-(L)1

Q. Zhou[1], B. Gao[2], J. Hu[3], J. Zhao[4], M. Wang[5], K. He[6], W. Zhang[7], C. Liu[8], J. Fang[4], X. Li[9], Z. Wang[10], M. Matos[11], V. Kwatra[12], X. Li[13], Y. Chen[13], J. Zhang[13], J. Wang[13], Y-L. Wu[1], [1]Guangdong Lung Cancer Institute, Guangdong Provincial People's Hospital (Guangdong Academy of Medical Sciences), Southern Medical University, Guangzhou/CN ,[2]Blacktown Cancer and Haematology Centre, Blacktown/AU ,[3]Fudan University Affiliated Zhongshan Hospital, Shanghai/CN ,[4]Beijing Cancer Hospital, Beijing/CN ,[5]Peking Union Medical Hospital, Beijing/CN ,[6]The Ohio State University College of Medicine, Columbus/OH/USA ,[7]The First Affiliated Hospital of Nanchang University, Nanchang/CN ,[8]Xinjiang Cancer Hospital, Urumqi/CN ,[9]The First Affiliated Hospital of Zhengzhou University, Zhengzhou/CN ,[10]Shandong Cancer Hospital, Jinan/CN ,[11]Pindara Private Hospital, Benowa/AU ,[12]Cancer Research South Australia, Adelaide/AU ,[13]BeiGene (Beijing) Co., Ltd., Beijing/CN

Introduction: There are limited treatment options for patients with advanced NSCLC who were previously treated with chemotherapy and/or anti-programmed cell death protein1 (PD1)/-programmed deathligand 1 (PD-L1) antibodies. Tislelizumab (TIS) is an anti-PD1 antibody. Sitravatinib (sitra) is a receptor tyrosine kinase inhibitor that can shift the immunosuppressive tumor microenvironment toward an immunostimulatory state. Combining sitravatinib with tislelizumab may potentially overcome initial checkpoint inhibitor resistance. We present efficacy/safety results from an openlabel, randomized, phase 3 trial evaluating TIS plus sitra versus docetaxel (doc) in patients with previously treated locally advanced/metastatic NSCLC (NCT04921358).

Methods: Adults (≥18 years) with unresectable locally advanced/metastatic histologically or cytologically confirmed NSCLC (ECOG PS ≤1), who were previously treated with ≤2 lines of systemic chemotherapy and anti-PD(L)1 antibodies were eligible. Patients were randomized (1:1) to TIS 200 mg intravenously once every 3 weeks (Q3W) in combination with sitra 100 mg orally once daily (TIS+sitra) or doc 75 mg/m2 intravenously Q3W. Patients were treated until disease progression, intolerable toxicity, death, or consent withdrawal. Co-primary endpoints were overall survival (OS) and independent-review committee (IRC)assessed progressionfree survival (PFS). Secondary endpoints included IRCassessed objective response rate (ORR) by RECIST v1.1 and treatmentemergent adverse events (TEAEs).

Results: As of Dec 20, 2023, 187 and 190 patients were randomized to TIS+sitra and doc, respectively (median age [TIS+sitra/doc]: 63.0/63.0 years; median followup: 8.0/7.6 months). Most patients (TIS+sitra/doc) were male (81.8%/79.5%), Asian (93.6%/93.2%), had an ECOG PS 1 (74.9%/75.8%), had received 1 line of prior chemotherapy (75.9%/73.7%), and had metastatic disease (77.0%/74.2%). Median OS (95% confidence interval [CI]) was 11.5 (9.4-14.6) and 11.4 (9.9-15.0) months with TIS+sitra and doc, respectively; hazard ratio (HR) (95% CI), 1.02 (0.75-1.39). Median IRCassessed PFS (95% CI) was 4.4 (4.0-5.7) (TIS+sitra) and 2.9 (2.6-4.2) months (doc); HR (95% CI): 0.82 (0.62-1.07). IRCassessed ORR (95% CI) was 12.3% (8.0%-17.9%) (TIS+sitra) and 12.6% (8.3%-18.2%) (doc). The incidences of TEAEs was higher with TIS+sitra than doc (Table). Grade ≥3 TEAEs occurring in ≥5% of TIS+sitra or doc groups were (TIS+sitra/doc): hypertension (13.4%/1.1%), pneumonia (9.1%/8.5%), palmarplantar erythrodysesthesia syndrome (6.5%/0%), hypokalemia (5.4%/2.3%), white blood cell count decreased (0%/29.4%), neutrophil count decreased (0.5%/28.8%), neutropenia (0.5%/7.3%), and febrile neutropenia (0%/5.6%). The trial was terminated due to safety risks/unfavorable benefit-risk analysis.

Conclusions: In patients with previously treated advanced/metastatic NSCLC, TIS+sitra showed similar efficacy to doc and was associated with a higher incidence of TEAEs.

Keywords: NSCLC, sitravatinib, tislelizumab

Table

Patients with treatment-emergent adverse events, n (%)	Tislelizumab + sitravatinib (N = 186)	Docetaxel (N = 177)
Any	183 (98.4)	162 (91.5)
Grade ≥3	121 (65.1)	100 (56.5)
Serious	83 (44.6)	66 (37.3)
Leading to death	15 (8.1)	5 (2.8)
Leading to treatment discontinuation (any component)	45 (24.2)	15 (8.5)
Any Immune-mediated AEs	91 (48.9)	18 (10.2)
Grade ≥3	18 (9.7)	4 (2.3)

OA06 NOVEL IMMUNOTHERAPY STRATEGIES AND COMBINATIONS
SUNDAY, SEPTEMBER 8, 2024 - 15:30 - 16:45

OA06.04 Phase II Study of Pembrolizumab and Itacitinib for Patients with Metastatic NSCLC Expressing PD-L1: Long-Term Follow up

M.E. Marmarelis[1], D.J. Cantor[2], D. Mathew[2], T. McWilliams[2], J. Bauml[3], W-T. Hwang[4], A. Singh[4], C. D'Avella[4], C. Davis[4], D. Ye[4], L. Sun[4], C. Ciunci[4], C. Aggarwal[4], R.B. Cohen[4], A. Minn[4], J. Wherry[4], C.J. Langer[4], [1]University of Pennyslvania, Philadelphia/PA/USA ,[2]University of Pennsylvania, Philadelphia, PA/PA/USA ,[3]Janssen, Philadelphia/PA/USA ,[4]University of Pennsylvania, Philadelphia/PA/USA

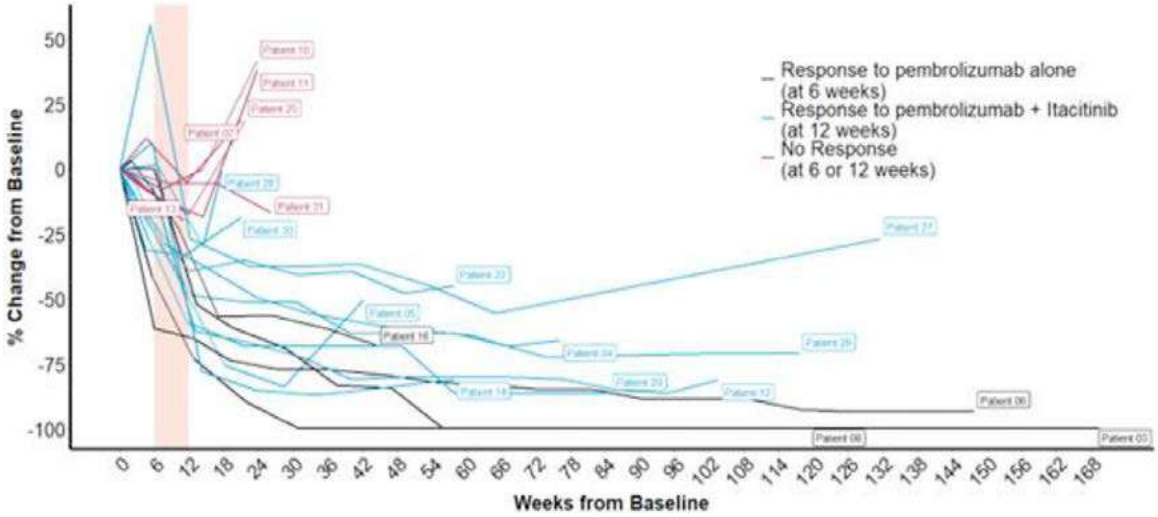
Introduction: Adaptive resistance to immunotherapy in metastatic non-small cell lung cancer (mNSCLC) remains a challenge. Preclinical work suggests that constitutive interferon signaling promotes resistance to immune checkpoint blockade and blocking JAK1/2 later during the course of immunotherapy can reverse this resistance. We present long-term follow up of a phase II clinical trial of pembrolizumab and 6 weeks of itacitinib (INCB039110; JAK1 inhibitor) as first-line therapy in mNSCLC patients (pts) with PDL1 expression ≥50% (NCT03425006).

Methods: Treatment-naïve pts with mNSCLC and ECOG PS 0-1 received pembrolizumab (200mg IV every 21 days). Itacitinib 200mg daily po was started on Cycle 3 Day 1 of pembrolizumab and continued for 6 weeks. Overall response rate (ORR) and best overall response (BOR) were determined by RECIST 1.1. Progression free survival (PFS), and overall survival (OS) were determined using Kaplan Meier methodology. Patients were categorized as having a response to pembrolizumab if their 6-week scan showed a PR/CR by RECIST 1.1 or as response to pembrolizumab + itacitinib if their 12-week (but not 6-week) scan showed a PR. Data cut-off for long-term follow up was December 1, 2023.

Results: Of 31 patients screened, 23 were enrolled between 10/16/2018 and 3/4/2021 and received at least 1 cycle of pembrolizumab: 56.5% female, median age 62 years (range, 41-78), 87% with smoking history, 78% adenocarcinoma, 22% squamous, 9/23 with PD-L1 ≥90%. 20 patients completed 12 weeks of treatment, 3 patients stopped the trial due to pembrolizumab toxicity (1), CNS progression after pembrolizumab (1) and patient decision (1). At 12 weeks ORR was 62% (13 partial response (PR), 6 stable disease (SD), 2 progressive disease (PD)). Best overall response was 66.7% (2 complete response (CR), 12 PR, 6 SD, 1 PD). Median PFS was 12.7 months (95% CI 4.82 - NA) and median OS was 53.4 months (95% CI 27.2 - NA). There was no difference in median PFS or OS between PDL1 50-89% and ≥90% groups. Figure 1 shows change in tumor burden over time in relation to study drug administration.

Conclusions: Treatment-naïve pts with mNSCLC and PD-L1 expression ≥50% treated with pembrolizumab and a brief course of JAK inhibition achieved an ORR of 62% at 12 weeks and improvement in mPFS and mOS compared to historical controls (Keynote 24: mPFS 10.3 mo, mOS 30 mo). Interferon signaling modulation through JAK1 inhibition may help prevent resistance to anti-PD1 therapy and should be studied further in a randomized trial.

Keywords: Immunotherapy, JAK, Pembrolizumab



OA06 NOVEL IMMUNOTHERAPY STRATEGIES AND COMBINATIONS
SUNDAY, SEPTEMBER 8, 2024 - 15:30 - 16:45

OA06.05 IL15 Superagonist (N-803, Anktiva) + Checkpoint Inhibitor (CPI) Prolongs OS in 2ndline or Greater NSCLC Patients Failing CPI

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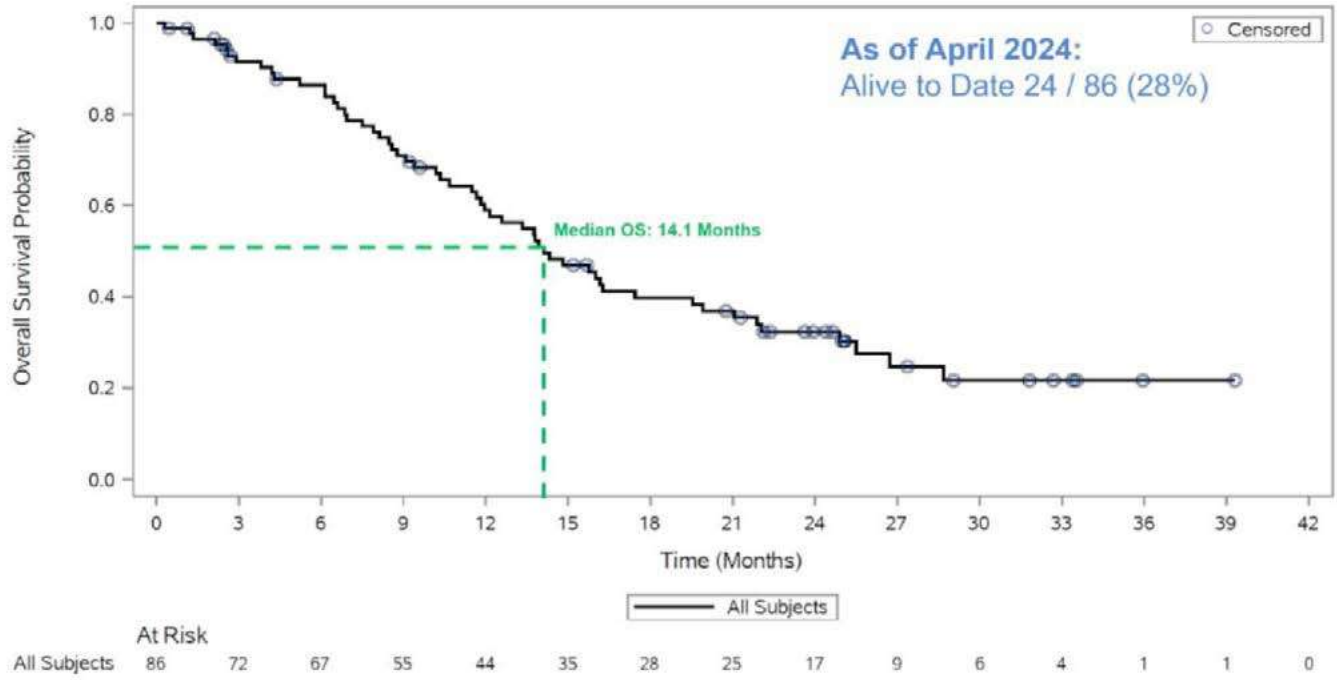
Introduction: A majority of NSCLC patients experience progression following CPI, with real-world data OS of 7 to 10 months. Current NCCN guidelines state that CPI is not recommended in NSCL patients after failure of CPI. In these patients with CPI resistance, tumor evasion occurs through MCH-1 loss. Anktiva, a novel IL-15/IL-15 Receptor Alpha complexed protein rescues checkpoint activity through activation of NK cells with induction of CD4+, CD8+ and memory T cells in 2nd line or greater NSCLC patients who failed CPI. QUILT 3.055, a phase 2b study of Anktiva in combination with CPI (nivolumab or pembrolizumab) in multiple tumor types including NSCLC who failed CPI.

Methods: We present mature OS data, based on 16.3 month mean follow-up of 86 patients with 2nd and 3rd line+ NSCLC previously treated and failed CPI alone or failed CPI combination with chemotherapy as their most recent prior therapy. Trial inclusion required investigator assessed progression on their last line of therapy for study entry. Patients received Anktiva 15mcg/kg SC every 3 weeks in combination with the same checkpoint inhibitor with which they had their most recent progression.

Results: The median OS (n=86) was 14.1 months (95% CI 11.7, 17.4) with 24 ongoing survival to date. In 3rd line+ve (n=25) median OS was 14.8 months (95% CI 9.1, 26.7). OS for PDL1+ve (>1%) (N=53) was 13.8 months (95% CI 10.2, 17.4) versus PDL1-ve (N=33) of 15.4 months (95% CI 11.5, 23.6). In 2nd line (n=61) there was no difference in OS between PDL1+ve and PDL1-ve with OS of 13.8 months versus 13.3 months respectively. The most common any grade AEs were injection site reaction 78 (91%), fatigue 46 (53%), chills 36 (42%) with 11 patients (13%) study drug discontinuation due to AEs. Grade 3+ AEs were seen in 35 (41%), no individual AE category was greater than 10%. The KM curve demonstrates long-term survival at ≥18 and ≥21 months of 28/86 (33%) and 26/86 (30%) patients respectively:

Conclusions: Anktiva plus CPI therapy in 2nd line or greater NSCLC demonstrated long-term median OS, independent of PDL1 status, and independent of prior lines of therapy in patients with acquired resistance to CPI. These findings support the novel mechanism of action of Anktiva to rescue CPI activity through the activation of NK and T cells, driving long-term memory, with median OS ongoing survival of 33% and 30% at 18 and 21 months respectively, exceeding the standard of care.

Keywords: immunotherapy, IL-15, checkpoint inhibitor



OA07 OPPORTUNITIES FOR OPTIMIZING SUPPORTIVE CARE
SUNDAY, SEPTEMBER 8, 2024 - 15:30 - 16:45

OA07.03 The Effect of Personalized Music Therapy on Perioperative Pain and Anxiety in NSCLC Patients

Y. Yuan[1], Y. Ku[1], W. Huang[2], M. Zheng[1], Y. Zhou[2], Y. Lin[2], R. Te[2], H. Zhou[2], J. Zhao[1], W. Lin[1], Q. Chen[1], B. Rao[2], S. Feng[2], J. Zhong[2], L. Kang[2], H. Long[2], [1]Sun Yat-sen University, Guangzhou/CN ,[2]Sun Yat-sen University Cancer Center, Guangzhou/CN

Introduction: Music therapy, with its advantages of high safety and absence of side effects, has gradually been accepted and applied in medical practice to alleviate patients' negative emotions and feelings. However, there is a lack of in-depth empirical research on the specific impact of music therapy on perioperative anxiety in patients with non-small-cell lung cancer.

Methods: We conducted a single-center, double-arm, open-label, phase 2 trial and randomly assigned patients with stage I or II NSCLC to receive personalized music therapy plus patient-controlled analgesia (PCA) pump (experimental group) or PCA pump alone (control group). Personalized music library was selected by music therapists based on psychosocial evaluation. The timetable of music therapy included: 40 minutes before surgery, during the surgery and 10 a.m./15 p.m./20 p.m. in three days after surgery. The primary end point was visual analogue scale of anxiety (VAS-A). Secondary end points included visual analogue scale of pain (VAS-P), dosage of analgesics and frontal middle theta power (Fmθ).

Results: A total of 45 patients underwent randomization; 30 were assigned to the experimental group and 15 were assigned to the control group. The experimental group showed significantly lower levels of VAS-A and VAS-P at each time point before and after surgery (P<0.01). We also observed a complete mediating role in the effect of music therapy on postoperative dyspnea symptom, with an effect size of 31.23% (Figure 1) and the score of dyspnea was consequently lower in experimental group at each observation time point (P<0.05), assessed by quality of life questionnaire. The electroencephalograph showed an increase in Fmθ power in the experimental group, while remained relatively stable in control group (P<0.05). The dosage of analgesics between two groups hadn't reached statistical difference.

Conclusions: Personalized music therapy significantly alleviating preoperative and postoperative anxiety and improving postoperative respiratory difficulty symptoms. Additionally, we found that the effect of music therapy in reducing dyspnea symptom appears to be achieved through the reduction of anxiety levels. Combining the changes in anxiety levels and Fmθ power before and after the intervention, we speculate that the mechanism by which music therapy improves anxiety may be related to eliciting positive emotions and shifting attention.

Keywords: Music Therapy, Enhanced Recovery After Surgery, Non-small-cell lung cancer

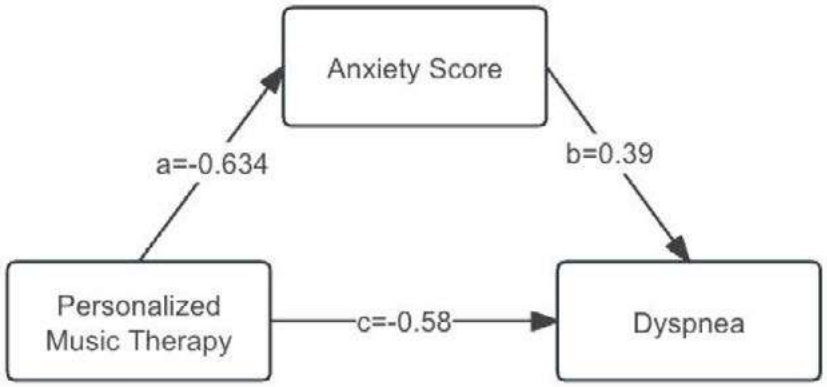


Figure 1. Schematic diagram of the mediating role of personalized music therapy on postoperative dyspnea symptom

Care Sequence®: Cancer Drug Therapy ☐ before surgery

Name _____ DOB _____ MRN _____ Today's Date _____

Goal of Care: *Curative* Histology _____ Stage: _____ Actionable biomarkers: _____

ONLY Checked care is in your care plan	Approximate time, order by month	Appointments & Notes
Planning and Preparation	month 1 m2 m3 m4 … m9+	
☐ Medical oncology consult, care planning		
☐ Surgeon consult		
☐ Radiation oncology consult		
☐ Biomarker testing		www.lungevity.org/4R/biomarker
☐ Complete tests and imaging		
☐ Pulmonary function test (PFT)		
☐ Fertility consult, treatment		
☐ Genetic counseling and testing		
☐ Clinical trial discussion, enrollment		
Prepare yourself and your health for treatment		**Start, then continue during treatment**
☐ Support: emotional, transportation, food, other		
☐ Financial, health insurance, copay assistance		
☐ Stop smoking, vaping, using tobacco		
☐ Stop or limit alcohol		
☐ See primary care, find if none: checkup, current medications, existing diseases (diabetes, other)		
☐ Discuss falls, frailty, memory concerns		
☐ Vaccines for you, household: Flu, DTaP, HPV, Shingles, Pneumococcal, COVID		
☐ See dentist if overdue for exam, cleaning		
☐ Get nutrition information or consult		
☐ Health Power of Attorney in medical records		
Cancer drug therapy		
☐ Finalize therapy plan		
☐ Port placement, if needed		
☐ Medication to take before cancer treatment		
☐ Medication to have, but do not start using		
☐ Anti-cancer therapy consent and education		
☐ Use barrier contraception / condoms		
☐ **Cancer drug (systemic) therapy** ☐ Chemotherapy ☐ Targeted therapy ☐ Immunotherapy		
☐ Side Effect Management		4Rplan.com/LC-SE/
☐ Medical oncology visits		
☐ Follow-up imaging		
☐ Other:		
☐ **Surgery**		
☐ **Additional anti-cancer drug therapy**		
☐ **Radiation therapy**		
☑ **Follow-up care**		

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OA07 OPPORTUNITIES FOR OPTIMIZING SUPPORTIVE CARE
SUNDAY, SEPTEMBER 8, 2024 - 15:30 - 16:45

OA07.04 Optimising Care of Older Patients with Lung Cancer - An Innovative Nurse-led Model of Care

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Introduction: Despite being recommended by many international organisations, geriatric screening and comprehensive assessment of older patients with lung cancer has not been adopted routinely. Given the median age of patients diagnosed with lung cancer is 70 years and many have comorbidities, there is a clear need for holistic patient assessment to inform management for this vulnerable group. We previously implemented a medical-led geriatric oncology model of care (ML-GOMOC). Although 85% of patients were screened, only 59% of eligible patients underwent comprehensive geriatric assessment and only 65% of patients were assessed prior to treatment. The ML-GOMOC did not meet the pre-defined criteria for feasibility or acceptability, hence there was an impetus to investigate a new model of care. The aim of this study was to develop, implement and evaluate a nurse-led geriatric oncology model of care (NL-GOMOC).

Methods: A NL-GOMOC was co-designed with key stakeholders including consumers. This involved a nurse using validated tools to screen and assess all new patients with lung cancer aged 65y+ or 50y+ for Aboriginal and Torres Strait Islander peoples. Tools included the Hospital and Anxiety Depression Scale, Geriatric Depression Scale and QLC-C30. Assessments included a Timed-Up-and-Go, miniCOG assessment, postural blood pressure and baseline blood tests. Clinical pathways of care were developed based on the assessments including nursing referrals to allied health and specific triggers for a comprehensive assessment at a multidisciplinary aged care clinic. Patients were subsequently discussed at a weekly multidisciplinary team meeting with clinicians and allied health to finalise management. The nurse conducted a follow-up phone call at 4-6 weeks post-review to assess if recommendations were being implemented.

Results: From June-December 2023, 102 patients were screened of whom 65 met eligibility criteria. 58 (89%) patients were assessed. Median age was 73y (range 65-86y). Twenty-eight patients (48%) were seen on the day of oncology appointment. Of the 53 patients who had treatment, 44 (83%) were seen prior to, 4 (8%) were seen on the day of and 5 (9%) were seen after commencement of treatment. The assessment identified polypharmacy in 26 (45%), cognitive deficits in 11 (19%) and postural hypotension in 2 (3%). Abnormal scores suggested depression in 9/57 (16%) and anxiety in 5/50 (10%) of patients. Referrals were made to dietitian (34, 59%), social work (26, 45%), occupational therapy (21, 36%), physiotherapy (20, 34%), speech pathology (5,9%) and clinical psychology (2, 3%). Six (10%) were referred via their general practitioner to a geriatrician for comprehensive geriatric assessment. All patients were discussed at the multidisciplinary team meeting and all had a follow-up phone call. High levels of satisfaction with NL-GOMOC were near ubiquitous at 98% (49/50) of surveyed patients.

Conclusions: Implementation of a NL-GOMOC for older patients with lung cancer increased the proportion of patients undergoing geriatric screening and assessment, when compared to the previous ML-GOMOC. Innovative models of care improve the uptake of evidence-based care for older people with cancer. Further assessment of NL-GOMOC including acceptability, feasibility and costing will be conducted at 12 months post-implementation.

Keywords: geriatric oncology, model of care, nurse

OA07 OPPORTUNITIES FOR OPTIMIZING SUPPORTIVE CARE
SUNDAY, SEPTEMBER 8, 2024 - 15:30 - 16:45

OA07.05 Improving Supportive and Social Care in Lung Cancer with the 4R Oncology Model for Patient Care Planning and Delivery

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Introduction: Patients with non-small cell lung cancer (NSCLC) have considerable needs for supportive care, social work and health maintenance before and during treatment. However, these needs are often difficult to identify and address given the complexity of NSCLC care. We implemented 4R Oncology model at 8 centers (4 community, 3 academic, 1 VA) and evaluated its impact on referrals to and receipt of supportive and social care in NSCLC. 4R (Right Info/Care/Patient/Time) facilitates timely delivery of comprehensive care and patient engagement in care with the use of patient and care team-facing care plans called 4R Care Sequences (see Exhibit for an example). Care Sequences encompass guideline-based direct cancer care, supportive care, social work and health maintenance in one concise care plan.

Methods: We compared 7 supportive and social care delivery metrics between the cohort of patients who received 4R (4R cohort, N=61) with the historical control cohort of patients who received care pre-4R implementation at the 8 participating centers (Control cohort, N=112). Each type of care was assessed for two aspects: whether a patient was referred to this care, and whether the referred patient received this care, i.e., completed the referral.

Results: We significantly improved referral rates for all 7 metrics (Table). All referral completion metrics improved numerically and 2 significantly (Table).

Conclusions: Patients who received 4R Care Sequences had markedly improved referrals to and receipt of supportive and social care. There is room to improve all of these metrics, and we continue refining the 4R Oncology model to support patients in completing referrals and in utilizing self-management resources.

Referral and completion of referrals to guideline-recommended care

Metric	NCCN Guideline	% of Patients referred to this care		Pvalue	% of referred patients who completed referrals (obtained this care		Pvalue
		4R cohort (N=61)	Control cohort (N=112)		4R cohort	Control cohort	
Primary care and chronic care	NSCLC	88%	46%	**0.03**	88% n=51	77% n=52	0.1
Smoking Cessation for people who smoke	NSCLC	93% n=28	46% n=80	**0.0001**	86% n=26	81% n=37	0.1
Help with transportation and practical needs	Distress	76%	24%	**0.0001**	93% n=44	70% n=27	**0.01**
Emotional Support	Distress	74%	35%	**0.0001**	88% n=43	74% n=39	0.1
Nutrition consultation and/or resources	NSCLC	69%	29%	**0.0001**	78% n=40	73% n=33	0.4
Financial and co-pay support	Distress	76%	24%	**0.0001**	89% n=44	33% n=27	**0.0001**
Information about side effects and self-management resources	Distress	92%	39%	**0.0001**	50% n=56	38% n=44	0.2

OA07 OPPORTUNITIES FOR OPTIMIZING SUPPORTIVE CARE
SUNDAY, SEPTEMBER 8, 2024 - 15:30 - 16:45

OA07.05 Phase 3 Study of HR20013 For Prevention of Cisplatin-based Chemotherapy-induced Nausea and Vomiting (PROFIT Study)

L. Zhang[1], Y. Zhao[1], M. Zhang[2], J. Yao[3], S. Leng[4], X. Li[5], L. Lin[6], J. Chen[7], S. Zhang[8], X. Qin[9], Z. Qin[10], T. Yi[11], R. Wang[12], X. Li[12], Y. Yu[13], Z. Wang[14], Q. Zheng[15], J. Mei[16], Y. Wang[17], H. Wang[18], [1]Sun Yat-sen University Cancer Center, Guangzhou/CN ,[2]The Second Hospital of Anhui Medical University, Hefei/CN ,[3]The First Affiliated Hospital of Henan University of Science and Technology, Luoyang/CN ,[4]Meihekou Central Hospital, Meihekou/CN ,[5]Linyi Cancer Hospital, Linyi/CN ,[6]Zhangzhou Municipal Hospital of Fujian Province, Zhangzhou/CN ,[7]Yichun People's Hospital, Yichun/CN ,[8]Yanbian University Hospital, Yanji/CN ,[9]Liuzhou People's Hospital, Liuzhou/CN ,[10]Zhejiang Provincial People's Hospital (Affiliated People's Hospital, Hangzhou Medical College), Hangzhou/CN ,[11]Xiangyang Central Hospital, Xiangyang/CN ,[12]Affiliated Zhongshan Hospital of Dalian University, Dalian/CN ,[13]Harbin Medical University Cancer Hospital, Harbin/CN ,[14]The First Affiliated Hospital of Jinzhou Medical University, Jinzhou/CN ,[15]Quzhou People's Hospital, Quzhou/CN ,[16]Zhengzhou People's Hospital, Zhengzhou/CN ,[17]Fujian Shengdi Pharmaceutical Co., Ltd, Shanghai/CN ,[18]Fujian Shengdi Pharmaceutical Co., Ltd, Wuhan/CN

Introduction: Cisplatin-based chemotherapy is still back-bone of treatment for advanced non-small cell lung cancer. Co-administration of multiple antiemetics that inhibit several molecular pathways involved in emesis is required to optimize control of cisplatin-based highly emetogenic chemotherapy-induced nausea and vomiting (HEC-CINV). HR20013 is a mixed formulation of HRS5580 (a novel NK-1 receptor inhibitor) and palonosetron (PALO) for intravenous (IV) infusion, which simultaneously inhibit NK-1 and 5-HT3 pathways. The study (NCT05509634) aimed to assess HR20013 versus fosaprepitant (FAPR) plus PALO (FAPR+PALO) regimen in preventing cisplatin-based HEC-CINV.

Methods: This multicenter, randomized, double-blind, double-dummy, positive-controlled, phase 3 trial compared HR20013 (N=373; IV, D1) with FAPR+PALO (N=377; IV, D1) in chemo-naïve patients (pts) receiving cisplatin-based HEC (cisplatin ≥60mg/m2). All pts also received oral dexamethasone (DEX) on days 1-4. Totally, pts were given identical blinded antiemetic treatment for 2 cycles. Stratification factors were gender, age (≥55 vs <55 y), and cisplatin plus other HEC drugs (yes vs no). Primary endpoint was complete response (CR; no emesis/no rescue) rate at overall phase (OP; 0-120 h) after cisplatin-based HEC in cycle 1. A noninferiority test was used for primary endpoint with a noninferiority margin of -10% for difference (D).

Results: Baseline characteristics were comparable between groups. CR rate at OP in cycle 1 was 77.7% vs 78.2% (D=-0.9% [95% CI: -6.7, 5.0]; 1-sided P<0.01), showing primary endpoint met non-inferiority. CR rates at OP in cycle 2, acute phase (AP; 0-24 h), delayed phase (DP; 24-120 h), and 0-168 h in cycle 1 and 2 were similar in the 2 groups, while that at beyond delayed phase (BDP; 120-168 h) in cycle 1 and 2 with HR20013+DEX were higher than FAPR+PALO+DEX (cycle 1: 90.3% vs 86.5%; cycle 2: 92.7% vs 87.8%; Table). Consistently, a trend of higher rates of complete protection (CP; no emesis / no rescue / no significant nausea [visual analogue scale score <25 mm]) and total control (TC; no emesis / no rescue / no nausea [visual analogue scale score <5 mm]) at BDP was noted with HR20013+DEX, particularly in cycle 2 (CP: 90.8% vs 86.3%; TC: 83.8% vs 78.6%). Rates of pts with no significant nausea, no emesis, and no rescue in cycle 1 and 2 were comparable. The 2 groups had a similar safety profile.

Conclusions: HR20013+DEX was non-inferior to FAPR+PALO+DEX in prevention of cisplatin-based HEC-CINV and well tolerated.

Keywords: cisplatin-based chemotherapy, antiemetic, complete response

	Cycle 1				Cycle 2			
	HR20013+DEX (N=373)	FAPR+PALO+DEX (N=377)	D	P	HR20013+DEX (N=314)	FAPR+PALO+DEX (N=336)	D	P
OP	290 (77.7)	295 (78.2)	-0.9 (-6.7, 5.0)	<0.01*	254 (80.9)	263 (78.3)	2.4 (-3.7, 8.5)	0.44
AP	340 (91.2)	339 (89.9)	1.0 (-3.2, 5.2)	0.64	293 (93.3)	306 (91.1)	2.2 (-1.9, 6.2)	0.30
DP	298 (79.9)	304 (80.6)	-1.2 (-6.8, 4.4)	0.68	255 (81.2)	267 (79.5)	1.5 (-4.5, 7.6)	0.62
BDP	337 (90.3)	326 (86.5)	3.7 (-0.9, 8.2)	0.11	291 (92.7)	295 (87.8)	4.8 (0.3, 9.2)	0.04
0-168 h	285 (76.4)	283 (75.1)	1.0 (-5.1, 7.0)	0.75	250 (79.6)	256 (76.2)	3.2 (-3.0, 9.5)	0.32

Data are n (%) or % (95% CI). *Only P for primary endpoint was 1-sided for the noninferiority test.

OA08 THE NEW GENERATION OF CYTOTOXICS
MONDAY, SEPTEMBER 9, 2024 - 10:45 - 12:00

OA08.03 Datopotamab Deruxtecan Vs Docetaxel in Patients with Non-Small Cell Lung Cancer: Final Overall Survival from TROPION-Lung01

J. Sands[1], A. Lisberg[2], I. Okamoto[3], L. Paz-Ares[4], R. Cornelissen[5], N. Girard[6], E. Pons-Tostivint[7], D. Vicente[8], S. Sugawara[9], M. Cobo Dols[10], M. Pérol[11], C. Mascaux[12], E. Poddubskaya[13], S. Kitazono[14], H. Hayashi[15], M.H. Hong[16], E. Felip[17], R. Hall[18], O. Juan-Vidal[19], D. Brungs[20], S. Lu[21], M. Garassino[22], E. Alexandris[23], Y. Zhang[23], P. Howarth[23], D. Uema[23], M-J. Ahn[24], [1]Dana-Farber Cancer Institute, Boston/MA/USA ,[2]Department of Medicine, Division of Hematology and Oncology, David Geffen School of Medicine, University of California Los Angeles (UCLA), Los Angeles/CA/USA ,[3]Department of Respiratory Medicine, Graduate School of Medical Sciences, Kyushu University, Fukuoka/JP ,[4]Hospital Universitario [12] de Octubre, Madrid/ES ,[5]Erasmus MC, Rotterdam/NL ,[6]Institut Curie, Paris/FR ,[7]University Hospital of Nantes, Nantes/FR ,[8]Hospital Universitario Virgen Macarena, Sevilla/ES ,[9]Sendai Kousei Hospital, Sendai/JP ,[10]Medical Oncology Intercenter Unit, Regional and Virgen de la Victoria University Hospitals, IBIMA, Málaga/ES ,[11]Centre Léon Bérard, Lyon/FR ,[12]Hopitaux Universitaire de Strasbourg, Strasbourg/FR ,[13]VitaMed LLC, Moscow/RU ,[14]The Cancer Institute Hospital of JFCR, Tokyo/JP ,[15]Kindai University Hospital, Osaka/JP ,[16]Yonsei Cancer Center, Severance Hospital, Seoul/KR ,[17]Vall d'Hebron University Hospital and Vall d'Hebron Institute of Oncology, Barcelona/ES ,[18]University of Virginia Health System, Charlottesville/VA/USA ,[19]Hospital Universitari i Politecnic La Fe, Valencia/ES ,[20]Southern Medical Day Care Centre, Wollongong/AU ,[21]Shanghai Lung Cancer Center, Shanghai Chest Hospital, Shanghai/CN ,[22]Department of Hematology/Oncology, The University of Chicago, Chicago/IL/USA ,[23]Daiichi Sankyo, Basking Ridge/NJ/USA ,[24]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul/KR

This abstract is under embargo until September 9 at 12:00 PDT.

OA08 THE NEW GENERATION OF CYTOTOXICS
MONDAY, SEPTEMBER 9, 2024 - 10:45 - 12:00

OA08.04 Plinabulin/Docetaxel vs. Docetaxel in 2L/3L NSCLC after Platinum Regimens (DUBLIN-3): A Phase 3 Randomized Controlled Trial

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Introduction: There remains an unmet need for effective and tolerable treatments of platinum refractory, advanced/metastatic non-small-cell lung cancer (NSCLC) without driver mutations.

Methods: DUBLIN-3 is a multicenter, single-blinded (patient) and randomized, phase 3 trial in 58 medical centers (US, China, and Australia). Patients with epidermal-growth-factor-receptor (EGFR) wild-type NSCLC, who progressed after first-line platinum-based therapy were enrolled. Patients were randomized (1:1) to receive docetaxel (75 mg/m2) on Day 1 and either plinabulin (30 mg/m2) or placebo on Days 1 and 8 in 21-day cycles until progression, unacceptable toxicity, withdrawal, or death. The primary endpoint was overall survival (OS) in the intent-to-treat (ITT) population. Treated patients were included in the safety analysis and ITT in the primary analyses (NCT02504489).

Results: Between 30-Nov-2015 and 06-Jan-2021, 559 patients received either docetaxel plus plinabulin (n=278 [male 199, female 79]) or docetaxel plus placebo (n=281 [male 207, female 74]). The original study was an adaptive design with two planned interim analyses and options to increase the sample size and to stop early due to futility; however, no sample size adjustment was made after the first interim analysis and the study continued without modifications. Plinabulin significantly improved OS; hazard ratio (HR) 0·82 (95% CI: 0·68, 0·99; p=0·0399) in the final analysis. Median OS was 10·5 months (95% CI: 9·34, 11·87) in the plinabulin group vs. 9·4 months (95% CI: 8·38, 10·68) in the control group. With additional 24-month follow-up after database lock, OS benefit sustains in the ITT population with median OS favoring the plinabulin group (10.8 vs. 9.3 month, HR=0.81, p=0.0027), and more pronounced in non-squamous population (11.4 vs. 8.8 months, HR=0.72, p=0.0078). The objective response rate (ORR) was significantly higher in the plinabulin group with 39 patients (14·0%) achieving partial responses compared with 24 patients (8·5%) in the control group (difference: 5·5%, 95% CI: 0·26, 10·72, p=0·0404). Median progression-free survival (PFS) was 3·3 months (95% CI: 2·89, 3·88) vs. 2·8 months (95% CI: 2·76, 2·93) (HR 0·79, 95% CI: 0·66, 0·96, p=0·0174).The 2- and 3-year survival rate was 22·1% vs. 12·5% (p=0·0072) and 11·7% vs. 5·3% (p=0·0393) for plinabulin vs. control group. Plinabulin significantly reduced Grade 4 neutropenia from 27·8% to 5·3% (p<0·0001). Furthermore, OS benefits were observed with more treatment cycles (≥4, 6, 8, 10, or 12 cycles), suggesting a durable anti-cancer benefit with plinabulin. Treatment-emergent-adverse-events occurred in 273/274 (99·6%) of patients in the plinabulin group and 276/278 (99·3%) in the control group. Higher incidences of Grade 3/4 gastrointestinal disorders (46 patients [16·8%] vs. 8 [2·9%]) and transient Grade 3 hypertension (50 patients [18·2%] vs. 8 [2·9%]) occurred in the plinabulin vs. control group. Treatment-emergent-death was 12 (4·4%) in the plinabulin group vs. 10 (3·6%) in the control group.

Conclusions: In patients with advance EGFR wild-type platinum refractory NSCLC, plinabulin combined with docetaxel was well-tolerated and statistically significantly improved OS/PFS/ORR with reduced severe neutropenia. A durable anti-cancer benefit was observed suggesting that plinabulin/docetaxel as a potential practice-changing treatment for advanced/metastatic NSCLC without driver mutations.

Keywords: Plinabulin, EGFR wild-type NSCLC, Docetaxel

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OA08.05 Tusamitamab Ravtansine vs Docetaxel in Previously Treated Advanced Nonsquamous NSCLC: Results from Phase 3 CARMEN-LC03 Trial

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OA08.06 Sacituzumab Govitecan vs Docetaxel in Patients with mNSCLC Non-responsive to Last Anti-PD-(L)1-containing Regimen: EVOKE-01

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Introduction: The phase 3 EVOKE-01 study included patients with metastatic non-small cell lung cancer (mNSCLC) progressing after platinum-based chemotherapy and anti-PD-(L)1 treatment. The primary endpoint of overall survival (OS) was not statistically significant; however, results showed numerical improvement favoring sacituzumab govitecan (SG) vs docetaxel (hazard ratio [HR], 0.84; 95% CI, 0.68-1.04). As response to anti-PD-(L)1 treatment has prognostic impact on OS, best response to last anti-PD-(L)1-containing regimen (non-responsive, stable disease [SD]/progressive disease [PD], vs responsive, complete response [CR]/partial response [PR]) was a stratification factor and prespecified subgroup for analysis. We report patient characteristics and results from this subgroup of the EVOKE-01 study (NCT05089734).

Methods: In EVOKE-01, patients were randomized to receive SG (10 mg/kg IV; days 1, 8) or docetaxel (75 mg/m2 IV; day 1) in 21-day cycles. The primary endpoint was OS. Key secondary endpoints included investigator-assessed progression-free survival (PFS) and objective response rate (ORR). In these subgroup analyses, outcomes were evaluated by objective response to last anti-PD-(L)1-containing regimen. OS of the non-responsive subgroup were further analyzed by histology (squamous and nonsquamous). Descriptive statistics are reported.

Results: The intent-to-treat (ITT) population included 63.5% (n=383) patients with disease non-responsive to last anti-PD-(L)1-containing regimen (n=192 SG; n=191 docetaxel) and 36.3% (n=219) with responsive. In the non-responsive subgroup, patient characteristics were balanced between the treatment arms (Table). In the non-responsive subgroup, median OS was 11.8 months with SG and 8.3 months with docetaxel (HR, 0.75; 95% CI, 0.58-0.97); for the responsive subgroup, HR was 1.09; 95% CI, 0.76-1.56. Improvement in OS with SG was observed regardless of whether patients had SD (HR, 0.79; 95% CI, 0.55-1.13) or PD (HR, 0.67; 95% CI, 0.46-0.98) as best response to last anti-PD-(L)1-containing regimen. The OS benefit of SG over docetaxel in the non-responsive subgroup was similar in both squamous (HR, 0.62; 95% CI, 0.38-1.02) and nonsquamous (HR, 0.79; 95% CI, 0.59-1.07) histology. The Table summarizes additional efficacy results. In the safety population, grade ≥3 treatment-emergent adverse event (TEAE) incidence was 66.6% (SG) and 75.7% (docetaxel). TEAEs led to death in 3.4% (SG) and 4.5% (docetaxel). Treatment-related TEAEs led to discontinuation in 6.8% (SG) and 14.2% (docetaxel).

Conclusions: SG demonstrated clinically meaningful OS improvement vs docetaxel in a subgroup of patients with mNSCLC non-responsive (SD/PD) to last anti-PD-(L)1-containing regimen. The benefit was observed regardless of SD or PD as best response to last anti-PD-(L)1-containing regimen or histology.

Keywords: sacituzumab govitecan, metastatic non-small cell lung cancer, Trop-2–directed antibody–drug conjugate

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OA08.07 Sacituzumab Govitecan + Pembrolizumab + Carboplatin in 1L Metastatic Non-Small Cell Lung Cancer: The EVOKE-02 Study

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Introduction: Pembrolizumab + platinum-based chemotherapy is standard of care first-line (1L) treatment for advanced/metastatic non-small cell lung cancer (mNSCLC) lacking actionable genomic alterations (AGAs) regardless of PD-L1 expression; however, novel combinations are needed to improve outcomes. Sacituzumab govitecan (SG) demonstrated durable activity in mNSCLC and was safely combined with pembrolizumab in the clinical setting. We report initial results by dose and histology from cohorts C (non-squamous) and D (squamous) of patients with mNSCLC treated in 1L setting with SG + pembrolizumab + carboplatin in the ongoing, multicohort, phase 2 study, EVOKE-02 (NCT05186974).

Methods: Adults without prior systemic treatment for mNSCLC, without AGAs, with an ECOG PS of 0-1, and with any PD-L1 tumor proportion score (TPS) via 22C3 assay were eligible. Patients received intravenous SG 10 or 7.5mg/kg (days 1, 8) + pembrolizumab 200mg (day 1; up to 35 cycles) + carboplatin AUC5 (day 1; initial 4 cycles only) in 21-day cycles. A safety run-in was conducted to assess dose-limiting toxicities (DLTs) and determine the recommended SG dose. The primary efficacy endpoint was independent review committee (IRC)-assessed objective response rate per RECIST v1.1. Secondary endpoints included IRC-assessed progression-free survival, duration of response, and safety.

Results: During the safety run-in (SG 10mg/kg, n=5), DLT criteria for dose reduction were not met. At a subsequent planned safety evaluation, SG dose was reduced to 7.5 mg/kg because of myelosuppression, mainly neutropenia. Among patients with non-squamous (n=54) and squamous (n=41) histology, median age was 67 and 68 years, 72.2% and 65.9% had an ECOG PS score of 1, and the majority (85.2% and 80.2%) had PD-L1 TPS <50%. Efficacy results by histology and safety results by dose are shown in the Table. Grade 3 rates of neutropenia were reduced at SG 7.5 mg/kg compared with SG 10 mg/kg (24.2% vs 65.5%).

Conclusions: SG + pembrolizumab + carboplatin demonstrated encouraging activity in patients predominantly with PD-L1 TPS<50% non-squamous and squamous non-AGA-driven mNSCLC. The safety profile of SG with standard doses of pembrolizumab and carboplatin is manageable at the 7.5 mg/kg dose with appropriate supportive measures.

Keywords: first-line, metastatic non–small cell lung cancer, Trop-2–directed antibody–drug conjugate

Table

Efficacy summary for patients with non-squamous and squamous histology		
	Non-squamous (n=51)[a]	**Squamous (n=41)**
Follow-up, median, months	8.4	8.1
IRC-assessed[b] ORR, % (95% CI)	43.1 (29.3-57.8)	39.0 (24.2-55.5)
PR, n	22	16
DOR, median (95% CI), months	6.8 (3.2–NR)	NR (5.5–NR)
PFS, median (95% CI), months	8.1 (5.3–NR)	11.1 (4.3–NR)
Safety summary for SG (10 kg/mg or 7.5 mg/kg) + pembrolizumab + carboplatin		
	SG 10 mg/kg + pembrolizumab + carboplatin (n=29)	**SG 7.5 mg/kg + pembrolizumab + carboplatin (n=66)**
Grade ≥3 TEAE, n (%)	26 (89.7)	56 (84.8)
Grade ≥3 Neutropenia, n (%)	19 (65.5)	16 (24.2)
Grade ≥3 Anemia, n (%)	10 (34.5)	21 (31.8)
TEAE leading to discontinuation of any study drug, n (%)	7 (24.1)	8 (12.1)
TEAE leading to death, n (%)	5 (17.2)	10 (15.2)
Treatment-related TEAE leading to death, n (%)	3 (10.3)	5 (7.6)

[a]3 patients in the non-squamous group had no measurable disease per IRC at baseline and were not included in the efficacy analysis.
[b]IRC assessment per RECIST v1.1.
DOR, duration of response; IRC, independent review committee; NR, not reached; ORR, objective response rate; PFS, progression-free survival; PR, partial response; SG, sacituzumab govitecan; TEAE, treatment-emergent adverse event.

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OA09.03 Randomized, Open-Label, Phase III Study of SAF-189s Versus Crizotinib in First-Line ALK-Positive Advanced Non-Small Cell Lung Cancer (NSCLC)

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Introduction: SAF-189s (Foritinib Succinate) is a highly-potent and brain-penetrating next-generation ALK/ROS1 inhibitor. SAF-189s has demonstrated promising clinical efficacy in phase II study. Here we report interim analysis (IA) results from REMARK study.

Methods: REMARK study was an open-label randomized phase 3 trial that enrolled previously untreated adult patients (pts) with ALK+ advanced NSCLC. Pts were stratified by baseline ECOG (0/1 vs. 2) and central nervous system (CNS) metastases status and then randomized at 1:1 ratio to receive SAF-189s 160 mg QD or crizotinib 250 mg BID orally. The primary endpoint was the progression-free survival (PFS) assessed by Independent Review Committee (IRC) per RECIST 1.1. Secondary endpoints included PFS by investigator (INV), objective response rate (ORR), time to response (TTR), duration of response (DOR), CNS ORR (C-ORR), C-TTR, C-DOR and time to CNS progression (C-TTP) by IRC and INV, overall survival (OS) and safety. The interim analysis was planned when approximately 83 PFS events were assessed by the IRC.

Results: From 31 Dec 2020 to 31 Mar 2022, 275 pts at 40 centers were randomized to receive either SAF-189s (n=139) or crizotinib (n=136). As cut-off date of 31 Mar 2024, median duration of follow-up was 16.7 months. SAF-189s demonstrated statistically significant improvement of IRC-assessed PFS over crizotinib with a hazard ratio (HR) of 0.23 (95% CI 0.14, 0.38). IRC-assessed median PFS was not reached in SAF-189s arm and 13.93 months in crizotinib arm. SAF-189s significantly reduced the risk of CNS progression compared to crizotinib (HR,0.04 [95%CI 0.01, 0.14]). There was also a trend to improve OS with SAF-189s over crizotinib (HR, 0.60 [95%CI 0.30, 1.20]). ORR was 92.8% in SAF-189s arm, 12% higher than in crizotinib arm (p=0.0035). Grade 3/4 treatment-related adverse events (TRAEs) occurred in 37.7% of pts with SAF-189s compared to 55.6% with crizotinib. Most common grade 3/4 TRAEs for SAF-189s was hyperglycemia, ALT increased and AST increased. No interstitial lung disease or visual loss was observed in SAF-189s arm. No TRAEs leading to death were reported in either arm.

Conclusions: SAF-189s demonstrated statistically significant and clinically meaningful improvement in PFS versus crizotinib. Safety profile of SAF-189s was consistent with previous reports and without new safety signals.

Keywords: Non-small cell lung cancer, ALK-Positive, Phase III

	SAF-189s (n=139)	Crizotinib (n=136)
PFS by IRC		
mPFS, months (95% CI)	NR	13.93
HR (95% CI)	0.23 (0.14, 0.38)	
PFS by INV		
mPFS, months (95% CI)	NR	13.80
HR (95% CI)	0.29 (0.19, 0.45)	
ORR by IRC, %	92.8	80.9
mDOR by IRC, months (95% CI)	NR	15.93
CNS-TTP by IRC, months	NR	19.32
HR (95% CI)	0.04 (0.01, 0.14)	
PFS of pts with baseline CNS metastases, months	-	9.56
HR (95% CI)	0.14 (0.05, 0.37)	
C-ORR by IRC, n (%)	10 (100)	9 (50.0)
TRAE, n (%)		
Any grade	135 (97.8)	133(98.5)
Grade ≥3	52 (37.7)	75 (55.6)
Leading to dose interruption	37 (26.8)	48 (35.6)
Leading to dose reduction	33 (23.9)	51 (37.8)
Leading to discontinuation	5 (3.6)	3 (2.2)

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OA09.04 Osimertinib with or without SRS for Brain Metastases from EGFRm NSCLC: Pooled Analysis of Two RCTs

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Introduction: The timing and benefit of stereotactic radiosurgery (SRS) in the management of untreated brain metastases (BM) in patients with epidermal growth factor receptor mutated (EGFRm) non-small cell lung cancer (NSCLC) is uncertain. Two randomized trials, LUOSICNS and TROG 17.02 OUTRUN, compared upfront osimertinib with salvage local therapies when required to upfront SRS followed by osimertinib. This pooled analysis reports on the primary outcome: intracranial progression-free survival at 12 months (ic-PFS), and secondary outcomes: overall survival (OS), self-reported cognitive deterioration (CD), salvage SRS (sSRS), and radionecrosis (RN).

Methods: Patients with EGFRm NSCLC with up to 10 minimally symptomatic BM at registration were included. SRS was delivered as single or multi-fraction regimens per protocol. In the SRS arm, osimertinib was commenced following the completion of SRS. Intracranial progression was defined per RANO-BM. RN was determined according to MRI and histological confirmation when available. Cognitive function was self-reported using EORTC-QLQ C30. CD was defined as the first of a 10-point decrease from baseline (with no subsequent improvement). A two-stage, fixed-effect Kaplan Meier estimate at 12 months was used for assessing the pooled difference in ic-PFS. One-stage proportional hazards models were used to determine the hazard ratio (HR) for ic-PFS and OS.

Results: Seventy-nine participants were included; 40 were randomized to upfront osimertinib (uOSI) and 39 to upfront SRS (uSRS). Median follow-up was 39 months for LUOSICNS and 33 months for OUTRUN. Median age was 67 years. Participants were predominantly female (67%), of Asian ethnicity (71%), never smokers (72%), and 89% had BM present at the time of their original diagnosis. The ic-PFS at 12 months was 70% (95% CI 52% to 93%) for uSRS, and 53% (95% CI 34% to 81%) for uOSI in LUOSICNS and 67% (95% CI 49% to 93%) for uSRS, and 67% (95% CI 49% to 90%) for uOSI in OUTRUN. The pooled estimate of its difference was 9% (95% CI -13% to 30%) higher for uSRS than uOSI. There was no statistically significant difference between arms for ic-PFS (HR 0.83, 95% CI 0.48 to 1.43) or OS (HR 0.66, 95% CI 0.35 to 1.24). The percentage of participants with self-reported CD at 12 months was 18% (3/18) for uSRS and 18% (2/11) for uOSI. The percentage of participants who had sSRS at 12 months was 5% (2/37) for uSRS and 18% (7/40) for uOSI. Ten percent of participants in the uSRS arm had grade two or more RN events: two grade two, one grade three, and one grade four.

Conclusions: This pooled analysis found insufficient evidence to suggest that upfront SRS improved ic-PFS at 12 months, OS, self-reported CD, or sSRS in patients with minimally symptomatic BM from EGFRm NSCLC. The results of this study should be interpreted within the context of the small sample size of the individual trials. Given the prolonged survival of these patients, differences in outcomes between treatment arms may become more apparent with longer follow-up.

Keywords: Brain Metastases, Non-small cell lung cancer, Osimertinib

OA09 TRAILBLAZING TARGETS: NEW INSIGHTS
MONDAY, SEPTEMBER 9, 2024 - 10:45 - 12:00

OA09.05 Subcutaneous vs Intravenous Amivantamab: Patient Satisfaction and Resource Utilization Results from the PALOMA-3 Study

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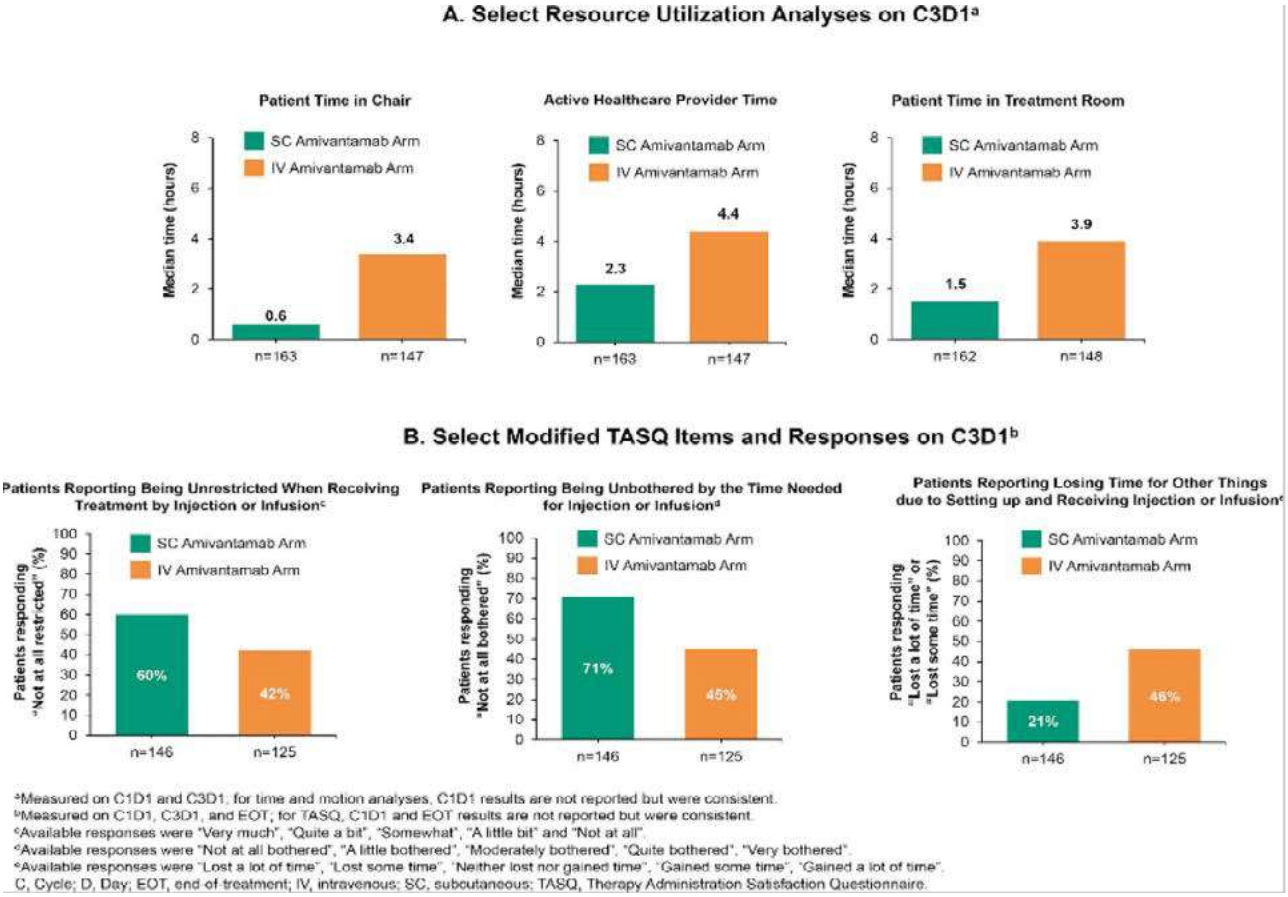
Introduction: Amivantamab plus lazertinib has shown antitumor activity in EGFR-mutated advanced NSCLC. Primary results from the phase 3 PALOMA-3 study (NCT05388669) demonstrated noninferior pharmacokinetics and objective response rate for subcutaneous vs intravenous amivantamab. Subcutaneous administration also offered substantially faster administration times and significantly higher patient-reported convenience (Leighl JCO 2024). Here, we present patient treatment satisfaction and resource utilization for subcutaneous amivantamab, providing further insights into its clinical benefits.

Methods: 418 patients with EGFR-mutated advanced NSCLC whose disease progressed on osimertinib and platinum-based chemotherapy were randomized 1:1 to subcutaneous (n=206) or intravenous amivantamab (n=212), both with lazertinib. Predefined secondary endpoints included resource utilization (assessed by time required for drug administration activities on cycle-1-day-1 [C1D1] and C3D1) and cancer therapy satisfaction (measured by the modified Therapy Administration Satisfaction Questionnaire [mTASQ] on C1D1, C3D1, and end-of-treatment). The mTASQ is a validated 12-item questionnaire where patients rated various aspects such as how restricted they felt during treatment, how bothered they were by administration time, and whether they felt they were losing or gaining time for other activities due to treatment duration.

Results: Across collected measures, subcutaneous amivantamab demonstrated improved resource utilization and patient satisfaction. Patient time in chair was substantially lower for subcutaneous amivantamab (C1D1: median [range], 0.4 [0-12.0] vs 6.5 hours [0-24.0]; C3D1: 0.6 [0-6.6] vs 3.4 hours [0.5-9.0]). This trend was consistent for active healthcare provider time and patient time in room (Figure A). More patients receiving subcutaneous vs intravenous amivantamab reported feeling unrestricted (C1D1, 66% vs 29%; C3D1, 60% vs 42%) and unbothered by administration time (C1D1, 69% vs 30%; C3D1, 71% vs 45%). Furthermore, fewer patients felt they lost time for other activities due to treatment duration (C1D1, 17% vs 46%; C3D1, 21% vs 46%; Figure B). Most patients receiving subcutaneous amivantamab reported mild-to-no pain (C1D1, 86%; C3D1, 84%), swelling (C1D1, 95%; C3D1, 95%), or redness (C1D1, 95%; C3D1, 94%) at the injection site. A higher proportion of patients preferred the subcutaneous injection to an intravenous infusion (C1D1, 77% vs 5%; C3D1, 81% vs 5%).

Conclusions: Intravenous amivantamab has demonstrated superior efficacy across multiple patient populations. Subcutaneous amivantamab provides the additional advantages of lower resource utilization and significantly higher patient satisfaction, and offers a convenient mode of administration for patients and healthcare providers, improving overall treatment experience.

Keywords: Amivantamab, NSCLC, subcutaneous



[a]Measured on C1D1 and C3D1; for time and motion analyses, C1D1 results are not reported but were consistent.
[b]Measured on C1D1, C3D1, and EOT; for TASQ, C1D1 and EOT results are not reported but were consistent.
[c]Available responses were "Very much", "Quite a bit", "Somewhat", "A little bit" and "Not at all".
[d]Available responses were "Not at all bothered", "A little bothered", "Moderately bothered", "Quite bothered", "Very bothered".
[e]Available responses were "Lost a lot of time", "Lost some time", "Neither lost nor gained time", "Gained some time", "Gained a lot of time".
C, Cycle; D, Day; EOT, end-of-treatment; IV, intravenous; SC, subcutaneous; TASQ, Therapy Administration Satisfaction Questionnaire.

OA09 TRAILBLAZING TARGETS: NEW INSIGHTS
MONDAY, SEPTEMBER 9, 2024 - 10:45 - 12:00

OA09.06 Health-Related Quality of Life (HRQoL) Outcomes with Adagrasib vs Docetaxel in KRASG12C-Mutated Advanced NSCLC in KRYSTAL-12

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Introduction: Adagrasib (ADA), a KRASG12C inhibitor, demonstrated a significant and clinically meaningful benefit in progression-free survival and objective response rate vs docetaxel (DOCE) in previously treated patients with KRASG12C-mutated advanced NSCLC in the phase 3 KRYSTAL-12 trial (NCT04685135). Here we report initial HRQoL results.

Methods: Patients with KRASG12C-mutated locally advanced or metastatic NSCLC who had previously received both platinum-based chemotherapy and anti-PD-(L)1 therapy were randomized 2:1 to receive ADA (600 mg BID orally) or DOCE (75 mg/m2 Q3W IV). HRQoL was evaluated using the Lung Cancer Symptom Scale (LCSS) and EQ-5D-5L. The LCSS average symptom burden index (ASBI) score evaluated six symptom-specific items using a visual analog scale (VAS; range 0-100), and the 3-item global index (3-IGI) evaluated symptom distress, interference with activities, and HRQoL (range 0-300); higher scores reflect worse symptom burden/HRQoL. The EQ-5D-5L instrument used a VAS (range 0-100) and utility index (UI) score (UK utility range -0.531 to 1); higher scores reflect better HRQoL. Data were collected on Day (D)1 and D15 of 3-weekly cycles (C)1-4, then on D1 of every cycle until the end of treatment visit (28-35 days after last dose). Changes from baseline over time were analyzed using a mixed-effect model for repeated measures (MMRM).

Results: The analysis population included 254/301 (84.4%) patients in the ADA arm and 112/152 (73.7%) in the DOCE arm who had data at baseline and ≥1 post-baseline visit(s) within 6 months. Completion rates among expected patients were >85% at most visits in both arms through C11, when there were ≥10 patients per arm with available data. Mean absolute scores for LCSS ASBI, symptom items, and 3-IGI mostly tended to improve over time in the ADA arm and worsen in the DOCE arm; mean EQ-5D-5L VAS and UI scores were mostly stable over time in the ADA arm and worsened in the DOCE arm (Table). In the MMRM analysis, the overall least squares mean change from baseline in LCSS ASBI score was -4.8 (95% CI, -6.3 to -3.3) with ADA and 4.8 (95% CI, 2.5-7.2) with DOCE, with a mean difference of -9.6 (95% CI, -12.3 to -7.0; P<0.0001). Time to definitive deterioration analyses will also be presented.

Conclusions: These results from KRYSTAL-12 suggest an improvement in symptom burden and HRQoL with ADA vs DOCE. Together with the efficacy results, these findings further support the use of ADA for patients with previously treated KRASG12C-mutated advanced NSCLC.

Keywords: adagrasib, NSCLC, KRASG12C

Mean (SD) absolute scores	Adagrasib	Docetaxel
Lung Cancer Symptom Scale[a]		
ASBI		
Baseline	26.4 (17.6)	26.6 (17.3)
C11D1	15.6 (15.7)	29.4 (21.8)
Cough		
Baseline	24.9 (29.4)	26.3 (27.6)
C11D1	11.0 (17.4)	20.8 (27.1)
Dyspnea		
Baseline	28.2 (29.0)	33.3 (29.5)
C11D1	17.3 (21.4)	40.4 (37.2)
Pain		
Baseline	25.4 (27.5)	27.4 (30.2)
C11D1	12.9 (20.7)	41.2 (36.6)
Fatigue		
Baseline	39.9 (28.6)	39.0 (29.9)
C11D1	26.3 (25.7)	52.7 (37.1)
Appetite loss		
Baseline	34.9 (30.0)	30.0 (26.7)
C11D1	24.0 (28.5)	21.0 (27.2)
3-IGI		
Baseline	105.6 (72.2)	108.9 (80.9)
C11D1	68.4 (68.3)	104.7 (89.7)
EQ-5D-5L[b]		
VAS		
Baseline	70.8 (20.4)	70.2 (19.3)
C11D1	76.2 (18.6)	65.8 (19.0)
UI		
Baseline	0.713 (0.229)	0.680 (0.260)
C11D1	0.754 (0.217)	0.555 (0.332)

[a]Range 0–100 (except for 3-IGI, range 0–300); higher scores reflect worse symptom burden and HRQoL; [b]VAS range 0–100, UI range –0.531 to 1; higher scores indicate better HRQoL.

3-IGI, 3-item global index; ASBI, average symptom burden index; C, cycle; D, day; HRQoL, health-related quality of life; SD, standard deviation; UI, utility index; VAS, visual analog scale.

OA10 DLL3 TARGETING BITE THERAPIES IN SCLC
MONDAY, SEPTEMBER 9, 2024 - 14:00 - 15:15

OA10.03 Tarlatamab Sustained Clinical Benefit and Safety in Previously Treated SCLC: DeLLphi-301 Phase 2 Extended Follow-up

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Introduction: Tarlatamab, a bispecific T-cell engager (BiTE®) immunotherapy that targets delta-like ligand 3 (DLL3) on SCLC cells, showed durable anticancer activity and a manageable safety profile in patients with previously treated SCLC in the DeLLphi-301 phase 2 study. At the primary analysis, median duration of response (DOR) was not reached, and overall survival (OS) data were immature (Ahn MJ, NEJM 2023). Here, efficacy and safety outcomes from longer follow-up of the DeLLphi-301 study are reported.

Methods: Tarlatamab 10 mg or 100 mg (Q2W) was evaluated in patients with SCLC who relapsed after 1 platinum-based regimen (± checkpoint inhibitor) and at least 1 other line of therapy. The primary efficacy endpoint was objective response rate (ORR) per RECIST 1.1 by blinded independent central review.

Results: Overall, 220 patients received tarlatamab. Data for the longer follow-up, median of 13.6 months (range 0.1-20.9) for efficacy outcomes, are shown in the Table. For the 10 mg group, the dose selected for subsequent trials, ORR was 40.4% and median DOR was not estimable, with responses ongoing in 19 of 40 (47.5%) responders at data cutoff. Median progression-free survival was 4.3 months and median OS was 15.2 months for the 10 mg group, with Kaplan-Meier estimates of OS at 6 and 12 months of 73.4% and 56.7%, respectively. The longer follow-up revealed no new safety signals in both dose groups: cytokine release syndrome, primarily grade 1 or 2, and no grade 4 or 5 occurrences, remained the most frequent adverse event (56.8%). Discontinuations due to treatment-related adverse events remained infrequent (2.7%). Results from an even longer follow-up will be presented.

Conclusions: Tarlatamab continued to achieve sustained responses and favorable long-term survival outcomes in patients with previously treated SCLC. Tarlatamab showed a favorable benefit-risk profile, supporting tarlatamab use in patients with previously treated SCLC. The longer follow-up at time of presentation will provide clearer insight on response durability and long-term survival.

Keywords: Tarlatamab, small cell lung cancer, long-term follow-up

	10 mg Tarlatamab (n = 99)*	100 mg Tarlatamab (n = 87)*
ORR, % (95% CI)†	40.4 (30.7, 50.7)	32.2 (22.6, 43.1)
Complete response, n (%)	2 (2.0)	6 (6.9)
Partial response, n (%)	38 (38.4)	22 (25.3)
Stable disease, n (%)	30 (30.3)	27 (31.0)
Progressive disease, n (%)	19 (19.2)	14 (16.1)
No post-baseline scan, n (%)	7 (7.1)	14 (16.1)
Duration of response, median, months (95% CI)	NE (6.9, NE)	8.1 (5.6, 12.7)
Time to response, median, months (Q1, Q3)	1.4 (1.3, 1.4)	1.4 (1.3, 1.4)
Disease control rate % (95% CI)	70.7 (60.7, 79.4)	63.2 (52.2, 73.3)
Duration of disease control, median, months (95% CI)	6.9 (5.4, 8.6)	5.6 (4.1, 8.4)
≥ 30% tumor shrinkage, n (%)	47 (47.5)	36 (41.4)
Median PFS, months (95% CI)	4.3 (3.0, 5.6)	3.2 (2.6, 4.2)
Median OS, months (95% CI)	15.2 (10.8, NE)	15.1 (10.1, NE)

*Includes patients who received at least 1 dose of tarlatamab, except patients in safety substudy (n = 34).
†Per RECIST 1.1, ORR was not evaluable in 3 (10 mg) and 4 patients (100 mg).
CI = confidence interval; NE = not estimable; RECIST = response evaluation criteria in solid tumors.

OA10 DLL3 TARGETING BITE THERAPIES IN SCLC
MONDAY, SEPTEMBER 9, 2024 - 14:00 - 15:15

OA10.04 Tarlatamab with a PD-L1 Inhibitor as First-Line Maintenance after Chemo-immunotherapy for ES-SCLC: DeLLphi-303 Phase 1b Study

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Introduction: Current first-line maintenance (1LM) therapies for extensive-stage small cell lung cancer (ES-SCLC) provide limited benefit, necessitating novel therapeutic approaches to improve outcomes. Tarlatamab, a bispecific T-cell engager (BiTE®) immunotherapy that directs cytotoxic T cells to delta-like ligand 3 (DLL3)-positive cancer cells, demonstrated durable response and clinically meaningful survival outcomes in patients with previously treated SCLC. Here, safety and efficacy data from the phase 1b, multicenter, open-label DeLLphi-303 study (NCT05361395) evaluating tarlatamab plus PD-L1 inhibitor as 1LM following chemo-immunotherapy are presented.

Methods: Patients with ES-SCLC that did not progress after completing 4-6 cycles of 1L platinum-etoposide with PD-L1 inhibitor (unless unavailable) were eligible. Within 8 weeks of starting the last chemo-immunotherapy cycle, patients received tarlatamab (10 mg IV Q2W) with atezolizumab (1680 mg IV Q4W) or durvalumab (1500 mg IV Q4W) until progression. Primary endpoints included dose-limiting toxicities (DLTs), treatment-emergent and treatment-related AEs (TEAEs, TRAEs). Secondary endpoints included progression-free survival (PFS), overall survival (OS), and disease control rate (DCR).

Results: At data cutoff (31May2024), 88 patients (male: 62.5%, median age: 64.0 years; number of prior 1L platinumetoposide cycles: 4, 86.4%; 5, 5.7%; 6, 8.0%) received tarlatamab with atezolizumab or durvalumab (Table). Median follow-up was 10.0 months (range: 1.4-20.4). No DLTs occurred. The most common all grade TEAEs were cytokine release syndrome (CRS; 53.4%), dysgeusia (47.7%), and fatigue (34.1%). The most common grade ≥ 3 TEAEs were hyponatremia (10.2%), neutropenia (6.8%), and anemia (6.8%). CRS primarily occurred in cycle 1 and was predominantly grade 1-2; grade 3 CRS occurred in 1 patient. Immune effector cell-associated neurotoxicity syndrome and associated neurological events occurred in 11.4%/2.3%/0% (any grade/grade 3/grade 4) of patients.

The median time from initiation of 1L chemo-immunotherapy to start of 1LM was 3.6 months (range 2.9-5.8). Beginning from 1LM, median PFS was 5.6 months (95% CI: 3.6-9.0) and median OS was immature due to insufficient follow-up time; Kaplan-Meier estimate for OS at 9 months was 88.9%. DCR was 62.5% (95% CI: 51.5-72.6); median duration of disease control was 9.3 months (95% CI: 5.6-not estimable).

Conclusions: Tarlatamab in combination with a PD-L1 inhibitor as 1LM demonstrated a manageable safety profile with durable disease control and notable survival outcomes in patients with ES-SCLC. No new or unexpected toxicities were identified. This study supports further investigation of tarlatamab in combination with a PD-L1 inhibitor as 1LM in the ongoing phase 3 DeLLphi-305 randomized controlled study (NCT06211036).

Keywords: Tarlatamab, Maintenance therapy, extensive-stage small cell lung cancer

Table: Safety and efficacy profile of 1LM tarlatamab + PD-L1 inhibitor

	Tarlatamab + atezolizumab (N = 48)	Tarlatamab + durvalumab (N = 40)	Overall (N = 88)
Treatment-emergent adverse events, n (%)	**48 (100.0)**	**39 (97.5)**	**87 (98.9)**
Grade ≥ 3	26 (54.2)	21 (52.5)	47 (53.4)
Grade 4	6 (12.5)	6 (15.0)	12 (13.6)
Fatal TEAEs	2 (4.2)[a]	0 (0.0)	2 (2.3)[a]
Leading to interruption of tarlatamab	14 (29.2)	11 (27.5)	25 (28.4)
Leading to discontinuation of tarlatamab	2 (4.2)	3 (7.5)	5 (5.7)
Survival KM estimates, % (95% CI)			
PFS, 6-month[b]	42.5 (26.1, 58.0)	47.5 (29.7, 63.3)	45.4 (33.4, 56.7)
PFS, 9-month[b]	26.8 (11.1, 45.3)	47.5 (29.7, 63.3)	39.3 (27.3, 51.0)
OS, 6-month[c]	93.4 (80.8, 97.8)	97.4 (82.8, 99.6)	95.1 (87.5, 98.2)
OS, 9-month[c]	86.7 (70.3, 94.4)	91.8 (76.6, 97.3)	88.9 (78.7, 94.3)

[a]All fatalities were due to PD; no fatal TRAEs
[b]PFS defined as interval from start of 1LM to PD or death; progression based on modified RECIST v1.1
[c]OS defined as interval from start of 1LM to death
1LM, first-line maintenance; CI, confidence interval; KM, Kaplan-Meier; OS, overall survival; PD, progressive disease; PD-L1, programmed death ligand 1; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors; TRAE, treatment-related adverse event.

OA10 DLL3 TARGETING BITE THERAPIES IN SCLC
MONDAY, SEPTEMBER 9, 2024 - 14:00 - 15:15

OA10.05 Phase I Trial of DLL3/CD3 IgG-Like T-Cell Engager BI 764532 in Patients with DLL3-Positive Tumors: Patients with LCNEC

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Introduction: Delta-like ligand 3 (DLL3) is expressed on many cancers, including large cell neuroendocrine carcinoma of the lung (LCNEC). Prognosis in patients with locally advanced/metastatic LCNEC is poor (5-year survival is ~5%) and there is a major unmet need for effective treatments. BI 764532 is a DLL3/CD3 IgG-like T-cell engager that binds simultaneously to DLL3 on tumor cells and CD3 on T-cells, resulting in the formation of a cytolytic synapse that initiates a selective, T-cell-mediated immune response directed at DLL3-expressing tumor cells. NCT04429087 is an ongoing Phase I trial of BI 764532 in patients with locally advanced/metastatic DLL3-positive small-cell lung cancer, extrapulmonary neuroendocrine carcinoma, or LCNEC. The key aim of Phase Ia is to determine the maximum tolerated dose (MTD) and/or the recommended dose for expansion of BI 764532. Other objectives include safety, tolerability, pharmacokinetics, pharmacodynamics, and preliminary efficacy (investigator review; Response Evaluation Criteria in Solid Tumors version 1.1). Here, we focus on patients with LCNEC.

Methods: BI 764532 was given intravenously in 4 regimens: Regimen A (fixed dose once every 3 weeks; Regimen B1 (fixed dose once weekly); Regimen B2 and Regimen B3 (step-in dose, followed by target dose). Treatment continued until disease progression, unacceptable toxicity, other reasons for withdrawal, or maximum treatment duration (36 months).

Results: As of February 21, 2024, 168 patients had ≥1 dose of BI 764532 (Regimen A: n=24; Regimen B1: n=10; Regimen B2: n=79; Regimen B3: n=55); 32 patients (19%) were ongoing. Six dose-limiting toxicities (DLTs) were reported during the MTD evaluation period: 1 patient on Regimen A (grade 3 confusion) and 5 patients on Regimen B2 (grade 4 cytokine release syndrome [CRS]; grade 3 CRS; grade 5 immune effector cell-associated neurotoxicity syndrome; grade 3 nervous system disorder; and grade 2 infusion-related reaction). No DLTs occurred in patients with LCNEC and the adverse event profile was consistent with the overall population. The MTD was not reached. Fourteen patients with LCNEC were treated. Ten (71%) patients were male. Median age was 58 years (range 32-79). ECOG PS (0/1/missing): 14%/79%/7%. Ten (71%) patients had received prior PD1/PD-L1 treatment and ten (71%) had received ≥2 prior lines of therapy. The incidence of treatment-related adverse events (TRAEs; any/grade ≥3) in patients with LCNEC was 86%/7%. The most common TRAEs (any/grade ≥3) were: CRS (36%/0%); dysgeusia (36%/0%); asthenia (21%/0%); and nausea (21%/0%). One patient (7%) had grade ≥3 eosinophilia. In 13 evaluable patients with LCNEC (Regimen A: n=2; Regimen B1: n=1; Regimen B2: n=6; and Regimen B3: n=4), overall response rate (ORR)/disease control rate across all dose levels was 54%/77% (70%/90% in 10 patients who received ≥90 µg/kg). Median duration of response has not been reached. The estimated 6-month rates of duration of response and progression-free survival (PFS) were 63% and 28%, respectively, and median PFS was 3.6 months (2.4-not calculated). At data cut-off, 5 of 7 responding patients (71%) were still on treatment.

Conclusions: BI 764532 showed promising efficacy and safety in patients with LCNEC, with an ORR of 70% at active dose levels.

Keywords: BI 764532, large cell neuroendocrine carcinoma, DLL3

OA10 DLL3 TARGETING BITE THERAPIES IN SCLC
MONDAY, SEPTEMBER 9, 2024 - 14:00 - 15:15

OA10.06 Impact of Brain Metastases on Safety and Efficacy of MK-6070, a DLL3-Targeting T Cell Engager, in Small Cell Lung Cancer

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Introduction: MK-6070 (aka HPN328) is a DLL3-targeting T cell engager being studied in an ongoing phase 1/2 trial in patients (pts) with high grade neuroendocrine tumors associated with DLL3 expression, including small cell lung cancer (SCLC). Brain metastases (BM) are frequent in SCLC and cause significant morbidity. We analyzed the characteristics and outcomes of pts with SCLC treated to date in the MK-6070 phase 1/2 study (NCTNCT04471727) according to the presence of BM.

Methods: Pts in the phase 1/2 trial receive MK-6070 IV weekly or Q2W with a priming dose preceding the target dose. Pts with BM are eligible if BM are asymptomatic, previously treated, and radiologically stable; radiotherapy for localized BM progression is allowed on study if pts are otherwise benefitting. Objective response rate (ORR) is determined using RECIST v1.1; a modified RECIST v1.1 assessing extracranial response (EC-ORR) is also used to include pts with systemic response and brain-only progression.

Results: As of 09 February 2024, 49 pts with SCLC were treated at ≥ 1.215 mg, the minimum effective dose of MK-6070. Median age was 64 (range, 41-81); 100% had ECOG PS 0-1. Median lines of prior therapy was 2 (range, 1-6), with 100% receiving prior platinum therapy, and 47 pts (96%) receiving prior anti-PD1/PD-L1 therapy. 28 pts (57%) had a history of BM and 21 (43%) had no history of BM. Pts with BM were more likely to have received prior brain radiation (BM, 96%; No BM, 19%); otherwise, baseline characteristics of pts with BM were similar to those without. Pts with BM had a numerically higher ORR (ORR 37% [95% CI, 19-58] with 1 CR, EC-ORR 52% [95% CI, 32-71]) and disease control rate (DCR 78% [95% CI, 58-91]) than those without (ORR and EC-ORR 19% [95% CI, 5-42] and DCR 48% [95% CI, 26-70]). CNS progression events occurred in 9 of 28 (32%) of pts with BM, with no such events observed in those without BM. 4 pts attained an extracranial partial response (EC-PR) but had CNS progression. These pts underwent radiotherapy to their progressive BM and remained on study for a median of 6.2 months (range 5.4-27.8 months, with treatment ongoing in 3 pts). 2 of 14 patients with brain non target lesions (NTLs) had confirmed responses in brain NTLs. TRAEs were similar between groups (BM, 96%; No BM, 95%), including cytokine release syndrome (CRS) (BM, 64%; no BM, 57%). Immune effector cell-associated neurotoxicity syndrome (ICANS) only occurred in pts with BM (BM [n=4] 14%; No BM, 0%). ICANS was G1 in 3 pts, G2 in 1 pt.

Conclusions: MK-6070 shows promising efficacy in pts with SCLC, including pts with BM, with 1 achieving a CR. Pts with EC-PRs were able to remain on study after brain-only progression for ongoing clinical benefit. This trial is ongoing and data continue to mature. Updated safety and efficacy data including duration of response will be presented.

Keywords: T-cell engager, DLL3, Brain metastases

OA11 SHIFTING THE BAR IN THE FRONT LINE IMMUNOTHERAPY SETTING
MONDAY, SEPTEMBER 9, 2024 - 14:00 - 15:15

OA11.03 Efficacy and Safety of Rilvegostomig, an Anti-PD-1/TIGIT Bispecific, for CPI-naïve Metastatic NSCLC with PD-L1 1-49% or ≥50%

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Introduction: Rilvegostomig is a bispecific mAb against PD-1 and TIGIT receptors, designed to enhance antitumour activity beyond PD-(L)1 therapy. The first-in-human study (ARTEMIDE-01, NCT04995523) in checkpoint inhibitor (CPI)-resistant metastatic non-small-cell lung cancer (NSCLC) showed encouraging safety and evidence of antitumour activity (Rohrberg ASCO 2023, #9050; Brandão ESMO 2023, #1446P). Here we report the first analysis of ARTEMIDE-01 in CPI-naïve patients with metastatic NSCLC and PD-L1 tumour proportion score (TPS) of 1-49% or ≥50%.

Methods: In this open-label, global, multicentre study, patients received rilvegostomig in Part C (PD-L1 TPS ≥1%, 750 mg Q3W) and Part D (PD-L1 TPS ≥50%, randomised 1:1 to 750 mg or 1500 mg Q3W). Patients were eligible based on local PD-L1 testing and retrospective central VENTANA SP263 PD-L1 testing was performed. Primary endpoints were objective response rate (ORR) by RECIST v1.1 and safety by CTCAE v5. Key secondary endpoints included duration of response (DoR) and progression-free survival (PFS).

Results: As of 7 July 2024, 95 patients received ≥1 dose of rilvegostomig and had ≥9 weeks follow-up. Of all enrolled patients (n=96), 16.7% had prior chemotherapy for metastatic disease and 13.5% and 21.9% had liver and brain metastases, respectively. Rilvegostomig was well tolerated with few treatment-related discontinuations (4.2%) and Grade ≥3 treatment-related adverse events (10.5%); there were no evident differences between 750 mg and 1500 mg in safety profile. In patients with PD-L1 TPS 1-49% (all received 750 mg), ORR was 29.0% (9/31, all confirmed) based on locally assessed PD-L1 TPS and 34.8% (8/23, all confirmed) based on central testing. In patients with PD-L1 TPS ≥50%, 95.3% (61/64) were randomised between the two doses; those receiving 750 mg had an ORR of 61.8% (21/34, 4 pending confirmation) based on locally assessed PD-L1 TPS and 68.2% (15/22, 3 pending confirmation) based on central testing. Those receiving 1500 mg had an ORR of 36.7% (11/30, 2 pending confirmation) based on locally assessed PD-L1 TPS and 35.7% (5/14, all confirmed) based on central testing. At data cutoff, 53.7% of patients remained on treatment. Response was ongoing in 28 (80%) confirmed responders. Among all confirmed responders (across PD-L1 levels and doses), median DoR was 10.5 months (95% CI, 6.4-not calculable).

Conclusions: In CPI-naïve patients, rilvegostomig showed a favourable safety profile and encouraging preliminary efficacy in those with PD-L1 TPS 1-49% and PD-L1 TPS ≥50%. Data support 750 mg Q3W as the pivotal dose for registrational studies.

Keywords: Metastatic NSCLC, PD-L1 positive, Immunotherapy

Table. Efficacy of rilvegostomig

PD-L1 status (based on local result)	TPS 1–49%	TPS ≥50%	
	750 mg	750 mg	1500 mg
Patients with first dose at least 9 weeks prior to data cutoff[a], N	**31**	**34[b]**	**30**
Confirmed and unconfirmed[c] CR or PR, n (%)	9 (29.0)	21 (61.8)	11 (36.7)
Stable disease, n (%)	11 (35.5)	9 (26.5)	9 (30)
Progression, n (%)	9 (29)	4 (11.8)	8 (26.7)
Not evaluable, n (%)	2 (6.5)	0	2 (6.7)

Data cutoff: 7 July 2024.
[a] Patients had opportunity for disease assessment scan 9 weeks after the first dose.
[b] 3 subjects from Part C had PD-L1 TPS ≥50% and were included in the analysis with patients in Part D.
[c] PR or CR pending confirmatory assessment.

CR, complete response; PD-L1, programmed cell death ligand-1; PR, partial response; TPS, tumour proportion score.

OA11 SHIFTING THE BAR IN THE FRONT LINE IMMUNOTHERAPY SETTING
MONDAY, SEPTEMBER 9, 2024 - 14:00 - 15:15

OA11.04 Volrustomig + platinum doublet chemotherapy (CTx) in first-line non-small cell lung cancer (NSCLC): Phase 1b trial update

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Introduction: Volrustomig, a novel PD-1/CTLA-4 bispecific antibody, has shown robust pharmacodynamic effect and clinical promise in multiple advanced solid tumors (Tran, AACR 2022; Albiges, ASCO 2022; Voss, ESMO 2023), and especially in PD-L1-negative first-line (1L) NSCLC (Ahn, ESMO 2022). PD-L1-negative NSCLC is a disease segment of key unmet need, with limited benefit gained from addition of anti-PD-(L)1 therapy alone to CTx, and where anti-PD-(L)1/anti-CTLA-4 therapy + CTx has previously shown clinical potential (Paz-Ares, Lancet Oncol 2021; Johnson, JCO 2023). Here we report updated results from patients with 1L advanced NSCLC treated with volrustomig 750mg + CTx in a global Phase 1b study.

Methods: Patients with 1L advanced NSCLC were treated with volrustomig 750mg + CTx Q3W based on histology: 120 nonsquamous (Nsq) NSCLC patients enrolled over two different time periods (Cohort 1A: n=66; Cohort 1B: n=54) and 20 squamous (Sq) NSCLC patients (Cohort 2). The primary endpoint was objective response rate (ORR) in the Nsq cohorts and safety in the Sq cohort. Secondary endpoints included safety, tolerability, and disease control rate (DCR). Exploratory endpoints included receptor occupancy and pharmacodynamic biomarkers of CTLA-4 blockade.

Results: Among 140 patients enrolled, 89 had PD-L1 tumor cell expression (TC) <1% NSCLC (63.6%), reflecting the unmet need and previously seen benefit of CTLA-4 inhibition in this population; median age was 68.0 years, 73.6% were males, 67.9% with ECOG performance status 1, 15.7% with liver metastases, and 15% with brain metastases. Efficacy outcomes are shown in the Table. Nearly all patients achieved disease control. Among evaluable patients with PD-L1 TC <1%, ORR in the Nsq (n=78) and Sq (n=10) cohorts was 42.3% and 50.0%, respectively. Median number of cycles was 6 (range 1-39); 97.1% and 75.7% of patients experienced all-grade and grade 3/4 treatment-related adverse events (AE), respectively. Seven treatment-related deaths occurred (two of which were volrustomig-related immune-related AEs): 6 in Cohort 1A, 0 in Cohort 1B, 1 in Cohort 2. Clinical peripheral T cell flow cytometry, TCR sequencing, and single-cell sequencing demonstrated greater T cell proliferation and memory T cell activation with volrustomig 750mg + CTx versus anti-PD1 + CTx.

Conclusions: Volrustomig 750mg + CTx demonstrates robust PD-1/CTLA-4 blockade, manageable safety, and promising efficacy in 1L advanced NSCLC, especially in patients with PD-L1 TC <1%. The ongoing phase 3 EVOLVE-Lung02 trial (NCT05984277) is evaluating volrustomig + CTx for metastatic NSCLC with PD-L1 TC <50%.

Keywords: NSCLC, immunotherapy, chemotherapy

Table 1. Efficacy outcomes

Outcome	Cohort 1, nonsquamous	Cohort 2 squamous
Response-evaluable, n	119*	20
Median follow-up, months (range)	8.9 (0.3–33.6)	17.6 (0.7–24.8)
ORR, % (95% CI)	43.7 (34.6–53.1)	65.0 (40.8–84.6)
DCR (CR+PR+SD), % (95% CI)	84.9 (77.2–90.8)	95.0 (75.1–99.9)
PD-L1 TC <1% subgroup	**n=78**	**n=10**
ORR, % (95% CI)	42.3 (31.2–54.0)	50.0 (18.7–81.3)

*One patient in Cohort 1 was excluded due to squamous histology
CI, confidence interval; CR, complete response; PD-L1, programmed death-ligand 1; PR, partial response; SD, stable disease

OA11 SHIFTING THE BAR IN THE FRONT LINE IMMUNOTHERAPY SETTING
MONDAY, SEPTEMBER 9, 2024 - 14:00 - 15:15

OA11.05 Results of a Phase III Trial of Prolgolimab with Chemotherapy as First-Line Therapy for Patients with Advanced Non-Squamous NSCLC: DOMAJOR

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Introduction: Prolgolimab is an IgG1 aPD-1 monoclonal antibody with the Fc-silencing 'LALA' mutation. Here we present the results of randomized, multicenter, double-blind, placebo-controlled, phase III clinical trial BCD-100-3/DOMAJOR (NCT03912389) to evaluate the efficacy and safety of prolgolimab in combination with pemetrexed and platinum-based chemotherapy (PTb CT) versus placebo in combination with pemetrexed and PTb CT in patients (pts) with previously untreated advanced non-squamous (a/ns) NSCLC without driving mutations EGFR and ALK and independent of PD-L1 expression level. 45 centers across Russia, EU, China were participated.

Methods: 292 pts with a/ns NSCLC were randomized 1:1 to receive 4 cycles of prolgolimab (3 mg/kg Q3W) together with pemetrexed, platinum drug (cis- or carboplatin) (group A) or placebo together with pemetrexed, platinum drug (cis- or carboplatin) (group B) followed by prolgolimab/placebo with pemetrexed as 1st line therapy for a/ns NSCLC until disease progression or toxicity (≤36 mos). Primary endpoint was OS in intention to treat (ITT) population. The main analysis was planned once 113 deaths have been reached.

Results: After a median follow-up of 18 mos, the median OS was not reached (95% CI 22.28; NA) in the group A versus vs 14.6 mos (95% CI 11.73; 19.15) in the group B (HR= 0.51, 95% CI 0.35; 0.73, p=0.0001). The estimated rate of overall survival at 24 mos was 59.0% in the prolgolimab-combination group vs 36.3% in the placebo-combination group. PD-L1 status is not a statistically significant predictor in both multi- and univariate Cox models (p>0.3). AUC of the time-dependent ROC-curve (AUC=0.6) suggests that level of PD-L1 expression did not predict survival probability. Median PFS was 7.7 mos in group A and 5.5 mos in group B (HR=0.65. 95% CI 0.49; 0.85, p=0.0004). ORR was 50.3% in the prolgolimab-combination group and 27.5% in the placebo-combination group (RR 0.21, 95% CI 0.11; 0.32). Adverse events (AEs) of any grade occurred in 97.2% (139/143) of pts in group A and 89.2% (132/148) in group B. AEs related to study therapy was 64.3% (92/143) in group A and 50% (74/148) in group B. Immune-related AEs occurred in 34.3% (49/143) of pts in prolgolimab-combination group. Discontinuation of the therapy due to AEs was required in 9.8% of pts in group A and in 8.8% pts in group B.

Conclusions: Prolgolimab with chemotherapy demonstrated significantly longer OS, PFS and ORR than chemotherapy alone in pts with a/ns NSCLC. PD-L1 status did not predict survival probability in the prolgolimab-combination group. Prolgolimab in combination with chemotherapy had favorable safety profile without any signs of unexpected toxicity. Most AEs related to study therapy were mild or moderate and did not require treatment discontinuation.

Keywords: prolgolimab, NSCLC, PD-1

OA11 SHIFTING THE BAR IN THE FRONT LINE IMMUNOTHERAPY SETTING
MONDAY, SEPTEMBER 9, 2024 - 14:00 - 15:15

OA11.06 Cemiplimab Monotherapy for First Line Advanced NSCLC Patients with PD-L1 Expression ≥50%: 5-y Outcomes of EMPOWER-Lung

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Introduction: Earlier data from EMPOWER-Lung1 have demonstrated a significant survival benefit and generally acceptablesafety profile of first line (1L) cemiplimab monotherapy vs chemotherapy foradvanced non-small cell lung cancer (aNSCLC) with PD-L1 ≥50% of tumor cells andno EGFR, ALK or ROS1 aberrations. Here, we report protocol pre-specified finaloverall survival (OS) analysis (after 476 events) with 5-year (y) follow-up. Wealso report outcomes of patients who continued cemiplimab at diseaseprogression with addition of chemotherapy as allowed in the protocol, investigatinga new alternative for patients progressing on 1L monotherapy.

Methods: EMPOWER-Lung 1 was amulticenter, open-label, randomized, phase 3 study of cemiplimab in patientswith treatment-naïve squamous or non-squamous NSCLC with PD-L1 ≥50%. Patientswere randomized 1:1 to cemiplimab 350 mg IV every 3 weeks for 2 years orinvestigator's choice of chemotherapy. The primary endpoints were OS andprogression-free survival (PFS) per Blinded Independent Review Committee(BIRC). For inclusion in the post progression analysis patients needed to have received1 dose of chemotherapy and have at least 1 scan following disease progression oncemiplimab; response was assessed by BIRC against a new baseline, defined asthe last scan prior to the initial dose of chemotherapy.

Results: Of 712 patients randomized to cemiplimab(357) or chemotherapy (355), 565 patients (284 cemiplimab, 281 chemotherapy) hadverified PD-L1 ≥50%. In this population, the median follow-up was 57.3 months(m; range: 46.5 : 78.4), median OS was 26.1 m (95% CI, 22.1, 31.9) for cemiplimabvs 13.3 m (10.5, 16.2) for chemotherapy, hazard ratio (HR) 0.585 (0.48, 0.72);median PFS was 8.1 m (6.2, 8.8) vs 5.3 m (4.3, 6.1), HR 0.500 (0.41, 0.61); objectiveresponse rate (ORR) was 46.5% (40.6%, 52.5%) vs 20.6% (16.1%, 25.8%). 5-year OSprobability is 29.0% (22.9%, 35.4%) for cemiplimab vs 15.0% (10.5%, 20.2%) for chemotherapy.Improved activity of cemiplimab was observed in patients with PD-L1 ≥90%: medianOS was 38.8 m (22.9, NE), median PFS was 14.7 m (10.2, 21.1), ORR was 60.6% (50.3%,70.3%) and 5-year OS probability is 39.8% (28.0%, 51.3%). Safety profile at 5years remains consistent with previous results for patients who received eitherintervention. Grade ≥3 treatment-emergent adverse events (TEAE) occurred in 45.8%of patients for cemiplimab and 51.6% for chemotherapy. In the 75 patients in the postprogression analysis of cemiplimab + chemotherapy, the ORR was 28.0% (18.2,39.6) and median PFS2 was 6.5 m (6.2, 8.3) in the post progression phase. MedianOS was 27.4 m (23.0, 31.9) from randomization, which includes median of 15.1 m(11.3, 18.0) after adding chemotherapy. The combination was generally welltolerated, with 27 patients (36.0%) experiencing grade ≥3 TEAEs during the postprogression phase.

Conclusions: At 5-y follow-up, 1L cemiplimabmonotherapy continued to show durable clinical benefits vs chemotherapy. Continuedcemiplimab with addition of chemotherapy as 2L therapy provided meaningfulclinical benefit, providing a potential new treatment option for patients whoprogressed on cemiplimab monotherapy.

Keywords: Cemiplimab, Advanced-NSCLC, 5-year outcomes

OA12 ADVANCING MULTIMODAL THERAPIES IN STAGE III NSCLC
MONDAY, SEPTEMBER 9, 2024 - 14:00 - 15:15

OA12.03 Osimertinib After Definitive CRT in Unresectable Stage III EGFR-mutated NSCLC: Safety Outcomes from the Phase 3 LAURA Study

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Introduction: Osimertinib, a third-generation, central nervous system-active EGFR-tyrosine kinase inhibitor, is recommended for EGFR-mutated advanced non-small cell lung cancer (NSCLC) and adjuvant treatment for resected EGFR-mutated NSCLC. In the Phase 3 LAURA study (NCT03521154), osimertinib given post-definitive chemoradiotherapy (CRT) demonstrated a statistically significant and clinically meaningful progression-free survival benefit vs placebo in patients with unresectable stage III EGFRmutated NSCLC without progression during/after CRT (hazard ratio 0.16 [95% CI 0.10, 0.24; p<0.001]). Here, we report an in-depth safety analysis from LAURA.

Methods: Eligibility: ≥18 years old (Japan ≥20 years), unresectable stage III EGFR-mutated (Ex19del/L858R) NSCLC without progression during/after definitive concurrent/sequential (c/s) CRT, WHO performance status 0/1; patients with asymptomatic radiation pneumonitis (RP)/pneumonitis post-CRT were eligible. Stratification: cCRT vs sCRT; stage IIIA vs IIIB/IIIC; Chinese vs nonChinese. Patients were randomized 2:1 to receive osimertinib 80 mg or placebo QD until disease progression (by blinded independent central review)/discontinuation. Open-label osimertinib was offered post-progression in both arms. Safety assessment schedule: baseline, Weeks 2, 4 and every 4 weeks thereafter until Week 24, every 8 weeks until Week 48, then every 12 weeks until treatment discontinuation. Toxicity management guidance required permanent discontinuation for symptomatic Grade (G) ≥3 RP/interstitial lung disease (ILD)/pneumonitis; study treatment could be restarted following interruption for symptomatic G2 events that resolved to G≤1; G1 events could continue with no dose modification.

Results: Overall, 216 patients were randomized: osimertinib n=143, placebo n=73. Baseline characteristics were generally well balanced across arms. Median total vs actual exposures were similar: osimertinib 24.0, placebo 8.3 months vs osimertinib 23.7, placebo 7.9 months, respectively. Incidence of any-cause G≥3 and serious adverse events (AEs): 35% and 38% (osimertinib) vs 12% and 15% (placebo), respectively; rates of exposure-adjusted G≥3 and serious AEs (per 100 patient-years) were similar between arms: 17.7 and 19.5 (osimertinib) vs 12.6 and 15.4 (placebo), respectively. RP (preferred term) was the most commonly reported AE (osimertinib 48%, placebo 38%), and the most common AE leading to protocol-mandated treatment interruption (osimertinib 32%, placebo 14%) and discontinuation (osimertinib 5%, placebo 3%). Most RP (grouped term) events were G1 (osimertinib 15%, placebo 19%) or G2 (osimertinib 31%, placebo 19%), with three G3 (osimertinib 2%) and no G4/5 events reported. Of the 69 osimertinib-treated patients with RP (grouped term), 32% (22/69) continued treatment without dose modification, 62% (43/69) interrupted treatment and subsequently restarted, and 6% (4/69) permanently discontinued treatment; 87% (60/69) continued osimertinib without recurrence of RP. ILD (grouped term) was reported by 8% (11/143) of osimertinib-treated patients; G1 n=4 (3%), G2 n=4 (3%), G3 n=2 (1%), G5 n=1 (<1%).

Conclusions: The safety profile of osimertinib after CRT was as expected and manageable. Dose interruptions due to AEs had limited impact on exposure. The majority of RP events were mild to moderate in severity and were managed effectively per protocol-mandated guidelines, with most patients able to continue or restart treatment without recurrence of RP. These safety data, together with the significant efficacy benefit observed, support osimertinib given post-definitive CRT as the new standard of care for unresectable stage III EGFR-mutated NSCLC.

Keywords: Osimertinib, Unresectable Stage III EGFR-mutated NSCLC, Safety

OA12 ADVANCING MULTIMODAL THERAPIES IN STAGE III NSCLC
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OA12.04 Neoadjuvant Concurrent Chemo-Immuno-Radiation Therapy Followed by Surgery for Stage III-N2 NSCLC: SQUAT Trial (WJOG 12119L)

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Introduction: Neoadjuvant chemo-immunotherapy has become a standard of care for patients with resectable stage II-III non-small cell lung cancer (NSCLC). However, while distant failure is greatly reduced in the chemoimmunotherapy arm, this is not the case for the local failure in the CheckMate 816 trial. We hypothesized that adding radiation therapy (RT) might improve local control. Therefore, we conducted a multicenter, prospective, single-arm, phase II trial [SQUAT (WJOG 12119L)], to evaluate neoadjuvant concurrent chemo-immuno-radiation therapy followed by surgical resection and adjuvant immunotherapy for resectable stage III-N2 NSCLC. The primary endpoint was the major pathologic response (MPR) rate according to an independent central review. This was already reported to be 63% with a 90% confidence interval(CI) of 47-78% in 2022. Here, we report the results from the final analysis, focusing on progression-free survival (PFS), overall survival (OS), and safety, which are key secondary endpoints.

Methods: Patients with resectable stage IIIA-B N2 NSCLC (TNM 8th edition) were enrolled to receive concurrent chemo-immuno-radiotherapy [weekly paclitaxel (40 mg/m2)/carboplatin (AUC 2) for 5 weeks plus involved-field RT 50 Gy] and immunotherapy [durvalumab (1500 mg) every 4 weeks for 2 cycles] followed by surgical resection and adjuvant immunotherapy (durvalumab every 4 weeks for up to 1 year). The sample size was determined to be 31 patients by assuming that the threshold and expected value of the MPR rate to be 40% and 65%, respectively, with a significance level α=0.05 (one-sided) and power of 0.8, adding a 10% allowance for ineligible patients.

Results: Between Jan. 2020 and Feb. 2022, 31 patients were enrolled from 10 institutions in Japan. Thirty-one and 30 patients were evaluated for safety and efficacy, respectively. Of 30 patients (median age, 64 years), 70% and 63% had clinical stage IIIA and non-squamous histology, respectively. At the time of data cutoff (Jan. 12th, 2024), the median duration of follow-up was 28 months (IQR 18-33 months). At 2 years, PFS and OS rates were 43% (95% CI 26-60%) and 76% (95% CI 56-88%), respectively. In an exploratory analysis, PFS and OS rates were numerically higher in patients who achieved MPR than those who did not (2-year PFS rate: 58% vs. 18%, 2-year OS rate: 84% vs. 64%, respectively). The incidence of grade 3 or 4 treatment-related adverse events was 48%. One patient had a treatment-related death due to myocardial infarction and interstitial pneumonia.

Conclusions: Our results demonstrated the impact of adding RT to neoadjuvant chemo-immunotherapy on long-term outcomes of patients with resectable stage IIIA-B N2 NSCLC for the first time.This treatment regimen shows high pathologic efficacy and feasibility, and may become a promising treatment for selected patients with stage II-III NSCLC.

Keywords: Non-small cell lung cancer (NSCLC), Neoadjuvant therapy, Durvalumab

OA12 ADVANCING MULTIMODAL THERAPIES IN STAGE III NSCLC
MONDAY, SEPTEMBER 9, 2024 - 14:00 - 15:15

OA12.05 APOLO: Phase II Trial of Induction Chemo-Immunotherapy Plus Chemoradiotherapy and Maintenance Immunotherapy in Stage III NSCLC

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Introduction: The standard treatment for unresectable stage III patients is concurrent chemo-radiotherapy followed by durvalumab for 1 year (PACIFIC regimen). All attempts to improve these outcomes have been unsuccessful. All efforts have indeed been in the concurrent or subsequent phase. However, in our NADIM study, the induction regimen with chemotherapy and immunotherapy provides high clinical and pathological response rates. In the present study, we aimed to explore the results of applying induction with chemo-immunotherapy followed by standard treatment with chemo-radiotherapy and subsequent maintenance for 1 year with atezolizumab immunotherapy. To our knowledge, this is the first study conducted in stage III with this approach.

Methods: Non-resectable stage IIIA-IIIB-IIIC NSCLC patients were enrolled in this phase II trial to evaluate the efficacy of the induction treatment (Atezolizumab 1200mg+ Carboplatin AUC5+Paclitaxel 200 mg/m2 for 3 cycles) and concurrent chemotherapy (CT) -radiotherapy (RDT) treatment for 3 cycles. At the end of concurrent treatment, Atezolizumab 1200mg maintenance treatment was administered for 12 months (16 cycles). The primary objective was to assess the progression-free survival (PFS) at 12 months, defining PFS as the time from inclusion until objective tumor progression or death.

Results: Patients were 31.2% female, 100% current/former smokers, 40.6% ECOG PS 0, 68.8% stage IIIB/IIIC (8th edition). Thirty-eight patients were included in the intention to treat (ITT) population and 32 patients in the per protocol population (PP), those who received at least two cycles of induction treatment or had at least the first tumor response evaluation. The maturity data at 24 months were 99.3% and the median follow-up was 25.3 months (95%CI: 23.5-25.7%). All 32 patients started concurrent CT-RDT treatment, 29 started maintenance treatment and 16 completed 16 cycles. In the ITT analysis: PFS at 12 months from the start of induction Ch-atezolizumab was 68.4% (95%CI: 51.1-80.6%). OS at 12 months from the patient enrollment was 86.8 % (95%CI: 71.2-94.3%). In the PP analysis: PFS at 12 months from the start of induction Ch-atezolizumab was 78.1% (95%CI: 59.5-88.9%). OS at 12 months from the patient enrollment was 90.6% (95%CI: 73.6-96.8%). In the ITT population, 94.7% of patients had grade 1/2 adverse effects (AE), and 23.7% had grade 3/4 AE in the induction phase. For concurrent CT-RDT phase and maintenance phase, these percentages were 65.8% and 57.9% for grade 1/2 and 34.2% and 13.2% for grade 3/4, respectively. One grade 5 AE was reported during the maintenance phase and was unrelated to Atezolizumab. We have not observed a significant relationship between primary endpoint and TMB or PDL1 expression or clinical variables.

Conclusions: Our study provides better results than those historically known (PACIFIC trial) and encourages the development of strategies like those already successfully used in earlier stages. Clinical Trial information: NCT04776447.

Keywords: APOLO Clinical trial, non resectable stage III NSCLC, induction CH_IO plus CR-RT and IO maintenance

OA12 ADVANCING MULTIMODAL THERAPIES IN STAGE III NSCLC
MONDAY, SEPTEMBER 9, 2024 - 14:00 - 15:15

OA12.06 Intensified Chemo-Immuno-Radiotherapy with Durvalumab for Stage III NSCLCs: A Single Arm Phase II Study - PACIFIC-BRAZIL (LACOG 2218)

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Introduction: Building on the PACIFIC study, PACIFIC-BRAZIL assessed efficacy and safety of an intensified regimen of induction chemotherapy plus durvalumab followed by concurrent chemoradiotherapy plus durvalumab, followed by consolidation durvalumab for stage III NSCLCs.

Methods: PACIFIC-BRAZIL was a phase 2, single-arm, multicenter trial for treatment-naïve stage III (TNM 8th edition) NSCLC patients, ECOG-PS 0-1, who were candidates for definitive chemo-radiotherapy. Patients received induction chemo-immunotherapy (two 21-day cycles of carboplatin AUC 6, paclitaxel 200mg/m^2 and durvalumab 1500mg) followed by concurrent chemo-immuno-radiotherapy (carboplatin AUC 2 and paclitaxel 50mg/m2 weekly for 6 weeks, plus durvalumab 1500mg every 21 days concurrently with intensity-modulated, image-guided radiotherapy to 60 Gy in 30 fractions over 6 weeks). Patients without progressive disease received consolidation immunotherapy (twelve 28-day cycles of durvalumab 1500mg). The primary endpoint was 12-month PFS (12m-PFS) computed from treatment initiation. A sample size of 48 patients would be necessary to reject the null hypothesis that 12m-PFS was ≤49%, considering a true 12m-PFS of 65% (one-sided alpha of 0.1, power 80%). An exploratory sensitivity landmark analysis was prospectively planned to contrast PFS results with those of PACIFIC, calculating the PACIFIC-BRAZIL PFS from the time of initiation of consolidation durvalumab (NCT04230408).

Results: From March/2021-July/2023, 49 patients were enrolled across 8 institutions (57% female, median age 67, 51% white, 43% black/mixed race, 84% current/former smokers, 41% non-squamous histology, 2%/37%/53%/8% stages IIA/IIIA/IIIB/IIIC, respectively); 94% and 82% of patients initiated concurrent chemo-immuno-radiotherapy and consolidation immunotherapy, respectively. Radiotherapy was given to >59 Gy in 93.4% of patients who initiated concurrent chemo-immuno-radiotherapy. Disease progression occurred in 4% of patients during induction chemo-immunotherapy and in none during concurrent chemo-immuno-radiotherapy. For 94% of censored patients, the minimum follow-up time was 12 months. The 12m-PFS was 68.1% (95%CI 56%-82.8%, P=0.0022 against the null hypothesis of 12m-PFS of 49%, binomial test). In a pre-planned sensitivity landmark analysis exclusively of patients who initiated consolidation immunotherapy (N=40), 12m-PFS was 66.4% (95%CI 51.7%-85.4%). There were no differences in 12m-PFS according to PD-L1 expression. Twelve-month overall survival was 81.2% (95%CI 70.8%-93.1%). The overall incidence of grade≥3 treatment-related adverse events (TRAEs) was 82% (25%, 65%, and 20% during induction chemo-immunotherapy, concurrent chemo-immuno-radiotherapy, and consolidation immunotherapy, respectively). Most common non-hematologic grade≥3 TRAEs were pneumonitis (14%), respiratory infections (6%), pneumonia, dyspnea, diarrhea, fatigue, and infusion-related reactions (4% each). Incidence of any-grade pneumonitis and esophagitis was 27% and 18%. There were seven grade 5 events (2 related, 5 unrelated to treatment): pneumonia (3), COVID-19 (2), sepsis (1), pneumonitis (1); 3 occurred during concurrent chemo-immuno-radiotherapy, and 3 occurred during consolidation immunotherapy.

Conclusions: PACIFIC-BRAZIL met its primary endpoint, demonstrating improved 12m-PFS compared to historical controls, both in the primary intention-to-treat analysis as well as in the sensitivity landmark analysis from initiation of consolidation immunotherapy. Although concurrent chemoradiotherapy followed by durvalumab remains the standard-of-care regimen for stage III unresectable NSCLC, our results may support further evaluation of induction chemo-immunotherapy prior to chemoradiotherapy. Given toxicities observed herein and the negative PACIFIC-2 study, immunotherapy added concurrently during chemoradiation may not be warranted.

Keywords: Stage III NSCLC, Induction Chemotherapy, Durvalumab

OA13 PERIOPERATIVE STRATEGIES 2
MONDAY, SEPTEMBER 9, 2024 - 15:30 - 16:45

OA13.03 Perioperative Durvalumab for Resectable NSCLC (R-NSCLC): Updated Outcomes from the Phase 3 AEGEAN Trial

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Introduction: In the phase 3 AEGEAN trial of patients with R-NSCLC, perioperative durvalumab plus neoadjuvant chemotherapy, versus neoadjuvant chemotherapy alone, significantly improved the primary endpoints of EFS and pCR, at their first planned interim analyses, with a safety profile consistent with the individual agents. Here, we report updated EFS results from the second planned interim analysis, interim DFS and OS results, and updated safety data, after all patients completed/discontinued treatment.

Methods: AEGEAN is a double-blind, placebo-controlled study (NCT03800134). Patients ≥18 years with treatment-naïve R-NSCLC (stage IIA-IIIB[N2]; AJCC 8th ed) and ECOG PS 0/1 were randomized (1:1) to neoadjuvant platinum-based chemotherapy plus durvalumab or placebo IV (Q3W, 4 cycles), followed by durvalumab or placebo IV (Q4W, 12 cycles), respectively, after surgery. Randomization was stratified by stage (II vs III) and PD-L1 status (<1% vs ≥1%; Ventana SP263). Efficacy analyses were performed in the mITT population (or its resected subpopulation), which excluded patients with documented EGFR/ALK aberrations. Primary endpoints: EFS per BICR (RECIST v1.1) and pCR, evaluated centrally. Key secondary endpoints: MPR, evaluated centrally, DFS (per BICR in the resected subpopulation), and OS. Safety was assessed in patients receiving treatment.

Results: 799/802 randomized patients received treatment (durvalumab arm, n=400; placebo arm, n=399). Baseline characteristics were largely balanced. As of 10-May-2024 (DCO), 86.9% and 88.5% had completed 4 cycles of neoadjuvant durvalumab or placebo, respectively, and 77.6% and 76.7% had completed surgery (mITT; durvalumab arm, n=366; placebo arm, n=374). Among patients who started adjuvant treatment (mITT; n=242; n=237), 68.6% and 63.7% had completed and 31.4% and 36.3% had discontinued treatment, most commonly due to progression (n=36 [14.9%]; n=70 [29.5%]). EFS benefit favoring the durvalumab arm remained consistent with that reported previously, including within the planned neoadjuvant platinum subgroups (Table). Clinically meaningful DFS improvement and an OS trend favoring the durvalumab arm were observed (Table). In exploratory analyses, EFS benefit was more pronounced in patients receiving adjuvant treatment and favored the durvalumab arm regardless of pCR status (to be presented), and improvement in lung cancer-specific survival was observed (Table). Maximum grade 3/4 AE rates were similar between arms during the overall period and occurred in 15.4% and 10.6% of patients during the adjuvant period (Table).

Conclusions: These findings, based on 18 months additional follow-up since the primary EFS analysis, further support perioperative durvalumab as a new treatment option for patients with R-NSCLC.

Keywords: Durvalumab, Perioperative, Overall survival

Endpoint	Durvalumab arm	Placebo arm	Treatment effect
EFS	n events/N (%): 124/366 (33.9)	n events/N (%): 165/374 (44.1)	HR (95% CI): 0.69 (0.55–0.88)[b]
	Median (95% CI), months: NR (42.3–NR)[a]	Median (95% CI), months: 30.0 (20.6–NR)[a]	
EFS (cisplatin subgroup)	n events/N (%): 28/100 (28.0)	n events/N (%): 42/96 (43.8)	HR (95% CI): 0.58 (0.35–0.93)[c]
	Median (95% CI), months: NR (NR–NR)[a]	Median (95% CI), months: 45.0 (13.9–NR)[a]	
EFS (carboplatin subgroup)	n events/N (%): 96/266 (36.1)	n events/N (%): 123/278 (44.2)	HR (95% CI): 0.75 (0.57–0.97)[c]
	Median (95% CI), months: NR (36.6–NR)[a]	Median (95% CI), months: 26.2 (20.6–NR)[a]	
DFS[d]	n events/N (%): 60/242 (24.8)	n events/N (%): 81/231 (35.1)	HR (95% CI): 0.66 (0.47–0.92)[b]
	Median (95% CI), months: NR (NR–NR)[a]	Median (95% CI), months: NR (41.5–NR)[a]	
OS	n events/N (%): 121/366 (33.1)	n events/N (%): 140/374 (37.4)	HR (95% CI): 0.89 (0.70–1.14)[b]
	Median (95% CI), months: NR (NR–NR)[a]	Median (95% CI), months: 53.2 (44.3–NR)[a]	
Lung cancer-specific survival[e]	n events/N (%): 80/366 (21.9)	n events/N (%): 117/374 (31.3)	HR (95% CI): 0.70 (0.52–0.93)[b]
	Median (95% CI), months: NR (NR–NR)[a]	Median (95% CI), months: NR (48.3–NR)[a]	
Maximum grade 3 or 4 all-causality AEs, n (%)	Overall period (n=401)[f]: 175 (43.6)	Overall period (n=398)[f]: 172 (43.2)	NA
	Adjuvant period (n=266)[g]: 41 (15.4)	Adjuvant period (n=254)[g]: 27 (10.6)	

Median EFS follow-up was 25.9 months (censored patients). [a]Kaplan–Meier method. [b]Stratified Cox proportional hazards model. [c]Unstratified Cox proportional hazards model. [d]Analyzed in patients in the mITT population who had tumor resection with R0/R1 margins and no evidence of disease in the first post-surgery scan. [e]Exploratory analysis including deaths reported to be related to 'disease under investigation' per investigator assessment. [f]First dose of study treatment until the earliest of: the last dose of study treatment or surgery + 90 days, date of the first dose of subsequent anti-cancer treatment, or the data cutoff date. [g]First dose of study treatment post-surgery until earliest of: last study treatment post-surgery + 90 days, date of first dose of subsequent anti-cancer treatment, or the data cutoff date. AEs, adverse events; BICR, blinded independent central review; CI, confidence interval; DCO, data cutoff; DFS, disease-free survival; ECOG PS, Eastern Cooperative Oncology Group performance status; EFS, event-free survival; HR, hazard ratio; IV, intravenous; mITT, modified intent-to-treat; MPR, major pathological response; NA, not applicable; NR, not reached; OS, overall survival; pCR, pathological complete response; PD-L1, programmed cell death-ligand 1; QXW, every X weeks; RECIST v1.1, Response Evaluation Criteria in Solid Tumors, version 1.1.

OA13 PERIOPERATIVE STRATEGIES 2
MONDAY, SEPTEMBER 9, 2024 - 15:30 - 16:45

OA13.04 ALINA Safety Results; Adjuvant Alectinib vs Chemotherapy in Patients with Resected ALK+ Non-Small Cell Lung Cancer (NSCLC)

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Introduction: ALINA (NCT03456076) is a global, open-label, phase III, randomized trial evaluating the efficacy and safety of adjuvant alectinib versus chemotherapy in patients with resected stage IB (≥4 cm)-IIIA (AJCC 7th edition), ALK+ NSCLC. A significant disease-free survival (primary endpoint) benefit was observed with alectinib versus chemotherapy (hazard ratio: 0.24, 95% CI: 0.13-0.43, p<0.0001; N=257 in the intention-to-treat population). We present additional data on safety outcomes.

Methods: Eligible patients (≥18 years old, with an ECOG PS 0/1 and completely resected, stage IB-IIIA, ALK+ NSCLC) were randomized 1:1 to receive oral alectinib (600 mg twice daily for 24 months) or platinum-based chemotherapy for up to four 21-day cycles. Safety monitoring, including assessment of the nature, frequency, and severity of adverse events (AEs), lasted up until 28 days after the last dose of study drug.

Results: At data cut-off (June 26th, 2023), median safety follow-up was 24.8 months and 3.7 months in the alectinib and chemotherapy arms, respectively. The five most reported AEs in the alectinib arm were: blood creatine phosphokinase (CPK) increased (43.0%), constipation (42.2%), aspartate aminotransferase increased (41.4%), alanine aminotransferase increased (33.6%), and blood bilirubin increased (33.6%). Most of these AEs were of low grade, non-serious, and did not require any dose modification. Table 1 presents time to onset and duration of these AEs. Table 2 presents AEs leading to dose reduction, interruption, and discontinuation in the alectinib arm in ≥3 patients: blood CPK increase led to dose reduction in 6.3% of patients and interruption in 5.5% of patients, and pneumonitis led to treatment withdrawal in 2.3% of patients.

Conclusions: Alectinib had a manageable safety profile; coupled with the previously reported efficacy data, these results support the use of adjuvant alectinib in patients with resected, stage IB-IIIA, ALK+ NSCLC. No new safety concerns were identified.

Keywords: NSCLC, alectinib, safety

Table 1. Time to onset and duration for the most frequently reported AEs in the alectinib arm

AE	Alectinib (n=128)
AST or ALT* increase	
Patients with AE, n (%)	56 (43.8)
Median time to first onset, days (IQR)	28.5 (18.5–68.0)
Median duration of AE, days (IQR)	43.0 (15.0–85.0)
Blood CPK increased	
Patients with AE, n (%)	55 (43.0)
Median time to first onset, days (IQR)	15.0 (15.0–16.0)
Median duration of AE, days (IQR)	18.0 (14.0–43.0)
Constipation	
Patients with AE, n (%)	54 (42.2)
Median time to first onset, days (IQR)	10.0 (5.0–22.0)
Median duration of AE, days (IQR)	184.5 (40.0–765.0)
Blood bilirubin† increase	
Patients with AE, n (%)	50 (39.1)
Median time to first onset, days (IQR)	43.0 (22.0–78.0)
Median duration of AE, days (IQR)	126.0 (43.0–576.0)

AEs, adverse events; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CPK, creatine phosphokinase; IQR, interquartile range. *Includes preferred terms aspartate aminotransferase increased and alanine aminotransferase increased. †Includes preferred terms blood bilirubin increased, bilirubin conjugated increased, hyperbilirubinemia, and blood bilirubin unconjugated increased.

Table 2. AEs in the alectinib arm leading to dose reduction, interruption, or treatment discontinuation in at least three patients

Safety	Alectinib (n=128)
Median treatment duration	23.9 months
Any AE leading to dose interruption, n (%)	35 (27.3)
Blood CPK increased	7 (5.5)
ALT increased	7 (5.5)
AST increased	6 (4.7)
COVID-19	6 (4.7)
Blood bilirubin increased	5 (3.9)
Myalgia	3 (2.3)
Any AE leading to dose reduction, n (%)	33 (25.8)
Blood CPK increased	8 (6.3)
Blood bilirubin increased	5 (3.9)
Any AE leading to treatment discontinuation, n (%)	7 (5.5)
Pneumonitis	3 (2.3)

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; COVID-19, Coronavirus disease 19; CPK, creatine phosphokinase.

OA13 PERIOPERATIVE STRATEGIES 2
MONDAY, SEPTEMBER 9, 2024 - 15:30 - 16:45

OA13.05 I-SABR-SELECT: A Radiomics-Based Model for Personalized Immunotherapy for Early-Stage Non-Small Cell Lung Cancer

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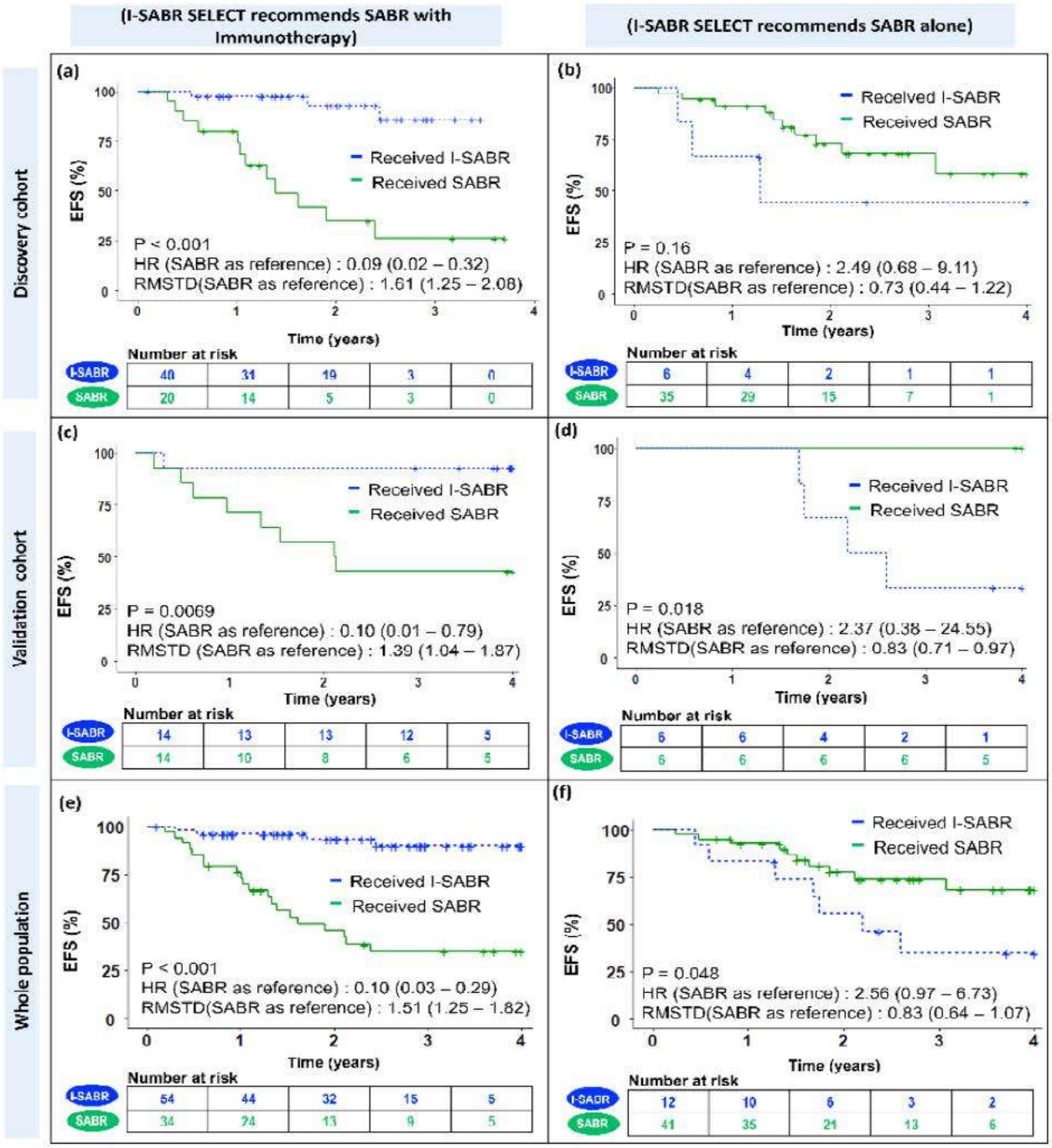
Introduction: Our recent phase 2 randomized clinical trial (I-SABR, NCT03110978) demonstrated improved event-free survival (EFS) from combining stereotactic ablative radiotherapy (SABR) with immune checkpoint inhibitor therapy for early-stage non-small cell lung cancer (NSCLC) relative to SABR alone. However, not every patient benefits from immunotherapy. We report here a secondary analysis in which clinical-radiomics, with machine learning, was developed into a model to identify patients who would or would not benefit from immunotherapy.

Methods: Subjects were 141 patients with early-stage NSCLC enrolled in the I-SABR trial, 101 in the discovery and 40 in the validation cohort. We used the discovery cohort to develop the I-SABR-SELECT framework to model treatment outcomes and inform patient selection for combining immunotherapy with SABR. We extracted radiomics patterns characterizing the tumor/peritumoral and lung regions and the angiogenesis network surrounding the tumor. Radiomics features were harmonized, qualified, and integrated with clinical factors for downstream selection to mitigate model overfitting. A random survival forest algorithm was applied to model relationships between patient characteristics and treatment outcome separately for I-SABR and SABR-only. Counterfactual reasoning was used to assess treatment effects and optimize selection. The model was evaluated separately in the discovery and validation cohorts and in an independent group of patients treated on the STARS trial of SABR for early-stage NSCLC.

Results: Overall, the modelrecommended that 46 of the 141 (33%) patients enrolled in I-SABR switchtreatments (34 of 75 [45%] in the SABR-only arm and 12 of 66 [18%] in theI-SABR arm). Patients treated according to this recommendation achievedsignificantly improved EFS in both arms during model discovery and validation.Stratified by this recommendation, patients who received I-SABR showed an EFSinterval 1.4 to 1.6 times longer than those who did not receive immunotherapy.Notably, patients who were treated according to the I-SABR-SELECTrecommendation to add immunotherapy had improved EFS with hazard ratio [HR,SABR as reference] = 0.09 ($p<0.001$) and HR = 0.10 ($p=0.0069$) for discoveryand validation cohort, respectively (Fig.1). Interestingly, subgroup ofsingle-arm STARS patients who were treated as recommended had better EFS with[HR, against subgroup as reference] = 0.25 ($p=0.04$). Shapley analysis revealedcertain clinical features including ECOG and radiomics features measuring tumorand surrounding blood vessel were highly associated with model prediction.

Conclusions: I-SABR-SELECT provides an individualized approach for guiding who needs immunotherapy combined with SABR for early-stage NSCLC.

Keywords: SABR, Immunotherapy, Radiomics


(I-SABR SELECT recommends SABR with Immunotherapy)
(I-SABR SELECT recommends SABR alone)
Discovery cohort
Validation cohort
Whole population
(a)
EFS (%)
Received I-SABR
Received SABR
P < 0.001
HR (SABR as reference) : 0.09 (0.02 – 0.32)
RMSTD(SABR as reference) : 1.61 (1.25 – 2.08)
Time (years)
Number at risk
I-SABR 40 31 19 3 0
SABR 20 14 5 3 0
(b)
P = 0.16
HR (SABR as reference) : 2.49 (0.68 – 9.11)
RMSTD(SABR as reference) : 0.73 (0.44 – 1.22)
I-SABR 6 4 2 1 1
SABR 35 29 15 7 1
(c)
P = 0.0069
HR (SABR as reference) : 0.10 (0.01 – 0.79)
RMSTD (SABR as reference) : 1.39 (1.04 – 1.87)
I-SABR 14 13 13 12 5
SABR 14 10 8 6 5
(d)
P = 0.018
HR (SABR as reference) : 2.37 (0.38 – 24.55)
RMSTD(SABR as reference) : 0.83 (0.71 – 0.97)
I-SABR 6 6 4 2 1
SABR 6 6 6 6 5
(e)
P < 0.001
HR (SABR as reference) : 0.10 (0.03 – 0.29)
RMSTD(SABR as reference) : 1.51 (1.25 – 1.82)
I-SABR 54 44 32 15 5
SABR 34 24 13 9 5
(f)
P = 0.048
HR (SABR as reference) : 2.56 (0.97 – 6.73)
RMSTD(SABR as reference) : 0.83 (0.64 – 1.07)
I-SABR 12 10 6 3 2
SABR 41 35 21 13 6

OA14 NEW HORIZONS IN TARGETING KRAS G12C
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OA14.03 Garsorasib in KRAS G12C-Mutated Non-Small-Cell Lung Cancer: Updated Results from a Phase 2 Study

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Introduction: Garsorasib (D-1553), a potent inhibitor of KRAS G12C, has shown robust anti-tumor activity and a well-tolerated safety profile in patients with non-small-cell lung cancer (NSCLC) harboring the KRAS G12C mutation, as previously reported (2024 AACR; Lancet Respir Med 2024). Here we provide the updated efficacy and safety data with longer follow-up.

Methods: This is an open-label, multicenter, single-arm phase 2 study (NCT05383898). Enrolled patients received garsorasib 600 mg twice daily in 21-day cycles. Eligible criteria included patients with locally advanced or metastatic NSCLC harboring KRAS G12C mutation, who had disease progression after prior anti-PD-(L)1 therapy and platinum-based chemotherapy or intolerance to the above regimens due to toxicity, and had measurable tumor lesions according to the RECIST, v1.1. The primary endpoint was objective response rate (ORR) evaluated by independent review committee (IRC) per RECIST v1.1. The secondary endpoints included duration of response (DOR), disease control rate (DCR), time to response (TTR), progression-free survival (PFS), overall survival (OS), and safety. Efficacy and safety were assessed in all patients who received at least one dose of garsorasib.

Results: A total of 123 patients (male 88%, median age 64, Asian 100%, prior systemic anticancer therapy 100%) were enrolled and treated. In this updated data cutoff (17 May 2024) compared to the prior data cutoff (17 November 2023), median duration of follow-up has increased from 7.9 months (IQR: 6.3-10.4) to 12.3 months (IQR: 6.6-15.0); 27 patients (22.0%) remain on treatment. IRC-confirmed ORR was 52.0% (95% CI: 42.8-61.1), and the DCR was 88.6% (95% CI: 81.6-93.6). The median TTR and DOR were 1.4 months (IQR: 1.4-1.9), and 12.5 months (95% CI: 8.3-NE), respectively. The updated median PFS was 9.1 months (95% CI:5.6-10.3). The median OS was estimated as 14.1 months (95% CI: 11.5-17.3). A total of 118 (95.9%) patients reported treatment-related adverse events (TRAEs) with 63 (51.2%) patients experiencing grade 3 or higher events. TRAEs led to dose reduction in 37 patients (30.1%), and to drug interruption in 51 patients (41.5%). No TRAE led to permanent discontinuation of garsorasib. The safety profile of garsorasib was similar to previously reported, and most of the adverse events were well managed.

Conclusions: Garsorasib has shown a high tumor response rate and long duration of response in a pretreated population of patients with KRAS G12C-mutated NSCLC. After prolonged follow up, the updated PFS and OS suggest a long-term clinical benefit, which will be further evaluated in a randomized, double-blind, controlled trial.

Keywords: Non-small-cell Lung Cancer, KRAS G12C mutation, Phase 2 study

OA14 NEW HORIZONS IN TARGETING KRAS G12C
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OA14.04 Efficacy and Safety of Olomorasib with Pembrolizumab + Chemotherapy as First-Line Treatment in Patients with KRAS G12C-Mutant Advanced NSCLC

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Introduction: The combination of targeted therapy plus chemo-immunotherapy represents a compelling opportunity to improve upon first-line (1L) outcomes in patients with KRAS G12C-mutant non-small cell lung cancer (NSCLC). Olomorasib is a potent, selective second-generation KRAS G12C inhibitor which has demonstrated promising activity with favorable tolerability in KRAS G12C-mutant NSCLC as monotherapy and combined with pembrolizumab. Here, we report the first clinical data describing olomorasib combined with chemo-immunotherapy.

Methods: In the phase 1 trial of olomorasib (NCT04956640), patients with advanced KRAS G12C-mutant NSCLC were enrolled into multiple cohorts. This includes an expansion cohort studying two doses of olomorasib (50mg and 100mg, orally twice daily) combined with standard chemotherapy platinum/pemetrexed and pembrolizumab (all at labeled doses). Any PD-L1 level (0-100%, via local testing) was permitted; and patients needing timely 1L therapy were permitted one cycle of SOC therapy prior to enrollment. Adverse events (AE) were assessed across all treated patients; objective response rate (ORR) per RECIST v1.1 was assessed in patients with at least one post-baseline response assessment or who had discontinued treatment before the first response assessment.

Results: Overall 89 patients received olomorasib+pembrolizumab (as of 31 May 2024). Here we report on the subset of 20 (50mg, n=9; 100mg, n=11) who also received chemotherapy in that regimen. Median age was 68 years (range, 56-81); 11 (55%) were PD-L1-negative, 7 (35%) were PD-L1-low, 1 (5%) was PD-L1-high and 1 (5%) was unknown; 8 (40%) patients received one cycle of SOC therapy prior to enrollment. Median duration of therapy was 4.2 months (range, 0.3-10.7) and 16 patients (80%) remained on study at time of data-cut. All grade TRAEs in >20% of patients were anemia (40%), nausea (35%), decreased appetite (25%), fatigue (25%), and neutrophil count decreased (25%); grade ≥3 TRAEs in ≥10% of patients were neutrophil count decreased (25%), anemia (20%), white blood cell count decreased (20%), platelet count decreased (15%), and diarrhea (10%). Potential grade 3 immune-related AEs included elevated ALT/AST (5%) and pneumonitis (5%). TRAEs resulted in olomorasib dose reduction in 2 patients (10%). TRAEs led to discontinuation of olomorasib (15%), pembrolizumab (10%), pemetrexed (10%), and platinum therapy (15%). Hematologic toxicity resulted in delay of the subsequent cycle of chemo in 3 patients (15%). Among the 18 efficacy-evaluable patients treated, ORR was 44% (7 partial response, 1 unconfirmed partial response and ongoing; 95% CI, 22-69) and disease control rate was 83% (15/18; 95% CI, 59-96).

Conclusions: Olomorasib combined with chemo-immunotherapy demonstrated a favorable safety profile, consistent with the safety profiles observed with other combinations of chemotherapy and targeted therapy. This demonstrates the feasibility of combining KRAS G12C inhibitors with chemo-immunotherapy. The ORR was lower in this first-line cohort compared to the prior report with olomorasib combined with pembrolizumab, representative of the higher risk patients with PD-L1-negative status, enrolled to the chemo-immunotherapy backbone. A global, registrational study investigating this combination in first-line NSCLC is currently enrolling (SUNRAY-01, NCT06119581).

Keywords: Dose selection, KRAS G12C, Olomorasib

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OA14.05 KRAS G12C Inhibitor IBI351 In Patients (pts) with Advanced Non-Small Cell Lung Cancer (NSCLC): Updated Results from a Pivotal Phase 2 Study

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Introduction: KRAS G12C mutation is a well-recognized and increasingly promising therapeutic target with significant unmet clinical needs in NSCLC pts. IBI351, also known as GFH925, is a potent covalent and irreversible inhibitor of KRAS G12C. Initial results of IBI351 monotherapy in previously treated NSCLC pts with KRAS G12C have been reported in ESMO Asia 2023 (LBA12). Here, we report updated results of this open-label, single-arm, pivotal phase 2 study.

Methods: Eligible NSCLC pts with KRAS G12C who failed standard therapy were enrolled. IBI351 600 mg was orally administered twice daily. Primary endpoint was confirmed objective response rate (ORR) assessed by independent radiological review committee (IRRC) as per RECIST v1.1. Other endpoints were safety, disease control rate (DCR), duration of response (DoR), progression-free survival (PFS) and overall survival (OS).

Results: As of December 13, 2023, 116 pts were enrolled (ECOG PS 1: 91.4%; brain metastasis: 30.2%; prior treatments with both anti-PD-1/PD-L1 inhibitors and platinum-based chemotherapy: 84.5%). As per IRRC assessment, confirmed ORR was 49.1% (95% CI: 39.7-58.6) and DCR was 90.5% (95% CI: 83.7-95.2). In 57 pts with confirmed response, median DoR was not reached with events occured in 22 (38.6%) pts. Median PFS was 9.7 months (95% CI: 5.6-11.0). OS data was immature. Treatment-related adverse events (TRAEs) occurred in 107 (92.2%) pts while 48 (41.4%) pts had grade≥3 TRAEs. Common TRAEs were anemia (44.8%), alanine aminotransferase increased (28.4%), aspartate aminotransferase increased (27.6%), asthenia (26.7%) and protein urine present (25.0%). TRAEs leading to treatment discontinuation occurred in 9 (7.8%) pts. In biomarker evaluable pts (n=95), all pts had positive KRAS G12C in tissue while 72 pts were blood positive and 23 pts were blood negative for KRAS G12C. Pts with KRAS G12C in both blood and tissue had higher tumor burden at baseline ($p < 0.05$) and worse PFS ($p < 0.05$). Tumor mutation profiling identified TP53 (45.3%), STK11 (30.5%) and KEAP1 (21.1%) as the most common genes co-mutated with KRAS G12C. Among 13 genes with mutation frequency ≥5%, mutations of 6 genes (STK11, KEAP1, PIK3CG, POLE, SMAD4, BRINP3) were significantly associated with worse PFS ($p < 0.05$). Mutation in STK11 also showed significant association with higher tumor burden at baseline and lower response rate ($p < 0.05$).

Conclusions: In KRAS G12C mutant NSCLC, updated results of IBI351 monotherapy continues to support its role as a new treatment option with sustained efficacy and manageable safety.

Keywords: NSCLC, KRAS G12C, pivotal study

OA14 NEW HORIZONS IN TARGETING KRAS G12C
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OA14.06 Divarasib Single-Agent Long-Term Follow-up and Atezolizumab Combination Treatment in Patients with KRAS G12C-Positive NSCLC

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Introduction: Divarasib (GDC-6036), an oral, highly potent, and selective KRAS G12C inhibitor (G12Ci), has shown encouraging clinical activity and tolerability as a single agent in patients with KRAS G12C-positive NSCLC. The tolerability and potent activity of divarasib render it an attractive partner for PD-L1/PD-1 inhibitors where combinations with other KRAS G12Cis have been challenged by toxicity. Here we report safety and clinical activity of single-agent divarasib and in combination with the PD-L1 inhibitor atezolizumab in NSCLC patients.

Methods: As part of an ongoing phase I study (NCT04449874), patients received single-agent oral divarasib 50-400 mg daily, or divarasib 200 or 400 mg daily in combination with atezolizumab (1200 mg IV every 3 weeks), until intolerable toxicity or disease progression. Safety (NCI-CTCAE v5), pharmacokinetics, and preliminary antitumor activity (RECIST v1.1) were assessed.

Results: As of January 1, 2024, a total of 65 NSCLC patients had received single-agent divarasib. Among 31 patients who continued single-agent divarasib beyond one year, 15 (48.4%) experienced a new-onset treatment-related adverse event (TRAE) after a year; no patients experienced new-onset Grade 3-5 TRAEs, and no new-onset TRAEs led to dose reductions or divarasib withdrawal. Among 44 patients who received 400 mg divarasib, the confirmed objective response rate (ORR) was 59.1%, and the median progression-free survival (PFS) was 15.3 months (95% CI, 12.3 to 25.9).

A total of 39 NSCLC patients received divarasib and atezolizumab in combination; 18 patients received 200 mg and 21 patients received 400 mg divarasib (35 patients had prior PD-L1/PD-1 inhibitor; 14 patients at each dose level had no prior KRAS G12Ci exposure). Median lines of prior systemic therapy was 2 (range 1-5) and median time on study treatment was 6.21 months (range 0.1-22.5). At least one TRAE was experienced by 36 (92.3%) patients; the most common TRAEs (≥15%) were nausea, diarrhea, vomiting, aspartate transaminase (AST) increase, decreased appetite, alanine transaminase (ALT) increase, and asthenia. Grade 3 TRAEs occurred in 10 (25.6%) patients, including 2 (5.1%) patients experiencing Grade 3 treatment-related ALT/AST increase (managed with drug interruption and steroids). No Grade 4 or 5 TRAEs were reported. AEs led to divarasib dose reduction in 10 (25.6%) patients. There were no divarasib withdrawals due to AEs; atezolizumab withdrawals due to AEs occurred in 6 (15.4%) patients. The pharmacokinetic profile of divarasib was similar in combination with atezolizumab when compared to single-agent. Among 27 patients with baseline measurable disease who had no prior KRAS G12Ci, the confirmed ORR was 55.6% (15 patients). Median PFS was not estimated due to limited follow-up.

Conclusions: Single-agent divarasib continued to demonstrate encouraging radiographic response rates and durable clinical activity alongside a tolerable safety profile, establishing promising combination potential with other anticancer therapies. Divarasib in combination with atezolizumab demonstrated an acceptable safety profile and preliminary clinical activity in patients with KRAS G12C-positive NSCLC.

Keywords: NSCLC, divarasib, KRAS G12c

OA15 PROFILING THE TUMOUR MICROENVIRONMENT OF LUNG CANCER METASTASIS, MONDAY, SEPTEMBER 9, 2024 - 15:30 - 16:45

OA15.03 Clinicogenomic Landscape of Lymph Node Metastases in TRACERx

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Introduction: The prognosis of non-small cell lung cancer (NSCLC) is strongly associated with nodal involvement. Systemic chemotherapy and/or immunotherapy are recommended after surgery for patients with LN metastases. However, we do not know who benefits from such additional treatment, and a better risk stratification is warranted. This study aimed to unveil clonal evolution and heterogeneity in lymph node metastases and gain further insights into LN-positive diseases in NSCLC.

Methods: Whole exome sequencing data from 370 primary tumor regions and 129 paired metastatic lymph node samples across 95 tumors from the TRACERx 421 cohort were integrated with anatomical information of lymph node samples. Using mutational profiles, the phylogenies of metastatic clones were inferred. We explored whether a single subclone (monoclonal) or multiple genetically distinct subclones (polyclonal) from the primary tumor were involved in the metastatic dissemination. Additionally, we explored postoperative ctDNA detection, also known as minimally residual disease (MRD), within a landmark analysis framework, where the landmark timepoint refers to establishing the MRD calling of a patient within 120 days following surgery. 112 patients in the TRACERx 421 cohort with postoperative plasma sampling performed were evaluable for landmark analysis based on ≥1 plasma sample obtained within 120 days of surgery before adjuvant therapy or relapse.

Results: In the phylogenetic analysis, 100/129 metastasized LN had monoclonal seeding and 29/129 polyclonal seeding. There were no differences in the modes of dissemination between N1 and N2 nodes (monoclonal: N1, 56/76; N2, 44/53). There were 16 patients with metastatic LNs sampled from multiple LN stations (36 samples). We observed one case whose metastatic clone of N2 node (#7) was disseminated from N1 node (#12). No N2 to N1 metastasis was observed. All other N2 node metastases were inferred as seeded from primary tumors. At the patient level, 7/16 were monoclonal seeding, and 9/16 were polyclonal seeding. These results suggest whilst most LNs are seeded by a single clone from the primary tumor, approximately half of the cases with multi-station LN metastases had distinct clones that metastasized to respective LNs, therefore, polyclonal seeding at a patient level. In the ctDNA analysis, patients with N2 diseases had significantly high landmark MRD positivity compared with N0/N1 (N0, 9/68; N1, 5/24; N2, 13/24; N2 vs N1 p= 0.036, N2 vs N0 p= 0.00015). Landmark-negative patients had better overall survival (OS) than landmark-positive patients, regardless of pN status. Notably, landmark-negative N2 disease patients showed significantly better OS compared with landmark-positive N0/1 patients (HR = 0.35, 95%CI: 0.12-0.98, p= 0.046).

Conclusions: Anatomical site of metastatic LN was not associated with modes of clonal dissemination. N2 disease was associated with a significantly higher rate of postoperative MRD detection supporting the current indication of adjuvant systemic treatment for patients with N2 disease. Furthermore, postoperative assessment of ctDNA may improve the relapse risk stratification compared with current TNM staging.

Keywords: lymph node metastasis, ctDNA

OA15 PROFILING THE TUMOUR MICROENVIRONMENT OF LUNG CANCER METASTASIS, MONDAY, SEPTEMBER 9, 2024 - 15:30 - 16:45

OA15.04 Multi-Omic Profiling of Paired Non-Small Cell Lung Cancer and Draining Lymph Nodes Reveals Novel T-Cell Differentiation Patterns

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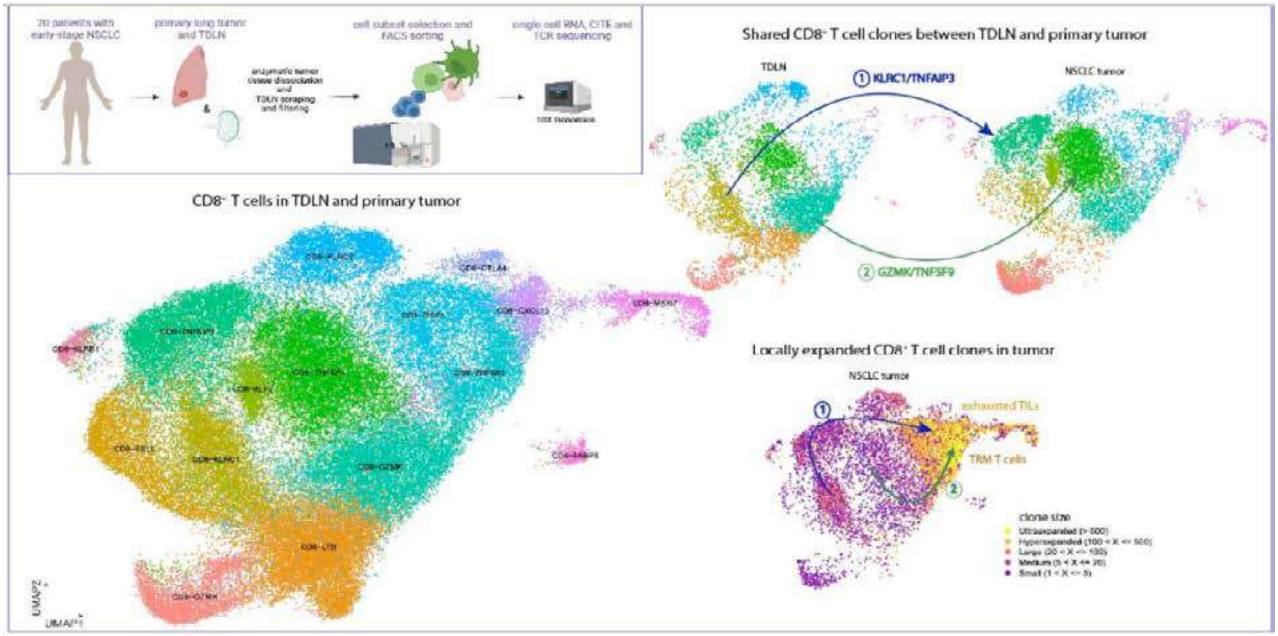
Introduction: Cancers including non-small cell lung cancer (NSCLC) contain tumor-infiltrating T-cells (TILs) critical for anti-tumor immunity and immunotherapy efficacy. Although TILs have been widely characterized, their origin remains largely unknown. Preclinical models and studies including mostly metastatic disease patient samples point to tumor-draining lymph nodes (TDLNs) as potential sites of origin for TILs. However, the developmental trajectory of T cells and its relation to other cell types is unclear.

Methods: We present the largest to date cohort of TDLNs and paired primary tumors (n=20) from patients with early-stage NSCLC post-resection. We FACS-sorted these samples for T-cells, myeloid and stromal cells, and performed single-cell RNA, CITE and T-cell receptor (TCR) sequencing.

Results: We identified 206,805 cells including 157,555 T-cells and found shared T-cell clones between TDLN and the primary tumor in all patients. Exhausted CD8+ TILs, characterized by increased expression of CTLA4, TIGIT, and HAVCR2 were markedly expanded, with few cells sharing TCRs with TDLN-T-cells. Instead, clonally related CD8+ T-cells present in both TDLN and tumor were characterized by an effector memory phenotype, belonging to individual clusters expressing GZMK, TNFSF9 (4-1BBL), KLRC1 (NKG2A), and TNFAIP3 (A20). Intriguingly, we could identify at least two different clonal trajectories leading to different TIL phenotypes not discovered before. Clonally related cells obtained different phenotypes when transitioning from TDLN to tumor, suggesting altered differentiation depending on the tissue microenvironment and presence of cognate antigen. More strikingly, cells stemming from the KLRC1/TNFAIP3-differentiation clusters were enriched for tissue resident memory (TRM) signatures. Moreover, these cells shared clonotypes with the TRM cluster in our dataset, pointing to a potential poised differentiation trajectory from this T-cell lineage compared to the GZMK/TNFSF9 clusters.

Conclusions: Using single-cell multi-omic profiling of TDLN and primary NSCLC tissues, we identified significant clonal relatedness between both sites in all patients investigated, and unveiled a yet unexplored complexity of TIL differentiation in NSCLC. Findings on the functional and prognostic consequences of this heterogeneity, and the biological processes driving differential T-cell differentiation will be presented at the conference.

Keywords: tumor immunology, T-cell, single-cell multi-omics



OA15 PROFILING THE TUMOUR MICROENVIRONMENT OF LUNG CANCER METASTASIS
MONDAY, SEPTEMBER 9, 2024 - 15:30 - 16:45

OA15.05 Single-Cell Spatial Architectures of Paratumor Zone Determines the Prognosis of Multiple Lung Cancers

X. Yuan[1], Z. Wang[1], X. Zhang[2], Z. Gao[3], J. Xu[2], Y. Li[1], F. Yang[1], J. Wang[1], K. Chen[1], [1]Peking University People's Hospital, Beijing/CN ,[2]Kanghui Biotechnology Corporation, Beijing/CN ,[3]Infinity Scope Biotechnology Co. Ltd., Hangzhou/CN

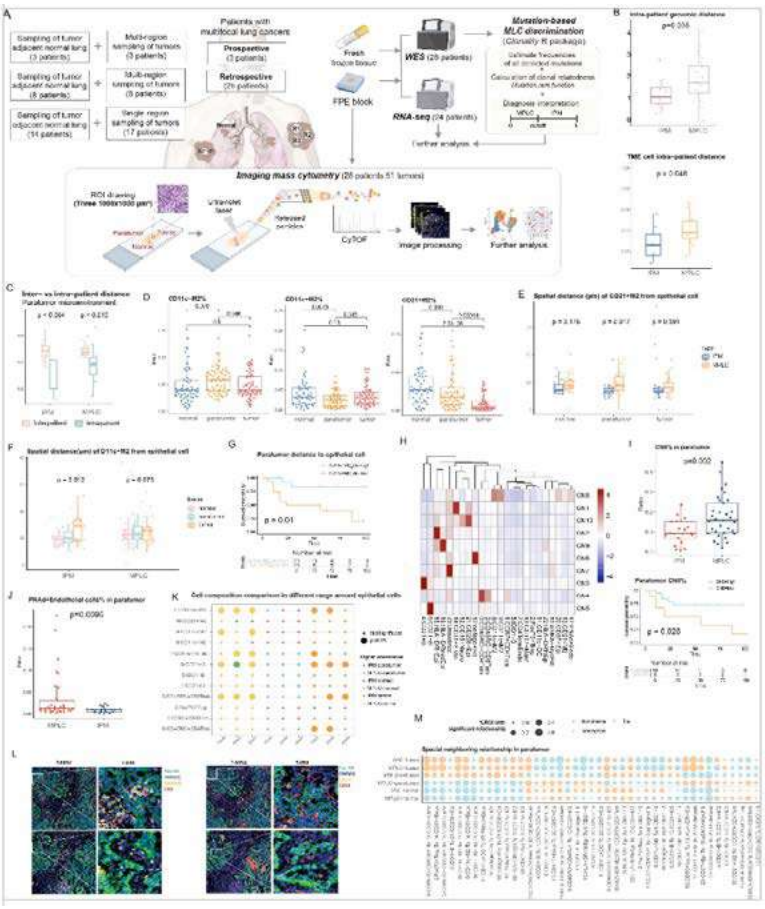
Introduction: Prognostic disparities have been observed within multiple lung cancers (MLCs), yet the underlying immune mechanisms remain elusive.

Methods: Twenty-eight patients with MLCs underwent surgical resection. Fifty-one tumors were subjected to imaging mass cytometry across the tumor region, paratumor zone, and adjacent normal tissue. Whole-exome sequencing and bulk RNA sequencing was also conducted. Multiple primary lung cancers (MPLC) and intrapulmonary metastases (IPM) were discriminated based on the mutation-derived probabilities of clonal relatedness.

Results: In comparison with MPLC, the architectures of tumor microenvironment are closer within IPM patients, reflecting the higher inter-tumor genomic similarity. MPLC paratumor regions exhibited greater similarity within individuals than between individuals, indicating the presence of field cancerization. Among the 23 cell subpopulations, the paratumor zone of MLCs is characterized by M2 macrophage compositions when compared with tumor and normal regions, demonstrating depleted CD11c+M2 and enriched CD11-M2 cells. CD21+M2 is another subset decreasing in the normal-paratumor-tumor sequence, which interacts with CCR7+CD4+ central memory T cell and IDO+B cells in MPLC paratumor area but avoids them in IPM. It's significantly closer to the malignant transforming epithelial cells in the IPM paratumor zone. The spatial distance between CD11c+M2 and paratumor epithelial cells in IPM is significantly less than that in the tumor, while the two are similar in MPLC, associated with worse disease-free survival (DFS). We further detected multicellular spatial organizations; one cell neighborhood characterized by three types of M2 macrophages is enriched in MPLC paratumor regions, and its abundance positively correlates with survival, a relationship that was not discovered in tumors. In addition, PNAd+Endothelial cells (representing tertiary lymphatic structure) are enriched in MPLC paratumor zone. CD45RO+CD8+ effective memory T cells, CD45RO+CD4+ effective memory T cells, and CD21- B cells also accumulates around epithelial cells (0-20μm range) of this region, which show strong interactions with malignant HLA-DRhigh epithelial cells, but displaying strong avoidance in IPM. These observations suggest the activation of anti-tumor immunity in MPLC paratumor zone against immune escape in IPM, explaining the superior prognosis of MPLC compared to IPM.

Conclusions: Our study highlights the parantumor immune microenvironment in the progression of MLCs.

Keywords: Multiple lung cancers, paratumor microenvironment, spatiomics



OA15 PROFILING THE TUMOUR MICROENVIRONMENT OF LUNG CANCER METASTASIS, MONDAY, SEPTEMBER 9, 2024 - 15:30 - 16:45

OA15.06 Spatiotemporal Genomic and Transcriptomic Analysis Reveal Molecular Landscape and Intratumoral Heterogeneity in Non-Smoking Lung Cancer

W. Wang, Y. He, K. Chen, Peking University People's Hospital, Beijing/CN

Introduction: Lung cancer is the world's leading cause of cancer death and its onset is largely attributable to direct tobacco exposure. However, its incidence in never-smokers remains a significant health problem globally. Previous studies on multiregion sequencing of lung cancer mostly focused on smokers, lacking a comprehensive analysis of lung molecular landscape in non-smokers. Hence, it is crucial to understand endogenous mutagen factors and intratumoral heterogeneity (ITH) underlying the unique characteristics of non-smoking lung cancer.

Methods: We performed comprehensive genomic and transcriptomic analysis of patient-matched early-stage lung cancer tumors, the predominant type of non-small cell lung cancer (NSCLC), and normal adjacent tissues obtained from Chinese CXDY cohort (n=127) representative of the non-smoking population. Compared to the Western smoking cohort (TRACERx cohort, n=421), we revealed the molecular landscape associated with early events and non-smoking-related processes in lung cancer.

Results: We sequenced the whole exome (127 patients, 389 regions) and transcriptome (115 patients, 304 regions) of CXDY lung cancer patients, which were characterized by a higher proportion of female (54.5%), subcapsular nodules (45.5%), adenocarcinoma (84.1%), and a lower proportion of smoking history (21.2%). These results indicate that there are significant differences in the epidemiological and clinicopathological characteristics of lung cancer between East and West. By constructing phylogenetic tree and calculating genome ITH, we revealed that Chinese NSCLC have more stable genomes characterized by higher SNV-ITH and lower SCNA-ITH. This difference is much stronger in smokers as compared to nonsmokers. Moreover, subclonal WGD events are more likely to occur in Chinese population than clonal WGD events. Compared with nonsmokers, mutations in smokers were significantly enriched in N MA (p=0.037) and NDR pathways (p=0.009). Transcriptional ITH was characterized by intratumour expression distance (I-TED), and it was found that smoking history and subclonal mutations (%) were important factors affecting I-TED, while subclonal SCNAs (%) were more important in TRACERx cohort. Transcriptome clustering of regions yielded two subtypes, C1 and C2. Non-smoking, female, stage I and adenocarcinoma were significantly concentrated in C1 subtype, which significantly involved in cell homeostasis and biological function. In contrast, C2 subtype are enriched in pathways related to DNA replication and cell division, suggesting poor prognosis. Immune-ITH was calculated using four common immunoinfiltration algorithms and found that non-smokers had significantly lower immune heterogeneity.

Conclusions: This study elucidated the comprehensive molecular structure and multi-omics ITH of non-smoking lung cancer, providing new insights into the development of treatment strategies for lung cancer.

Keywords: Non-smoking lung cancer, multiregion sequencing, molecular landscape

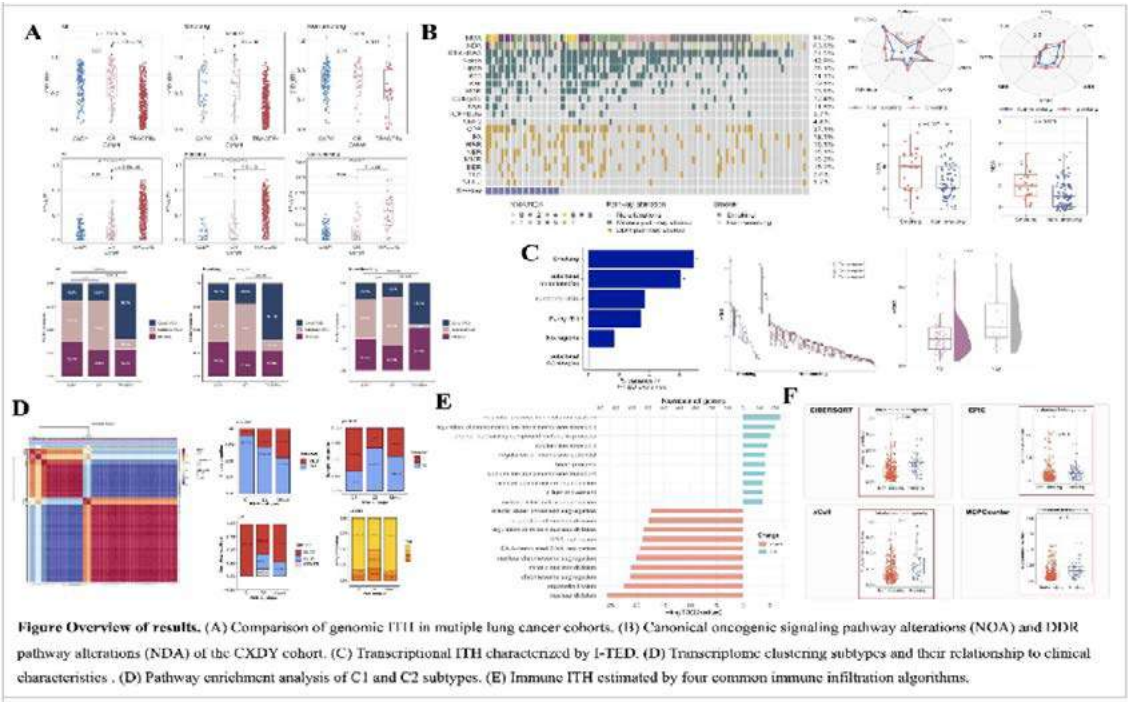


Figure Overview of results. (A) Comparison of genomic ITH in mutiple lung cancer cohorts. (B) Canonical oncogenic signaling pathway alterations (NOA) and DDR pathway alterations (NDA) of the CXDY cohort. (C) Transcriptional ITH characterized by I-TED. (D) Transcriptome clustering subtypes and their relationship to clinical characteristics . (D) Pathway enrichment analysis of C1 and C2 subtypes. (E) Immune ITH estimated by four common immune infiltration algorithms.

OA16 TRANSFORMING CANCER THERAPY: BIOMARKERS AND NOVEL ADCS
TUESDAY, SEPTEMBER 10, 2024 - 13:30 - 14:45

OA16.03 Telisotuzumab Vedotin in Asian Patients with C-Met Protein-Overexpressing Non-Squamous EGFR WT NSCLC: Results from LUMINOSITY

H. Horinouchi[1], J-Y. Hung[2], Z-Y. Ding[3], S-H. Lee[4], C. Liu[5], J. Looman[6], C. Ratajczak[6], H. Alhasani[6], M. Li[6], S. Xia[6], S. Lu[7], [1]National Cancer Center Hospital, Tokyo/JP ,[2]Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung/TW ,[3]West China Hospital, Chengdu/CN ,[4]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul/KR ,[5]The Affiliated Cancer Hospital of Xinjiang Medical University, Xingjiang/CN ,[6]AbbVie Inc., North Chicago/IL/USA ,[7]Shanghai Lung Cancer Center, Shanghai Chest Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai/CN

This abstract is under embargo until September 10 at 11:35 PDT.

OA16 TRANSFORMING CANCER THERAPY: BIOMARKERS AND NOVEL ADCS
TUESDAY, SEPTEMBER 10, 2024 - 13:30 - 14:45

OA16.04 Preliminary Results from a FIH Study of GQ1005, A Novel HER2-ADC, in Patients with Advanced HER2-Expressing Solid Tumors and HER2-Mutated NSCLC

C. Zhou[1], B. Yang[2], Y. Sun[3], W. Zhuang[4], L. Wang[5], T. Deng[6], X. Li[7], J. Zhang[8], Q. Wang[9], W. Li[1], Y. Yang[6], Q. Song[2], A. Xiong[10], [1]Shanghai Pulmonary Hospital, Shanghai/CN ,[2]The Fifth Medical Center of PLA General Hospital, Beijing/CN ,[3]Shandong First Medical University Affiliated Tumor Hospital, Shandong/CN ,[4]Fujian Cancer Hospital, Fuzhou/CN ,[5]Shandong First Medical University and Shandong Academy of Medical Sciences, Shandong/CN ,[6]Tianjin Medical University Cancer Institute and Hospital, Tianjin/CN ,[7]The First Affiliated Hospital of Zhengzhou University, Zhengzhou/CN ,[8]Fudan University Shanghai Cancer Hospital, Shanghai/CN ,[9]Henan Cancer Hospital, Affiliated Cancer Hospital of Zhengzhou University, Zhengzhou/CN ,[10]Shanghai East Hospital Affiliated to Tongji University, Shanghai/CN

Introduction: GQ1005 is an innovative antibody-drug conjugate that specifically targets HER2-expressing tumor cells using Topoisomerase I inhibitors (DXd) delivered through a stable and cleavable linker. Preclinical studies have shown that GQ1005 exhibits similar antitumor efficacy to Enhertu and better stability than Enhertu, with a notable absence of toxicity, suggesting a superior therapeutic profile. This report presents initial findings from an ongoing phase I clinical trial, which seeks to assess the safety, tolerability, pharmacokinetics, and antitumor efficacy of GQ1005 in patients with advanced solid tumors expressing HER2 and patients (pts) with HER2-mutated NSCLC.

Methods: Patients aged 18 years and older with locally advanced or metastatic solid tumors previously treated with standard therapy and with a measurable disease according to RECIST v1.1 criteria were included in the study. The Maximum Tolerated Dose (MTD) was determined using the Bayesian Optimal Interval (BOIN) design. GQ1005 was given intravenously at a specified dose (2, 4, 6, 7.2, and 8.4 mg/kg) Q3W until either intolerable toxicities occurring or disease progressed.

Results: As of March 26th, 2024, 131 patients with HER2-expressing or HER2-mutated advanced solid tumors predominantly in breast (70), lung (34) and gastric/gastroesophageal junction (19), were enrolled. Median age was 56 (from 34 to 74), and the patients had median 3 (range, 1-11) prior lines of anti-tumor therapies, 76% had an ECOG performance status of 1. The median exposure time of GQ1005 was 15.9 weeks (range 3.0-60.9). No DLT was observed in all doses, hence MTD was not achieved. Every patient experienced treatment-related adverse events (TRAEs). Drug-related AEs led to discontinuation in 6 patients (4.6%) and death in 1 patient (0.8%). The most common all-grade TRAEs (>15.0%) were elevated aspartate aminotransferase (41.2%), nausea (40.5%), anemia (35.1%), alanine aminotransferase increased (31.3%), leukopenia (26.0%), decreased appetite (26.0%), thrombocytopenia (25.2%), neutropenia (22.9%), vomiting (22.1%), fatigue (19.8%), proteinuria (17.6%), and dry eye (15.3%). Grade ≥3 TRAEs occurred in 21 patients (16.0%), including anemia (3.8%), decreased lymphocyte count (3.8%),γ-glutamyltransferase (GGT) increase (3.8%), leukopenia (2.3%), thrombocytopenia (1.8%) and nausea (0.8%) . Interstitial lung disease occurred in 12 patients (9.2%) and most of them were reported in 8.4mg/kg dose. Among 119 evaluable patients, 1 case had complete response, 52 cases achieved partial response, the unconfirmed ORR was 44.5%, and the unconfirmed DCR was 81.5%. In 34 patients with advanced HER2-mutated NSCLC with median age of 59.5 (range 38-74), 50% had prior ≥2 lines of anti-tumor therapies. No DLTs occurred and Grade ≥3 TRAEs were recorded in 6 pts (17.6%). AEs were manageable and tolerable, consistent with previous findings. 32 pts had at least 1 tumor assessment. Moreover, best tumor response was observed in 12/32 (37.5%) pts, and DCR was 90.6% (29/32).

Conclusions: Based on the initial data from the first-in-human trial, GQ1005 shows great potential for excellent tolerability and promising antitumor activity in patients with heavily pretreated HER2-expressing advanced solid tumors and HER2-mutated NSCLC. The phase Ib trial in four cohorts with a dose of 7.2 mg/kg is ongoing. (NCT06154343)

Keywords: a novel antibody-drug conjugate targeting HER2, GQ1005, HER2-mutated NSCLC

OA16 TRANSFORMING CANCER THERAPY: BIOMARKERS AND NOVEL ADCS
TUESDAY, SEPTEMBER 10, 2024 - 13:30 - 14:45

OA16.05 Trastuzumab Deruxtecan Monotherapy in Pretreated HER2-overexpressing Nonsquamous Non-Small Cell Lung Cancer: DESTINY-Lung03 Part 1

D. Planchard[1,2], H.R. Kim[3], T. Suksombooncharoen[4], R. Li[5], J. Samol[6,7,8], Y. Runglodvatana[9], K-Y. Lee[10], G-C. Chang[11,12,13], D. Kowalski[14], J-Y. Han[15], S. Saw[16,17], Y. Huang[18], A. Sookprasert[19], E. Nakajima[20], J. Alfon[21], Y-T. Chang[20], J.C-H. Yang[22,23], [1]Gustave Roussy, Villejuif/FR ,[2]Paris-Saclay University, Paris/FR ,[3]Division of Medical Oncology, Yonsei Cancer Center, Seoul/KR ,[4]Chiang Mai University, Chiang Mai/TH ,[5]St Luke's Medical Center, Quezon City/PH ,[6]Tan Tock Seng Hospital, Novena/SG ,[7]Johns Hopkins University, Baltimore/MD/USA ,[8]Nanyang Technological University, Novena/SG ,[9]Faculty of Medicine Vajira Hospital, Bangkok/TH ,[10]Shuang Ho Hospital, Taipei Medical University, New Taipei City/TW ,[11]Chung Shan Medical University, Taichung/TW ,[12]Chung Shan Medical University, Taichung/TW ,[13]Chung Shan Medical University Hospital, Taichung/TW ,[14]Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw/PL ,[15]National Cancer Center, Goyang/KR ,[16]National Cancer Center Singapore, Singapore/SG ,[17]Duke-National University of Singapore Medical School, Singapore/SG ,[18]National University Cancer Institute, Singapore/SG ,[19]Khon Kaen University, Khon Kaen/TH ,[20]AstraZeneca, Gaithersburg/MD/USA ,[21]AstraZeneca, Barcelona/ES ,[22]National Taiwan University Hospital, Taipei/TW ,[23]National Taiwan University Cancer Center, Taipei/TW

Introduction: Trastuzumab deruxtecan (T-DXd) 5.4 mg/kg is approved in several regions, including the US and EU, for patients with unresectable or metastatic human epidermal growth factor receptor 2 (HER2) mutant non-small cell lung cancer (NSCLC) who have received prior systemic therapy. HER2 overexpression in NSCLC is associated with limited treatment response and a poor prognosis. In DESTINY-Lung01, T-DXd monotherapy (5.4 mg/kg; n=41) demonstrated encouraging antitumor activity in extensively pretreated patients with unresectable and/or metastatic HER2-overexpressing (HER2-OE) NSCLC; the confirmed objective response rate (ORR) was 34.1% (95% confidence interval [CI] 20.1, 50.6). DESTINY-Lung03 (NCT04686305) is an open-label, multicenter, Phase 1b, multipart study evaluating T-DXd-based treatments in patients with HER2-OE NSCLC. Here, we report the efficacy and safety of T-DXd monotherapy in Part 1 of DESTINY-Lung03.

Methods: Patients with HER2-OE unresectable, locally advanced or metastatic NSCLC with disease progression on or after one or two prior regimens received T-DXd 5.4 mg/kg intravenously every 3 weeks. HER2-OE was defined as ≥25% of tumor cells with immunohistochemistry (IHC) 2+ or 3+ by central testing using the DAKO HER2-low IHC assay. The endpoints of the T-DXd monotherapy arm were investigator-assessed confirmed ORR, duration of response (DOR), and progression-free survival (PFS); overall survival (OS); and safety.

Results: At data cutoff (DCO; October 23, 2023), 36 patients with HER2-OE NSCLC had received T-DXd 5.4 mg/kg; median (range) duration of T-DXd total treatment was 7.2 (0.7-19.8) months and median (range) duration of follow up was 11.7 (1.4-21.2) months. Patients were predominantly female (61.1%) and from Asia (88.9%); median age (range) was 66.5 (47-80) years, and targeted therapy was the most common prior treatment modality (58.3%). Additional patient characteristics and safety data are in the table. The confirmed ORR was 44.4% (95% CI 27.9, 61.9), and median DOR was 12.2 (95% CI 5.5, not estimable) months. Median PFS was 8.2 (95% CI 6.7, 11.1) months and median OS was 14.7 (95% CI 14.6, not estimable) months. At DCO, the adjudication committee determined that there were no cases of drug-related interstitial lung disease/pneumonitis; adjudication committee review is ongoing. Updated efficacy and safety results will be available for the presentation.

Conclusions: T-DXd monotherapy (5.4 mg/kg) demonstrated encouraging antitumor activity in patients with pretreated advanced or metastatic HER2-OE NSCLC, consistent with results from DESTINY-Lung01. The safety profile was acceptable and generally manageable, consistent with the known profile of T-DXd.

Keywords: HER2 expression, Trastuzumab deruxtecan, Antibody-drug conjugate

Patient characteristics	**N=36***
Median age, years (range)	66.5 (47–80)
Sex, n (%)	
Male	14 (38.9)
Female	22 (61.1)
Region, n (%)	
Europe	3 (8.3)
Asia	32 (88.9)
US/South America	1 (2.8)
Smoking history, n (%)	
Current	3 (8.3)
Former	10 (27.8)
Never	23 (63.9)
Stage of disease, n (%)	
III	3 (8.3)
IV	30 (83.3)
Missing	3 (8.3)
ECOG performance status, n (%)	
0	12 (33.3)
1	24 (66.7)
CNS metastases present at baseline, n (%)	9 (25.0)
HER2 IHC status, n (%)	
IHC 3+	16 (44.4)
IHC 2+	20 (55.6)
Safety	
Drug-related adverse events, n (%)	34 (94.4)
Drug-related Grade ≥3 adverse events	15 (41.7)
Drug-related serious adverse events, n (%)	6 (16.7)
Drug-related adverse events leading to discontinuations, n (%)	2 (5.6)
Drug-related adverse event with outcome death, n (%)	1 (2.8)†

*Patients who received ≥1 dose of T-DXd; †neutropenic colitis. CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; T-DXd, trastuzumab deruxtecan

Table 1. Characteristics of Different MDC Cohorts

Characteristics	Eligible by US Preventive Services Task Force 2021 criteria			Ineligible
	1 LDCT	> 1 LDCT	0 LDCT	
	N = 79	N = 26	N = 803	N = 838
Demographics				
Age				
Median (Q1-Q3)	68(64-73)	72(69.25-75)	67(62-73)	71(61-79)
Sex, n (%)				
Female	44(55.7)	12(46.15)	368(45.83)	445(53.1)
Male	35(44.3)	14(53.85)	435(54.17)	393(46.9)
Race, n (%)				
White	65(82.28)	22(84.62)	556(69.24)	536(63.96)
Black	13(16.46)	4(15.38)	239(29.76)	255(30.43)
Ethnicity, n (%)				
Hispanic/Latino	0	0	11(1.37)	25(2.98)
Not Hispanic/Latino	77(97.47)	26(100)	784(97.63)	780(93.08)
Insurance, n (%)				
Medicare	52(65.82)	23(88.46)	533(66.38)	521(62.17)
Medicaid	3(3.8)	0	23(2.86)	17(2.03)
Commercial	24(30.38)	3(11.54)	229(28.52)	280(33.41)
Self-Insured	0	0	18(2.24)	20(2.39)
Clinical factors				
Smoking status, n (%)				
Active	52(65.82)	16(61.54)	492(61.27)	208(24.82)
Quit	27(34.18)	10(38.46)	311(38.73)	406(48.33)
Never	0	0	0	200(23.87)
Unknown	0	0	0	25(2.98)
Charlson comorbidity score, n (%)				
0	16(20.25)	4(15.38)	148(18.43)	297(35.44)
1	47(59.49)	16(61.54)	443(55.17)	369(44.03)
2	16(20.25)	6(23.08)	212(26.4)	172(20.53)
Cancer and treatment				
Clinical stage, n (%)				
Stage I	55(69.62)	20(76.92)	287(35.74)	324(38.67)
Stage II	6(7.59)	1(3.85)	105(13.08)	85(10.14)
Stage III	10(12.66)	3(11.54)	183(22.79)	178(21.24)
Stage IV	8(10.13)	2(7.69)	228(28.39)	251(29.95)
Histology, n (%)				
Adenocarcinoma	49(62.03)	12(46.15)	352(43.84)	452(53.94)
Squamous	22(27.85)	11(42.31)	284(35.37)	196(23.39)
Small cell	3(3.8)	2(7.69)	80(9.96)	67(8)
Primary tumor size (mm)				
Median (Q1-Q3)	20(15-32.25)	15(12-22)	34(20-55)	30(18-46.25)
Treatment, n (%)				
Surgery Alone	35(44.3)	11(42.31)	160(19.93)	170(20.29)
Any Surgery	47(59.49)	13(50)	294(36.61)	299(35.68)
Number of LDCT scans before diagnosis, n (%)				
0	0	0	803(100)	838(100)
1	79(100)	0	0	0
2	0	14(53.85)	0	0
>= 3	0	12(46.15)	0	0
Duration for first LDCT scan to lung cancer diagnosis, days				
Median (IQR)	57(29-205)	915(492-1210)		
Duration from last LDCT to lung cancer diagnosis				
Median (IQR)		96(49-248)		
Overall Survival (95% CI)				
1-Year Aggregate	92(86, 98)	96(88, 100)	70(67, 74)	74(70, 77)
3-Year Aggregate	79(69, 90)	90(77, 100)	49(45, 53)	56(53, 61)
5-Year Aggregate	72(60, 87)	90(77, 100)	41(37, 45)	49(45, 54)
Adjusted Hazard Ratio (age, sex, race, insurance, smoking status, Charlson co-morbidity score)				
Aggregate	0.37(0.23, 0.61)	0.16(0.04, 0.66)	Ref	0.92(0.78, 1.08)
p-Value	0.0001	0.0106		0.3125

OA17 INCREASING ACCESS TO EARLY LUNG CANCER DETECTION
TUESDAY, SEPTEMBER 10, 2024 - 13:30 - 14:45

OA17.03 Missed Opportunities for Early Lung Cancer Detection in a Multi-Disciplinary Thoracic Oncology Clinic Cohort

W.T. Liao[1], A.T. Patel[1], F. Caro[1], J. Roma[1], W. Marshall[1], J. Goss[1], C. Fehnel[1], A. Mehrotra[1], O. Ogbeide[1], P. Lammers[1], k. Tonkin[2], J. Machin[2], M. Ray[3], M.P. Smeltzer[3], R.U. Osarogiagbon[1], [1]Baptist Cancer Center, Memphis/TN/USA ,[2]Baptist Memorial Hospital, Memphis/TN/USA ,[3]University of Memphis, Memphis/TN/USA

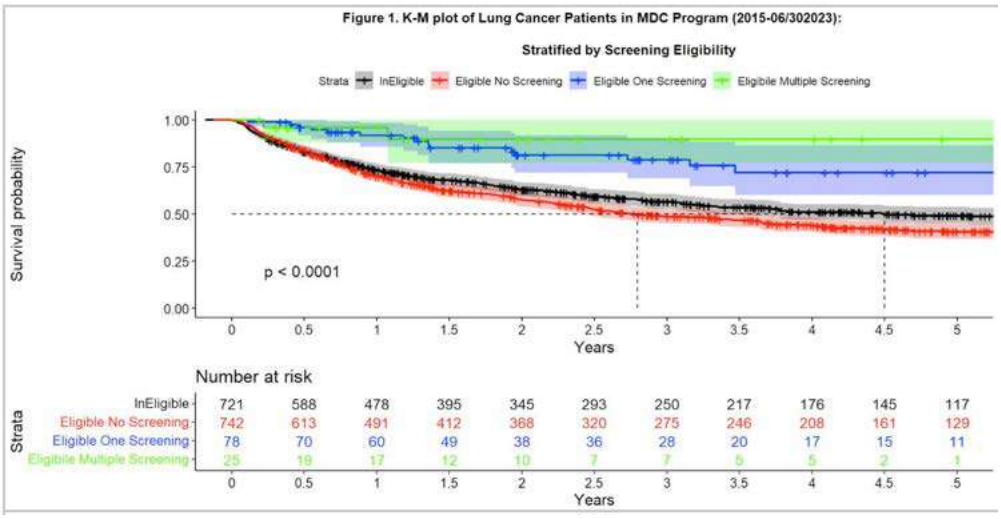
Introduction: Lung cancer screening (LCS) reduces mortality, but few eligible patients undergo screening; adherence to subsequent screening rounds is low; eligibility criteria disqualify many people who develop lung cancer. We quantified these barriers in a community cohort.

Methods: We retrospectively evaluated all patients diagnosed with lung cancer from 2015-2023 in a Multi-disciplinary Thoracic Oncology Program. Patients categorized as: eligible, 1 low-dose CT scan (LDCT) before diagnosis; eligible, >1 LDCT done; eligible, no LDCT ('missed opportunity cohort' [MOC]); ineligible for LCS. We compared overall survival (OS) between groups with adjusted hazard ratios (aHR) from proportional hazards models controlling for age, sex, race, insurance, smoking history and Charlson co-morbidity scores.

Results: Of 1,746 patients, 4.5%, 1.5%, 46.0% and 48.0% had 1 LDCT, >1 LDCT, were MOC, and ineligible for LCS, respectively. Among the MOC, 71% were seen in the healthcare system in the 24 months preceding lung cancer diagnosis. Among those ineligible for screening, 24% had never smoked, 62% had insufficient pack-year history or excessive quit duration, 11% were age-ineligible.Age, race, and clinical characteristics across groups are shown in Table. Treatment was surgery alone in 44% v 42% v 20% v 20%, and included surgery (with or without other modalities) in 59% v 50% v 37% v 36%, respectively. OS differed significantly by group (Figure, Table). In multivariable analysis, using the MOC for reference, the aHR were: 0.37(0.23-0.61) for single screening, 0.16(0.04-0.66) for multi-screened and 0.92(0.78-1.08) for ineligible cohorts.

Conclusions: Mismatch between eligibility criteria and true risk was the biggest barrier to LCS; missed opportunity to screen eligible patients was the second largest barrier. The MOC had the worst OS and most had clinical encounters within 2 years of diagnosis. Patients whose cancer was diagnosed after >1 LDCT had better OS than those diagnosed after one LDCT.

Keywords: Barriers, Screening, Early Stage



OA17 INCREASING ACCESS TO EARLY LUNG CANCER DETECTION
TUESDAY, SEPTEMBER 10, 2024 - 13:30 - 14:45

OA17.04 Implementation of a Natural Language Processing (NLP) Model to Detect Incidental Lung Nodules in a Nationwide Health Care Network

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Introduction: Lung cancer is one of the leading causes of morbidity and mortality worldwide, with late diagnosis contributing to its high lethality rate. Lung cancer screening has shown an overall survival benefit, but its implementation in Brazil is incipient and has many challenges. In this study, we report the first results of an NLP model developed and implemented in a nationwide healthcare network to detect incidental suspicious nodules in chest computed tomography (CT) scans.

Methods: A previously validated NLP approach was applied to chest CT reports in 11 hospitals located in two Brazilian States. The developed algorithm identifies suspicious lesions with a minimum diameter of 6mm associated with pre-defined risk descriptors, including comparative changes. Data were collected from November 2022 to August 2023. All reports identified as positive were referred to a nurse navigator and, if indicated, to an appointment with a multidisciplinary thoracic oncology team. Here, we report the results obtained from one hospital in São Paulo city selected for the pilot study, utilizing the navigation strategy within optimized deadlines (maximum five days), being followed up through a digital communication platform (Redcap).

Results: The program evaluated a total of 67,599 chest CT reports, and 1,212 cases (1.79%) were identified for follow-up investigation in the 11 hospitals. In the specific pilot hospital unit in São Paulo city, 140 CT scans (1.26%) were captured for follow-up out of 11,108 CT scans evaluated. Of these, 104 patients (64.5%) attended consultations with specialists. Seventy-two follow-up CT scans were performed, and 45 patients are still in the program. Fourteen patients (13.4%) underwent transthoracic CT-guided biopsy, of which eight were diagnosed with surgically treatable lung cancer. Two patients were considered inoperable and referred for non-surgical treatment. The confirmation rate of neoplastic diagnosis in incidental findings was approximately 11.57%, with 57% of diagnosed cases eligible for curative surgical treatment.

Conclusions: These first results indicate that the developed NLP algorithm has effective applicability in detecting suspicious lung lesions, with a significant rate of early-stage lung cancer diagnoses. With the implementation of well-defined workflows, it is possible to streamline the investigation and follow-up process of suspicious cases, allowing for earlier diagnoses and a more effective therapeutic approach. This strategy can potentially complement a challenging lung cancer screening program in a continental country like Brazil. Further investigations will address the false-positive rate and long-term patient outcomes.

Keywords: screening, artificial intelligence, lung cancer

OA17 INCREASING ACCESS TO EARLY LUNG CANCER DETECTION
TUESDAY, SEPTEMBER 10, 2024 - 13:30 - 14:45

OA17.05 A Randomized Controlled Trial of a Digital Lung Health Intervention to Facilitate Smoking Cessation and Lung Cancer Screening

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Introduction: A sub-analysis of the National Lung Screening Trial data found that screening with low-dose computed tomography (LDCT) combined with smoking cessation nearly doubled the benefit in reducing lung cancer deaths compared to LDCT screening alone. Despite the fact that US and International guidelines recommend LDCT screening for eligible candidates, uptake remains low. Most research has focused on integrating smoking cessation into lung cancer screening programs. Engaging individuals who are smoking and at high-risk for lung cancer and educating them about LDCT screening is a critical next step to promote lung health. This study tested the efficacy of a digital counseling intervention (video-call counseling, nicotine replacement therapy, digital personal stories and LDCT decision-aide) compared to standard care (brief advice, quitline referral and LDCT decision-aide) on 7 and 30-day point prevalence abstinence (PPA) rates at 3 and 6-months after study entry and lung cancer screening adoption at 6-months.

Methods: Community-based adults who were smoking > 5 cigarettes/day and eligible for lung cancer screening were recruited using multiple methods including Facebook ads across 19 states during the height of covid-19. Data including demographics, tobacco use, and lung health were collected electronically. Participants were randomized on a 1:1 ratio to the intervention (Digital) vs. standard care (Brief) arms after the baseline assessment. Self-reported and biochemically verified 7 and 30-day PPA rates were obtained at 3 and 6-months after entry to the study. Fisher exact test and Wilcoxon rank-sum test were used for analyses. Intent-to-treat analyses examined differences in self-reported 7 and 30-day PPA at 3 and 6-months between the arms.

Results: One hundred-fifty-three participants were randomized to the Digital (n=75) or the Brief (n=78) arms. Mean age of participants was 62.7 years (SD 4.7), 75.7% were female, 93.4% were white, and 27.9% had < high school education. The average age for smoking initiation was 16.4 years (SD 3.2), mean pack-year history was 43.1 (SD 7.7), and 38.1% of participants indicated that they were ready to quit smoking. Overall, 35.3% were extremely worried about getting lung cancer and 61.1% were not aware of or hadn't thought about getting lung cancer screening. As compared to the Brief arm: the Digital intervention had higher rates of self-reported 7-day PPA at 3 (52% vs. 20%, p<0.001) and 6-months (43% vs.13%, p< 0.001); higher rates of self-reported 30-day PPA at 3 (40% vs. 12%, p<0.001) and 6-months (38% vs. 14%, p=0.004); and had higher rates of biochemically verified 7-day PPA at 3 (32% vs. 15%, p=0.008) and 6-months (24% vs.10%, p=0.03). Participants in the Digital arm also had higher rates of lung cancer screening completion at 6-months after study entry (46.7% vs. 22.6%, p<0.001) as compared to the Brief arm.

Conclusions: The Digital intervention increased smoking cessation and receipt of lung cancer screening compared to the Brief arm (standard care) during covid-19. Facebook was the most effective recruitment method. This intervention can be scaled up and implemented broadly across the US to promote lung health, earlier detection of lung cancer and ultimately decreased mortality from lung cancer.

Keywords: lung cancer screening, smoking cessation, digital intervention

OA17 INCREASING ACCESS TO EARLY LUNG CANCER DETECTION
TUESDAY, SEPTEMBER 10, 2024 - 13:30 - 14:45

OA17.06 Impact of Using Smoking Duration in Place of Pack-Years as Eligibility Criteria for Lung Cancer Screening to Reduce Racial and Ethnic Disparities

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Introduction: In 2021, the United States Preventive Services Task Force (USPSTF) expanded the lung cancer (LC) screening eligibility criteria by lowering minimum cumulative smoking exposure from 30 to 20 pack-years. Despite this, underrepresented minorities (e.g., African American adults) - who exhibit higher LC incidence at lower cumulative intensity but over longer duration - still experience disparity in LC screening eligibility when using pack-years. Consequently, smoking duration has been proposed as an alternative criterion and shown to reduce the screening disparity between African American and White adults. However, potential disparities across other racial groups when using this measure is unknown.

Methods: We used data from 105,261 adults with smoking history from the prospective, population-based Multiethnic Cohort Study (MEC), which enrolled five US racial and ethnic groups (African American, Japanese American, Latino, Native Hawaiian, and White). We evaluated screening eligibility under the 2021 USPSTF criteria, i.e., USPSTF-2021, (≥ 20 pack-years, ≤15 quit-years, and age 50-80) and identified a smoking duration threshold (smoking duration >30 years, ≤15 quit-years, and age 50-80, i.e., 'duration-based criteria') yielding eligibility closest to USPSTF-2021. Racial disparity was evaluated by calculating eligibility-to-incidence ratio (E-I ratio) by race and ethnicity. Sensitivity, specificity, and number needed to screen (NNS) over six years were used as screening performance indicators. Risk model-based criteria based on a well-established model recently calibrated for race (PLCOm2012update) was also evaluated.

Results: The cohort was 18.3% African American, 25.9% Japanese American, 20.3% Latino, 7.9% Native Hawaiian, and 25.9% White adults. The overall 6-year LC incidence rate was 1.4%. The overall USPSTF-2021 eligibility rate was 24.0%, with >30 years smoking duration threshold yielding the most comparable eligibility rate (27.5%). Under USPSTF-2021, a large disparity was observed especially among African American adults compared to White adults with a 53% lower E-I ratio (E-I ratio: 9.5 vs. 20.3). This disparity was substantially reduced using duration-based criteria (E-I ratio: 13.6 vs. 19.3) while retaining overall screening performance vs. USPSTF-2021 (sensitivity 66.1% vs. 57.7%, specificity 73.0% vs. 76.5%, and NNS 30 vs. 30). After matching eligibility rate of duration-based criteria (using 6-year risk ≥ 1.1%), risk-based criteria further minimized disparities and increased screening performance across all racial and ethnic groups (sensitivity 72.0%, specificity 73.1%, NNS 28, E-I ratio in African Americans vs. Whites 17.5 vs. 21.0, see Table).

Conclusions: Smoking duration could reduce LC screening disparity without compromising screening performance, but risk model-based screening may be superior to either duration-based or USPSTF-21 criteria.

Keywords: Lung cancer screening, Racial disparities, Eligibility criteria

Table. E-I ratio and screening performance of lung cancer screening criteria based on USPSTF 2021 guidelines, smoking duration and risk model by race and ethnicity groups

	Overall cohort			White			African American		
Screening Criteria*	USPSTF-21	Duration-based	Risk model-based	USPSTF-21	Duration-based	Risk model-based	USPSTF-21	Duration-based	Risk model-based
% Eligible	24.0	27.5	27.5	30.2	28.8	31.3	21.4	30.4	39.3
E-I ratio	17.3	19.8	19.8	20.3	19.3	21.0	9.5	13.6	17.5
Sensitivity (%)	57.7	66.1	72.0	70.2	70.7	79.9	44.0	60.9	70.6
Specificity (%)	76.5	73.0	73.1	70.4	71.8	69.4	79.2	70.3	61.4
NNS	30	30	28	29	28	27	22	23	25
	Latino			Native Hawaiian			Japanese American		
Screening Criteria	USPSTF-21	Duration-based	Risk model-based	USPSTF-21	Duration-based	Risk model-based	USPSTF-21	Duration-based	Risk model-based
% Eligible	15.7	25.1	14.4	25.1	26.1	28.2	25.5	26.5	25.3
E-I ratio	21.1	33.7	19.3	16.8	17.5	18.9	22.0	22.9	21.9
Sensitivity (%)	53.5	69.8	59.7	55.2	60.8	64.0	62.5	67.3	72.4
Specificity (%)	84.6	75.3	86.0	75.3	74.4	72.3	75.0	73.9	75.3
NNS	40	49	33	31	29	30	36	35	31

Abbreviations. Eligibility-Incidence ratio (E-I ratio); United States Preventive Services Task Force (USPSTF); Number needed to screen (NNS)

Footnotes:
* Duration-based criterion was determined using smoking duration > 30 years threshold in place of 20 pack-years in USPSTF 2021 guidelines, which yielded eligibility rate closest to that of USPSTF 2021 guidelines; Risk model-based criterion was determined using 6-year risk ≥ 1.1% threshold, which yielded the same eligibility rate as duration-based criterion above.

OA18 PLEURAL, MEDIASTINAL AND UNDIFFERENTIATED THORACIC CANCERS
TUESDAY, SEPTEMBER 10, 2024 - 15:00 - 16:15

OA18.03 Real-World Data on the Efficacy and Safety of Lenvatinib in Patients with Previously Treated Thymic Carcinoma

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Introduction: The efficacy and safety of lenvatinib in patients with previously treated thymic carcinoma were explored in the REMORA trial, however, there is scarce data in actual clinical settings.

Methods: We performed a retrospective, multicenter study of consecutive patients with advanced or recurrent thymic carcinoma who received lenvatinib between March 23, 2021, and October 31, 2022. The primary outcome was the objective response rate (ORR) to second- or later-line treatment. Setting the threshold and expected value of the primary outcome at 25% and 38%, the planned sample size was 80 patients. We performed subgroup analysis based on whether patients met the key eligibility criteria for the REMORA trial.

Results: In total, 107 patients from 31 institutions across Japan were enrolled, with 87 receiving lenvatinib as second- or later-line chemotherapy. The median age of these 87 patients was 64 years (range, 38-79), and 56 (64%) were males. The histological type of 71 patients (82%) was squamous cell carcinoma. Seventy-seven patients (89%) had a prior history of taxane-platinum combination chemotherapy. Fifty-one patients (59%) met the REMORA trial eligibility criteria. The median observation period was 13.2 months (interquartile range, 8.8-18.9). Of the 87 patients, 81 patients with target lesions were included in the primary outcome analysis. Among these 81 patients, ORR was 30% (90% confidence interval [CI]: 21.3-39.1). Respective ORR values for patients who met or did not meet the REMORA trial eligibility criteria were 28% and 31%. Among the 87 patients, the disease control rate was 92% (95% CI: 84.1-96.7). The median progression-free survival was 10.2 months (95% CI: 7.0-13.2). The median overall survival was not reached (NR; 95% CI: 18.0-NR). Treatment-related adverse events of any grade occurred in 87 patients (100%), the most common being hypertension (75%), proteinuria (66%), and fatigue or malaise (56%). Grade 3 or higher adverse events occurred in 56 patients (64%), the most common being hypertension (22%), proteinuria (17%), and decreased platelet count (10%). Drug-induced interstitial lung disease occurred in two patients (2%): one patient with grade 2 and one patient with grade 3. Adverse events leading to dose interruption or dose reduction occurred in 75 patients (86%), the most common being proteinuria (23%), hypertension (21%), palmar-plantar erythrodysesthesia syndrome (16%), and decreased platelet count (16%). Adverse events leading to treatment discontinuation occurred in 20 patients (23%), the most common being anorexia (6%), left ventricular systolic dysfunction (2%), and fatigue or malaise (2%). Two patients (2%) died from adverse events, one from arterial thromboembolism and one from pleural infection.

Conclusions: These findings suggest that lenvatinib as a second- or later-line treatment for patients with advanced or recurrent thymic carcinoma is effective but may be less effective in real-world clinical practice than in the REMORA trial. No new safety signals were observed. There was no positive correlation between efficacy and meeting the key eligibility criteria for the REMORA trial. Further investigations are needed to identify factors that influence lenvatinib efficacy. Clinical study information: UMIN000051645.

Keywords: thymic carcinoma, lenvatinib, real-world

OA18 PLEURAL, MEDIASTINAL AND UNDIFFERENTIATED THORACIC CANCERS
TUESDAY, SEPTEMBER 10, 2024 - 15:00 - 16:15

OA18.04 Pembrolizumab Plus Lenvatinib in Second-Line Pleural Mesothelioma Patients: A Single Arm Phase II Study (PEMMELA Cohort 2)

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Introduction: In the recent findings of PEMMELA cohort 1, the combination of pembrolizumab, an anti-PD-1 antibody, plus lenvatinib, a multi tyrosine kinase inhibitor, showed clinical activity in patients with pleural mesothelioma (PM) who were pre-treated with chemotherapy. The objective response rate (ORR) in that study (58%), was the highest achieved for patients with PM in later-line thus far. As nivolumab plus ipilimumab immunotherapy (nivo-ipi) is currently approved as first-line treatment in patients with PM, we aimed to evaluate clinical activity and toxicity of pembrolizumab plus lenvatinib after first-line nivo-ipi. To our knowledge, this is one of the first studies investigating immunotherapy after progression on immunotherapy in patients with pleural mesothelioma.

Methods: PEMMELA cohort 2 is a prospective single-center, single-arm, open-label, investigator-initiated phase 2 trial of pembrolizumab (200 mg once every three weeks intravenously) plus lenvatinib (20 mg once daily orally) in patients with PM who progressed after nivo-ipi (n=20). Main eligibility criteria were age 18 years or older, histologically proven PM, ECOG PS 0-1, and measurable disease according to the modified Response Evaluation Criteria in Solid Tumors (mRECIST) version 1.1 for PM. Treatment continued up to two years or until unacceptable toxicity or disease progression occurred. The primary endpoint was ORR (proportion of patients with complete response (CR), or partial response (PR)) assessed by the local investigator, taking into account the immunotherapy related rules for response evaluation of iRECIST. Secondary endpoints included safety, disease control rate (DCR) at three and six months, progression-free survival (PFS) and overall survival, as well as ORR and PFS determined by an independent radiologist. (ClinicalTrials.gov, NCT04287829).

We hypothesized that the combination treatment would result in 25% ORR in comparison with 5% response rate using anti-PD-1 monotherapy. The null hypothesis that true response rate is 5% could be rejected with 90% confidence if at least three of 20 patients had an objective response.

Results: Between November 2022 and March 2024, all patients were included. At the data cut-off (31 January, 2024), only 17 patients had received enough cycles of treatment to evaluate response and toxicity. Preliminary results showed that eight patients had reached PR as best overall response (47.1%, 95% CI 23.0-72.2%, p<0.0001), of which 5 a confirmed PR (29%, 95% CI 10.3-56.0%, p=0.001). Eleven (65%) patients developed grade 3-4 treatment-related adverse events (AE's), of which most common grade 3 events were hypertension (29%), malaise (12%), and musculoskeletal pain (12%). No grade 5 events occurred. Six treatment-related serious adverse events were observed in five patients. Thirty-nine% of the patients required at least one dose reduction due to toxicity. Updated results of all patients will be presented at the congress.

Conclusions: This study met its primary endpoint, showing very promising clinical activity of pembrolizumab plus lenvatinib also in patients with PM who progressed after nivolumab plus ipilimumab.

Keywords: mesothelioma, pembrolizumab, lenvatinib

OA18 PLEURAL, MEDIASTINAL AND UNDIFFERENTIATED THORACIC CANCERS
TUESDAY, SEPTEMBER 10, 2024 - 15:00 - 16:15

OA18.05 Neoadjuvant Versus Adjuvant Therapy for Locally Advanced Esophageal Squamous Cell Carcinoma: A Randomized Clinical Trial

Y. Zhu[1,2], X. Sun[3], L. Wu[1,2], Q. Chen[4], Q. Wei[5], P. Ye[6], S. Han[2], X. Yu[2], J. Liu[4], Q. Zhao[4], Y. Jiang[4], X. Zhou[4], W. Zhang[7], W. Mao[4], Y. Xu[1,2], [1]Shanghai Pulmonary Hospital, Shanghai/CN ,[2]The Cancer Hospital of the University of Chinese Academy of Sciences (Zhejiang Cancer Hospital), Hangzhou/CN ,[3]The Cancer Hospital of the University of Chinese Academy of Sciences (Zhejiang Cancer Hospital), Department of Radiation Oncology/CN ,[4]The Cancer Hospital of the University of Chinese Academy of Sciences (Zhejiang Cancer Hospital), Shanghai/CN ,[5]The Second Affiliated Hospital, Zhejiang University School of Medicine, Shanghai/CN ,[6]The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou/CN ,[7]Fudan University, Shanghai/CN

Introduction: Although neoadjuvant concurrent chemoradiotherapy (NCCRT) followed by surgery is the standard-of-care for locally advanced esophageal squamous cell carcinoma (ESCC) in the Western world, adjuvant sequential chemoradiotherapy (ASCRT) remains a primary choice in China. The current study (NEOTERIC Trial) aimed to investigate whether NCCRT followed by surgery is superior to surgery followed by ASCRT for locally advanced ESCC in the Chinese population.

Methods: Patients with clinically resectable, locally advanced (cT1-2N1M0 or T3-4N0-1M0) ESCC were randomly assigned to receive either NCCRT or ASCRT. The primary endpoint was disease-free survival (DFS); secondary endpoints included overall survival (OS), R0 resection rate, and toxicities.

Results: From April 2012 to November 2016, 204 patients were randomly assigned to either NCCRT (n=100) or ASCRT (n=104) arm. NCCRT significantly improved median DFS from 14.0 months to 51.0 months (hazard ratio [HR], 0.652; 95%CI, 0.467-0.910; P=0.010). The 1-year, 3-year, and 5-year DFS rates in the NCCRT group were 76.0%, 54.5%, and 46.6%, compared with 53.6%, 33.9, and 30.0%, respectively, in the ASCRT group. The median OS for patients receiving NCCRT was 79.0 months (95% CI, not estimated [NE]-NE) and 38.0 months (95%CI, 23.7-52.3) with ASCRT (HR, 0.660; 95%CI, 0.456-0.953; P=0.025). The OS rates at 1, 3, and 5 years were 88.9%, 68.7%, and 56.7% in the NCCRT arm, compared with 85.6%, 50.8%, and 39.5%, respectively, in the ASCRT arm. A significant improvement in the R0 resection rate was observed after NCCRT compared with ASCRT (96.6% vs. 85.6%; P=0.012). The in-hospital mortality rates were 3.4% in the NCCRT arm and 1.9% in the ASCRT arm (P=0.662).

Conclusions: NCCRT, compared with ASCRT, demonstrated improvements in DFS with acceptable toxicities in Chinese resectable locally advanced ESCC.

Keywords: neoadjuvant chemoradiotherapy, adjuvant chemoradiotherapy, esophageal squamous cell carcinoma

OA18 PLEURAL, MEDIASTINAL AND UNDIFFERENTIATED THORACIC CANCERS
TUESDAY, SEPTEMBER 10, 2024 - 15:00 - 16:15

OA18.06 Characteristics and Outcomes of Patients with SMARCA4-Deficient Undifferentiated Thoracic Tumors

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Introduction: SMARCA4-deficient undifferentiated thoracic tumors (UT) are a recently defined group of highly aggressive cancers in which the effectiveness of standard treatments for non-small cell lung cancer is unknown. We analyzed the clinical and pathologic characteristics and outcomes of a multicenter cohort of patients with SMARCA4-deficient UT.

Methods: We collected clinical and demographic variables from five academic institutions for patients whose tumors met the criteria for SMARCA4-deficient UT (undifferentiated morphology and loss of SMARCA4/BRG1 by immunohistochemistry) described in the 5th Edition (2021) WHO Classification of Thoracic Tumours.

Results: We identified 92 patients with SMARCA4-deficient UT. Median age was 65 (range 32 to 89); 63% were men and 70% were white. Only 3% had never smoked cigarettes; the remaining with a tobacco history had median 40 pack-year exposure. 58 patients (63%) had stage IV disease at diagnosis, with an additional 16 (17%) developing recurrent/metastatic disease. Patients diagnosed with early-stage disease (7% stage I, 7% stage II, 24% stage III) had metastatic recurrence at median 8 months (range 1.7 to 78 months, IQR 13.9). Of tumors tested for PD-L1, 9/55 (16%) had expression ≥ 50% and 24 (44%) were negative. Tumor mutational burden was available in 48 cases (52%); median was 10.5 mutations/megabase (range 1.6 to 48). Next-generation sequencing was performed in 65 cases (71%). Relevant mutations of interest included those in SMARCA4 (75%), TP53 (72%), KEAP1 (26%), STK11 (18%), and KRAS (17%). Of the patients with metastatic disease, 58 (78%) received first-line systemic treatment. Seven of 16 (44%) who did not were considered too ill to receive treatment at presentation. Median number of lines in the metastatic setting was 1 (range 0 to 5). Patients most commonly received combination chemotherapy and immunotherapy (41%), followed by chemotherapy (33%), immunotherapy monotherapy or doublet (16%), and agents on a clinical trial (7%). Median time on first-line treatment was 1.2 months (IQR 4 months). Median progression-free survival (PFS) for patients with metastatic disease receiving first-line treatment was 1.7 months. Patients who received immunotherapy (doublet or monotherapy) as first-line treatment had median PFS 3.0 months, those who received chemotherapy-immunotherapy had median PFS 1.7 months, and those who received chemotherapy alone had median PFS 1.5 months. Median overall survival (OS) from metastatic diagnosis was 6.7 months. There were five patients who experienced durable responses (≥ 2 years) without progression: two of these received combination chemotherapy and PD-1 inhibitor, two received PD-1 inhibitor monotherapy, and one received PD-1/CTLA-4 inhibitor doublet immunotherapy. PD-L1 expression was high in only one of these patients. TMB ranged from 9.1 to 31.6 in these tumor samples.

Conclusions: This multi-institution retrospective cohort analysis revealed a population of patients with highly clinically aggressive disease, with exceptionally short progression-free survival to standard therapies and poor overall survival upon diagnosis. Clinicians treating patients with this disease should be aware of the possibility of rapid progression on standard therapies, though a small proportion of patients may demonstrate remarkable response to immunotherapies. Early enrollment in prospective clinical trials should be considered.

Keywords: SMARCA4-deficient undifferentiated thoracic tumors, Real world data, Clinical outcomes

MINI ORAL ABSTRACT SESSIONS

MA01 ADVANCES IN TREATMENT FOR STAGE III NSCLC
SUNDAY, SEPTEMBER 8, 2024 - 14:00 - 15:15

MA01.03 Neoadjuvant Alectinib in Potentially Resectable Stage III ALK-Positive NSCLC: Interim Analysis of ALNEO-GOIRC-01-2020 Phase II Trial

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Introduction: Stage III Non-Small Cell Lung Cancer (NSCLC) is a heterogeneous group of tumors with a wide spectrum of clinical presentations and no single definitive therapeutic approach. The role of neoadjuvant alectinib in stage III ALK-positive NSCLC is still unclear. We designed a phase II, open-label, single-arm, multicenter study aimed at investigating the activity and safety of alectinib in potentially resectable locally advanced stage III ALK-positive NSCLC patients (ALNEO trial, EUDRACT number 2020-003432-25).

Methods: Treatment-naïve patients with potentially resectable stage III ALK-positive NSCLC, ECOG PS≤1 were registered to receive neoadjuvant alectinib for 2 cycles (8 weeks) followed by surgery and adjuvant alectinib for 24 cycles (96 weeks). The primary endpoint was major pathological response (MPR). Secondary endpoints included pathological complete response (pCR), objective response (OR), event-free survival (EFS), disease-free survival (DFS), overall survival (OS), adverse events (AEs). According to the Simon's two stage design (P0=20%, P1=40%), an interim analysis was conducted to test if at least 5 major pathological responses (MPR) were documented among the first 18 enrolled patients.

Results: To date, the results are available in 25 patients registered in 20 Italian Oncology Centers from May 2021. Median age was 56 years (Interquartile Range [IQR], 49-67 years), 17 (68%) patients were female and 14 (56%) were never smokers. Clinical stage according to the 8th AJCC TNM was IIIA in 14 (56%) and IIIB in 11 (44%) patients. The most represented stage was T3N2 (n=6, 24%), followed by T1aN2 (n=4, 16%) and T4N2 (n=4, 16%). All the patients completed the neoadjuvant phase and 21 (84%) underwent surgery, which consisted of lobectomy in 17 (81%), pneumonectomy in 2 (9.5%) and other surgery in 2 (9.5%) patients. Among patients who completed surgery, R0 was achieved in 18 (86%) patients. Overall, an OR was observed in 17 of 25 (68%) patients. In the interim analysis population, MPR was achieved in 7 (39%) patients and pCR in 3 (17%) patients. Presently, adjuvant treatment was started in 17 (68%) patients with a median interval from surgery of 5.1 weeks (IQR, 2.7-6.0 weeks). After a median follow-up of 10.8 months (IQR, 5.6-22.5 months), median EFS, DFS and OS were not reached. None of the patients experienced treatment-related Grade≥3 AEs during neoadjuvant phase.

Conclusions: Results of the first stage interim analysis allowed to continue the accrual in order to reach the total of 33 planned patients. Neoadjuvant alectinib appeared to be safe in potentially resectable locally advanced stage III ALK-positive NSCLC patients. The study is partially supported by Roche S.p.A.

Keywords: Neoadjuvant alectinib, Stage III, ALK positive

MA01 ADVANCES IN TREATMENT FOR STAGE III NSCLC
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MA01.04 AFT-46: CHIO3: Chemotherapy Combined with Immune Checkpoint Inhibitor for Operable Stage IIIA/B Non-Small Cell Lung Cancer

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Introduction: The optimal treatment of Stage IIIA/B (N2) NSCLC remains undefined given impressive outcomes with chemoradiation followed by immunotherapy as well as neo-adjuvant or peri-operative chemoimmunotherapy with surgical resection. In other stage III NSCLC trials, nodal downstaging after neoadjuvant therapy has been associated with improved survival. This trial focused on operable stage III (N2) NSCLC and uniquely sought to evaluate N2 nodal clearance (N2NC) rates after treatment with chemotherapy and durvalumab as the primary endpoint. NCT04062708

Methods: This was an open-label, single arm phase 2 trial including participants from 9 US hospitals. Eligible patients had surgically resectable stage III NSCLC with pathologically proven N2 disease, PS 0-1. N3 and EGFR mutation were exclusionary. Patients received 4 cycles of platinum doublet + durvalumab followed by lobectomy or greater, optional postoperative radiation to 54 Gy, and adjuvant durvalumab Q4 weeks for one year. The primary endpoint was an increase in N2NC (ypN0) from a historical rate of 30% with platinum doublet chemotherapy to 50%.

Results: Planned accrual was 55 patients with 42 patients undergoing resection and thus evaluable for N2 status. DSMB recommended study closure as the primary endpoint was met on interim analysis. 37 patients were enrolled and are evaluable for safety; 1 is currently receiving neoadjuvant therapy. 29 patients underwent resection. Reasons for coming off study before surgery were: 4 progressive disease, 2 toxicity. One patient was found to be ineligible after receiving 1 cycle of treatment. N2NC was 75.9%, 95%CI: 56.5-89.7% (22/29 surgical patients) (Table). Pathologic complete response was noted in 8/29 patients (27.6%). R0 resection was achieved in 27/29 patients (93.1%).

Conclusions: Neoadjuvant durvalumab plus chemotherapy followed by resection is an effective strategy for stage III (N2) NSCLC, with N2NC more than twice the historical ypN0 rate with platinum doublet alone. In this locally advanced group with proven N2 disease of NSCLC, surgical resection after chemoimmunotherapy was feasible with low rates of perioperative toxicity and high rates of R0 resection (93.1%).

Keywords: Stage 3 (N2) lung cancer, perioperative immunotherapy, locally advanced NSCLC resection

Characteristics		**N=37**	**Percent**
Histology	Squamous	11	29.7%
	Adenocarcinoma	25	67.5%
	Large Cell/NE	1	2.7%
AJCC 8th edition cTNM	cT1N2	14	37.8%
	cT2N2	11	29.7%
	cT3N2	10	24.3%
	cT4N2	2	5.4%
RESULTS:			
Total enrolled		37	
Patients off study before surgery		7	18.9%
Patients currently on neoadjuvant therapy		1	2.7%
Surgical Resection		29/36	80.6%
	Lobectomy	27/29	93.1%
	Pneumonectomy	2/29	6.9%
Resection Completeness	R0	27/29	93.1%
	R1	2/29	6.9%
	R2	0/29	0%
Surgical Approach	Thoracotomy	11/29	37.9%
	VATS	2/29	6.9%
	Robotic	16/29	55.2%
N2NC		**22/29**	**75.9%**
Path CR		8/29	27.6%

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MA01.05 Efficacy and Safety of Neoadjuvant Camrelizumab and Apatinib Combined with Chemotherapy in Stage IIIA (N2) NSCLC: A Single Arm, Phase II Trial

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Introduction: Camrelizumab (an anti-programmed cell death protein-1 antibody) combined with apatinib (an antiangiogenic agent) has conferred benefits for advanced non-small cell lung cancer (NSCLC). This study aimed to assess the efficacy and safety of camrelizumab and apatinib alongside chemotherapy in patients with resectable stage IIIA (N2) NSCLC as neoadjuvant therapy.

Methods: In this phase II trial, patients with histologically confirmed resectable stages IIIA (N2) NSCLC received the combination of chemotherapy, camrelizumab (200 mg, q3w) and apatinib (250 mg, once daily). Patients underwent surgery after 2-3 cycles of treatment. The primary endpoint was the major pathological response (MPR) rate. Secondary endpoints included pathological complete response (pCR) rate, R0 resection rate, objective response rate (ORR) and safety. This trial was registered with ChiCTR.org.cn (ChiCTR2200059608), and is ongoing but no longer recruiting patients.

Results: Between August 4, 2021 to September 2, 2023, among 29 patients who received neoadjuvant therapy, 19 underwent complete resection. The disease control rate and ORR was 86.2% (95% CI: 72.2%-97.8%) and a downstaging rate of 20.7% (95% CI: 6.9%-36.4%). In the subgroup of 19 patients who underwent surgery, the MPR rate was 36.8% (95% CI: 16.3%-58.7%), and the pCR rate was also 36.8% (95% CI: 16.3%-58.7%). Nonsurgical grade 3/4 adverse events (AEs) were reported in 19 (65.5%) of the 29 patients, with the most common AEs being leukopenia (31.0%), thrombocytopenia (17.2%), rash (17.2%) and fatigue (13.8%). Survival results were not reported due to immature data.

Conclusions: Camrelizumab plus apatinib combined with chemotherapy showed clinically meaningful anti-tumor activity and manageable safety, with few hematologic toxicities, and might be a potential treatment option in patients with resectable stage III NSCLC.

Keywords: Neoadjuvant Immunotherapy, Antiangiogenic therapy, Efficacy

MA01 ADVANCES IN TREATMENT FOR STAGE III NSCLC
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MA01.07 Long-Term Analysis of NRG-LU001, Randomized Phase II Trial of Concurrent Chemoradiotherapy (ccrt) -/+ Metformin in Locally Advanced NSCLC.

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Introduction: The highly active glycolytic metabolism of non-small cell lung cancer (NSCLC) is an attractive target for metabolic therapies. NRG-LU001 (NCT02186847) was a phase II trial that found that the addition of anti-diabetic agent metformin, a mitochondrial inhibitor, to the standard of care cCRT did not improve 1-year progression-free survival (PFS) in locally advanced (LA)-NSCLC. Here, we present the long-term analysis with 5-year follow-up.

Methods: Stage IIIA/B NSCLC, unresected, non-diabetic, patients were randomized (1:1) to either carboplatin-paclitaxel chemotherapy concurrent with chest RT (60Gy), followed by consolidation carboplatin-paclitaxel chemotherapy (Control Arm) or the same and oral metformin (2000mg daily) during cytotoxic therapy (Experimental Arm). The primary endpoint of this trial was 1-year PFS. Secondary outcomes included overall survival (OS), rates of local-regional and distant failure, and rates of adverse events. PFS and OS were estimated with the Kaplan-Meier method; local-regional progression and distant metastasis were estimated using the cumulative incidence method. Adverse events (AEs) were graded with CTCAE v.4.0. Exploratory landmark analysis was conducted to mitigate immortal bias when evaluating outcomes among patients compliant with metformin.

Results: A total of 170 patients were accrued and randomized between Aug. 2014 and Dec. 2016. As of Sep. 2023, minimal additional toxicity was reported and no significant difference was detected in the rates or grade of toxicity between the two arms.1- 2- and 5-year PFS was 60.4%, 40.3% and 29.2% in Control [(95%CI: 48.5, 70.4); (95%CI: 29.2, 51.1); (95%CI: 19.3, 39.7)] vs 51.3%,34.5% and 24.3% in the Metformin arm [(95%CI: 39.8, 61.7), (95%CI: 24.2, 45.1) and (95%CI: 15.5, 34.3)], respectively, (multivariable Cox proportional HR=1.21(95%CI: 0.84, 1.75), p=0.152). OS at 2- and 5-years was 65.3% and 38.1% for Control [(95% CI:53.6, 74.7); (95%CI: 27.1, 49.0)] vs 65.3% and 41.2% for the Metformin arm [(95%CI: 53.1, 74.5); (95%CI: 30.1, 52.0)], respectively, (HR=1.04 (95%CI:0.71, 1.53) p=0.828. Deaths due to disease were 76.5% vs 63.0%, respectively. No significant differences were found in the rates of local-regional and distant failures. In a posthoc analysis investigating the role of metformin compliance, a landmark analysis was conducted among those who survived 3 months or longer. 74 patients received no metformin, 46 patients received >95%of the protocol-recommended drug dose, and 31 received <95% of the recommended dose. 2- and 5-year OS rates in those three groups were 68.1%and 39.7% [(95%CI: 56.0, 77.5), (95%CI:28.3, 50.8)], 75.9% and 55.2% [(95%CI:60.7, 85.9), (95%CI:39.4, 68.4)] and 51.6% and 22.6% [(95%CI:33.0,67.4), (95%CI:10.0, 38.3)], respectively. No formal statistical comparison was made given the exploratory nature of this analysis.

Conclusions: NRG-LU001 long-term outcomes show that oral daily metformin was well-tolerated in combination with cCRT treatment for LA-NSCLC. In the per-protocol analysis, metformin did not improve PFS and OS and did not alter the rates of local-regional failure or distant metastasis. Nevertheless, long-term OS outcomes in this trial compare favorably to those of control and interventional arms of recently reported trials. The impressive OS rates detected in patients of the metformin arm who adhered to the protocol-recommended drug dose warrant further investigation in future studies.

Keywords: Unresected LA-NSCLC, Chemo-radiotherapy, Metformin

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MA01.08 Five-Year Clinical Outcomes of Perioperative Nivolumab and Chemotherapy in Stage III Non-Small-Cell Lung Cancer (NADIM Trial)

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Introduction: Perioperative immunotherapy has shown to improve short-term outcomes for resectable NSCLC patients. However, the long-term benefits still remain unclear. Our study presents the 5-year survival outcomes of the NADIM I trial (NCT03081689).

Methods: NADIM was an open-label, multicenter, single-arm phase 2 trial involving 18 participant hospitals in Spain designed to investigate the feasibility, safety and efficacy of perioperative chemoimmunotherapy in 46 resectable stage IIIA (7th edition) NSCLC patients. Three cycles of neoadjuvant chemotherapy (intravenous paclitaxel and carboplatin) in combination with nivolumab were administered. After surgery, adjuvant intravenous nivolumab monotherapy was administered for 1 year. The 5-year survival outcomes and biomarker analysis were secondary objectives.

Results: According to the analysis of the intent to treat (n= 46) population, the five-year progression-free survival rate was 65.0% (95%CI 49.4-76.9) and the overall survival rate was 69.3% (95%CI 53.7-80.6). The 5-year PFS and OS rates considering only cancer-specific events, were 75.8% (95% CI 60.6-58.8) and 82.2% (95% CI 67.6-90.7), respectively. Patients who achieved complete pathological responses (CPR) showed a significant increase in their 5-year PFS and OS rates, reaching 92.0% (95%CI 70.5-97.9) and 95.8% (95%CI 73.9-99.4), respectively. Moreover, low ctDNA burden at baseline (i.e. SumMAF<1%), ctDNA clearance (i.e. undetectable ctDNA after neoadjuvant treatment), and high adjuvant treatment compliance (i.e received ≥50% of scheduled adjuvant cycles) were associated to better long-term survival. PD-L1 tumor proportion score and tumor mutational burden (TMB) were not associated with 5-year survival outcomes. Additionally, no deaths related to treatment, safety data or unexpected long-term toxicities were observed. PD-L1 tumor proportion score and tumor mutational burden (TMB) were not associated with 5-year survival outcomes. Additionally, no deaths related to treatment, no concerning safety data or unexpected long-term toxicities were observed

Conclusions: These results demonstrate robust long-term benefit of perioperative chemo-immunotherapy in resectable stage IIIA NSCLC patients, with no reported long-term toxicities, reinforcing the use of this therapeutic approach in the future. The study also highlights the importance of complete pathological responses and ctDNA status as prognostic biomarkers in these patients.

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MA01.09 Definitive Chemoradiation Followed by Immunotherapy vs. Surgery for cT4N2M0 NSCLC: A Contemporary Nationwide Analysis.

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Introduction: The optimal treatment regimen for cT4N2(IIIB) NSCLC, remains debated. PACIFIC-2 recently reported higher than expected treatment mortality and disappointing DFS, suggested to be due to a preponderance of T4 tumors and need for large radiation fields. Given these results, it is conceivable that surgery may be preferred in carefully selected cT4N2 patients.

Methods: Using the National Cancer Database (2015-2020) we identified patients with cT4N2M0 NSCLC (8thEdition AJCC) who received definitive chemoradiation (54-66 Gy) followed by immunotherapy (PACIFIC) (started within 90 days of chemoradiation) or curative-intent surgery in the setting of a multimodality treatment approach (salvage resections >150 days after chemoradiation excluded). We used logistic regression to identify associations with the use of surgery. After propensity-matching to adjust for differences among groups (age, sex, race, comorbidities, type of facility, and tumor site) overall survival was compared using the Kaplan-Meier method.

Results: A total of 1,908 patients were identified of whom 918 (48.1%) underwent PACIFIC and 990 (51.9%) underwent surgery. Patients who underwent surgery were younger (median 65 vs. 66 years, p<0.001), more often white (85.5% vs. 81.4%, p=0.013), and more likely had no comorbidities (Charlson-Deyo Index=0 65.3% vs. 56.5%, p<0.001) than those who received PACIFIC. In multivariable analysis, female sex (aOR 1.36, 95%CI 1.03-1.80), income above national median (aOR 1.40, 95%CI 1.04-3.52), adenocarcinoma histology, (reference: squamous; aOR 1.49, 95%CI 1.19-1.99,) non-central tumors (reference: central tumors; right tumor: aOR 1.49, 95%CI 1.19-1.99 and left tumor 2.84, 95%CI 1.54-5.23,) and treatment at an academic facility (aOR 1.38, 95%CI 1.03-1.86) associated with increased use of surgery. As expected, later years of diagnosis associated with decreased used of surgery (aOR 0.19, 95%CI 0.16-0.22). A total of 875 (88.4%) patients in the surgery group had a lobectomy, with negative margins in 83.1%(Fig-1A). After matching (1:1, PACIFIC vs. surgery), 1,422 patients were evaluated. Those in the surgery cohort had improved survival compared to the PACIFIC cohort (HR 0.81, 95%CI 0.68-0.95)(3-Yr OS: 60.9% vs. 52.9%, Median OS 54.4 vs. 40.4, p=0.011). In subgroup analysis, the OS benefit was more robust in patients who received neoadjuvant/perioperative approach (N=409)(HR 0.70, 95%CI 0.58 to 0.85)(3-Yr OS: 64.8%, Median OS: not-reached, p<0.001) (Fig 1B).

Conclusions: In selected patients, surgery is associated with improved overall survival compared to chemoradiation followed by immunotherapy. While we need prospective data to validate these findings, clinical stage IIIB(N2) patients should be considered for perioperative regimens in multidisciplinary tumor boards.

Keywords: Stage III NSCLC, Perioperative approach, Definitive chemoradiation and immunotherapy

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MA01.11 Unveiling Gene Expression and Immune Contexture in Stage II/III NSCLC Patients Receiving Neoadjuvant Pembrolizumab and Chemotherapy

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Introduction: Neoadjuvant chemo-immunotherapy (NCIT) has the potential to mitigate surgery-induced immunosuppression, thereby improving surgical and survival outcomes of non-small cell lung cancer (NSCLC) patients who present resectable lesions. Nevertheless, there is an unmet clinical demand to identify promising biomarkers through coordinated immune and molecular profiling.

Methods: We performed whole transcriptome sequencing on 26 baseline and 24 surgical samples obtained from 26 patients histologically diagnosed with stage II/III resectable NSCLC who received neoadjuvant pembrolizumab and chemotherapy followed by complete surgery. Our analysis focused on elucidating gene expression patterns and immune cell characteristics within the tumor microenvironment (TME), aiming to decipher their correlation with pathological complete response (pCR) and clinical outcomes, including event-free survival (EFS), disease-free survival (DFS), and overall survival (OS).

Results: Baseline pCR tumors demonstrated upregulated expression of immunomodulator genes, including HLA-C (P=0.02), HLA-E (P=0.01), and B2M (P=0.08) involved in antigen presentation, BTN3A1 (P=0.04) and CD274 (P=0.03) in co-inhibitory pathways, and HMGB1 (P=0.01) in innate immune regulation, compared to non-pCR tumors. In post-NCIT surgical samples from pCR patients, increased expression of IGHD, LILRA6, and ICOSLG was observed, all associated with positive regulation of immune response, while the expression of CEACAM6 participating in cell adhesion and tumor progression was decreased. Additionally, baseline pCR tumors showed higher TMEscore (P=0.09) and infiltration of activated dendritic cells (P=0.06), along with an elevated proportion of naïve B cells in surgical samples of pCR patients. Although plasma cell and NK cell populations consistently decreased in surgical samples compared to baseline tumors regardless of pathological response, non-pCR patients exhibited greater infiltration of CD8+ T cells (P<0.01) and increased immune cell penetration (P<0.001) in surgical samples, indicating a persistent anti-tumor response. Notably, baseline MGAT5B expression predicted pathological response (area under the curve: 0.86) and correlated with shorter DFS and EFS (both P=0.03). Surgical CEACAM6 levels served as an adverse biomarker for DFS and EFS (P=0.03 and P=0.04). A similar trend was observed for OS, although the difference between patients with or without these gene expression signatures did not reach statistical significance, presumably due to restraint sample size.

Conclusions: Our research reinforces the use of pCR as a surrogate endpoint in neoadjuvant settings. Moreover, the identification of molecular biomarkers linked to pathological and survival outcomes provides valuable insight to inform optimal treatment decision-making, guide postoperative therapy, and improve the chances of curing for stage II-III patients with resectable NSCLC.

Keywords: Neoadjuvant chemo-immunotherapy, Tumor immune landscape, Pathological complete response

MA01 ADVANCES IN TREATMENT FOR STAGE III NSCLC
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MA01.12 Survival Outcomes and Pathologic Response after Chemo-Immunotherapy in Resectable NSCLC: An Individual Patient Data Meta-Analysis

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Introduction: Neoadjuvant chemoimmunotherapy has reshaped the treatment landscape for resectable NSCLC, yet the prognostic significance of pathologic response remains unclear. We conducted a systematic review and individual patient data metanalysis to evaluate the impact of achieving pCR or MPR on EFS and assessed the influence of adjuvant immunotherapy.

Methods: This is an individual patient data metanalysis of randomised clinical trials of neoadjuvant or perioperative anti-PD-(L)1 in combination with platinum-based chemotherapy in patients with resectable NSCLC. IPD was extracted from Kaplan-Meier curves for pCR and/or MPR of the included studies. Survival outcomes were compared between patients achieving pCR or MPR and those who did not, considering both intention-to-treat and resected populations.

Results: Achieving pCR or MPR was associated with improved EFS across all trials (pCR, HR 0.12, 95% CI 0.07-0.20; MPR, HR 0.19, 95% CI 0.14-0.28, respectively, fig.1) with a 24 months EFS rate for patient who achieved pCR of 94% and 87% for those with MPR (p=0.222). Independently from pCR status patients who were randomised to an experimental arm that included adjuvant immunotherapy, did not show improved EFS in ITT and resected population (p=0.222 in pts achieving pCR for no-adjuvant vs adjuvant; p=0.678 for pts with no-pCR for no adjuvant vs adjuvant).

Conclusions: Our study showed a significant survival benefit in patients who achieved either pCR or MPR after neoadjuvant chemo-immunotherapy. No differences in survival were found between pCR and MPR patients. Additionally, the use of adjuvant immunotherapy after tumour resection did not improve survival outcomes in both patients with or without pCR.

Keywords: Neoadjuvant, Chemo-immunotherapy, pCR

MA01 ADVANCES IN TREATMENT FOR STAGE III NSCLC
SUNDAY, SEPTEMBER 8, 2024 - 14:00 - 15:15

MA01.13 Adherence to Treatment Protocol of Patients Submitted to Neoadjuvant (Chemo) Immunotherapy in Resectable NSCLC: Ameta Analysis

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Introduction: Neoadjuvant immunotherapy (IO) alone or associated with standard chemotherapy in resectable non-small-cell lung cancer (NSCLC) is currently an area of great interest. Data regarding the adherence to treatment protocols of neoadjuvant treatments including IO will guide the definition of the best course of treatment. We performed a metanalysis including studies on the use of IO neoadjuvant protocols in resectable NSCLC to evaluate the adherence rate to the treatment and surgical outcomes.

Methods: A systematic review of PubMed and Embase with meta-analyses was performed. Included studies were prospective clinical trials of preoperative IO alone or in combination with chemotherapy in resectable NSCLC. Research cutoff was March 2023. Two authors (P.B. and F.G.) independently and in duplicate screened the abstracts of all publications obtained by the search strategies to identify studies. Primary outcomes were adherence to medical treatment (calculated as omission of therapy rate, incomplete therapy rate, omission of surgery rate) and postoperative outcomes (R0 rate and microscopically uncomplete resection rate).

Results: We included 27 studies with a total of 2656 patients. 21 studies were phase 2, 6 phase 3 and one phase 1b. All studies were started in the time frame between 2013 and 2020. In 17 studies IO was associated to chemotherapy per protocol. Figure 1 reported the list of the studies included.As expected, almost all patients received at least one administration of therapy (omission of therapy 0%, 95% CI 0.00-0.01), while 7% of patients received and incomplete number of cycles according to the protocol (95% CI 0.04-0.10, figure 1). Surgery was not performed in the 13% of patients (95% CI 0.10-10.16, figure 1). In those patients who received induction therapy and surgical resection R0 was reached in 94% of cases (95% CI 0.93-0.96) while a macroscopic complete resection or an explorative intervention was reported in 2% of patients (95% CI 0.02-0.03).

Conclusions: The adherence to treatment protocols appears to be a critical point in NSCLC patient's candidate to radical surgery. Data from the present literature showed a low incomplete therapy rate. Nonetheless, 13% of patients could not receive surgical resection. In those patients who concluded the neoadjuvant and surgical treatment, surgical results were satisfactory with a 94% rate of R0.Our data show that IO neoadjuvant treatment currently has an acceptable adherence rate with good surgical results. A better definition of neoadjuvant duration and doses might further improve adherence results.

Keywords: Immunotherapy, Neoadjuvant therapy, surgery

MA02 INNOVATION IN LUNG CANCER SCREENING AND EARLY LUNG CANCER DETECTION
SUNDAY, SEPTEMBER 8, 2024 - 15:30 - 16:45

MA02.03 Circulating T Cell Receptor Repertoire Analysis Improves Cancer Early Detection

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Introduction: Cancer screening by liquid biopsy promises to detect cancer early when it can be cured. However, current liquid biopsy approaches based on circulating tumor DNA (ctDNA) detect only a minority of early-stage cancers, because these tumors shed little ctDNA and plasma sample volume is limited. For liquid biopsy to realize its potential for the early detection of cancer, sensitivity for the earliest stage disease must be improved. (This abstract is an update of an abstract previously presented at the AACR 2024 annual meeting.)

Methods: We set out to improve sensitivity of liquid biopsy for cancer early detection by exploiting tumor recognition by T cells through sequencing of the circulating T cell receptor repertoire. Using gDNA extracted from blood buffy coats, we studied a cohort of 439 lung cancer patients (86% with stage I disease) and 553 subjects without cancer, enriched for older individuals with a history of smoking. We performed genomic DNA TCR beta chain sequencing to yield a median of 80,921 TCR clonotypes in cancer patients and 112,083 clonotypes in non-cancer controls. We built a TCR sequence similarity nearest neighbor graph to cluster 69M distinct TCR clonotypes into TCR repertoire functional units (RFUs). The TCR frequencies of RFUs were tested for association with cancer status and significantly associated RFUs were combined using a support vector machine model into a TCR RFU cancer score. This model was evaluated by 10-fold cross-validation (CV) and compared to a ctDNA panel of 237 mutation hotspots in 154 lung cancer driver genes (IDT™) and to a panel of 17 lung cancer related protein biomarkers (Olink®) in 86 subjects.

Results: We identified 197 cancer-associated TCR RFUs at FDR≤0.10, including 110 RFUs that were enriched in cancer samples with a TCR count log2-fold change between 0.06 and 0.61, and 87 that were enriched in controls with a log2-fold change between 0.07 and 0.40. We observed 77 of the 110 cancer-enriched RFUs had decreasing TCR counts with increasing age across the cohort, coupled with the higher counts in cancer patients relative to age-matched controls. The TCR RFU cancer score achieved a cross-validated test ROC AUC of 0.70 for cancer status prediction, with the AUC for stage I cancers exceeding that of stage II-IV (0.71 vs. 0.64). 49% of stage I cancers (test samples of each CV fold) were detected by the TCR model at a specificity of 80%. We saw a substantial gain in sensitivity for stage I cancer when TCR RFUs were added to ctDNA and proteins, with a ~20%-point increase seen at the 90% target specificity level typical for cancer screening tests. Interestingly, sensitivity was not improved by addition of TCR analysis for later stage (II-IV) lung cancer, highlighting the already strong performance of existing plasma analytes for the detection of later stage disease.

Conclusions: We demonstrate detection of a significant fraction of early lung cancer cases from blood by analyzing the circulating TCR repertoire and show that this signal is complementary to established analytes such as proteins and ctDNA.

Keywords: early detection, liquid biopsy

MA02 INNOVATION IN LUNG CANCER SCREENING AND EARLY LUNG CANCER DETECTION
SUNDAY, SEPTEMBER 8, 2024 - 15:30 - 16:45

MA02.04 High Detection Rate of Blood MicroRNA Test in Lung Cancer Screening Eligible Individuals

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Introduction: Low dose computed tomography (LDCT) lung cancer screening (LCS) can reduce mortality in high-risk individuals, but the majority of heavy smokers proved to be reluctant to undergo radiologic examinations. A non-invasive blood test might circumvent this problem, as it happened with PSA in prostate cancer. The BioMILD trial aimed to test the contribution of blood microRNA assay to LDCT screening in heavy smokers.

Methods: We have evaluated here the diagnostic efficacy of a LCS strategy offering baseline LDCT and one annual repeat only to individuals with positive microRNA assay. Non LCS-eligible BioMILD participants, below the age of 55 years, were excluded from this analysis.

Results: From the total cohort of 3139 participants, 781 (24.9%) had a positive microRNA assay, and among them 37 LCs were detected at 2 years, representing 58.7% of all detected LCs, and 56.5% of stage I/II. LC incidence was 4.7% in microRNA+ and 1.1% in microRNA- subjects (P<0.0001). With the same reimbursement of 120€ given for every blood assay and LDCT, the cost of each detected LC would be approximately 12,000€ for standard LCS and 15,000€ for miRNA based LCS.

Conclusions: In the subset of LCS eligible BioMILD participants, upfront blood microRNA assay showed a high sensitivity for LC detection, particularly in early-stage disease, with reasonable costs. Such a non-invasive blood test strategy might contribute to improve LCS recruitment of heavy smokers aged 55 years or older.

Keywords: screening, blood biomarkers, microRNA

		Total	MSC -	MSC+	P-VALUE
		3139	2358 (75.1%)	781 (24.9%)	
LC within 2 years		**63**	**26 (41.3%)**	**37 (58.7%)**	**<0.0001**
Stage	I/II	46 (73.0%)	20 (43.5%)	26 (56.5%)	0.5581
	III/IV	17 (27.0%)	6 (35.3%)	11 (64.7%)	
Histology	Adenocarcinoma	42 (66.7%)	21 (50.0%)	21 (50.0%)	0.0600
	Other	21 (33.3%)	5 (23.8%)	16 (76.2%)	

MA02.05 Inter-Reader Agreement of AI Versus Human Readers in Baseline LDCT Lung Nodule Classification; A UKLS Trial Dataset Sub-Study

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Introduction: Lung cancer screening is a public health focus, with an increasing number of implementation studies, regional, and national programs commencing each year. This has led to a substantial rise in the number of LDCT scans which radiologists need to analyse. AI is being proposed as a solution, especially if it can be used as a first-read-filter to accurately rule-out negative cases where no, or only small lung nodules are present. A key challenge in the analysis of lung nodules on LDCT scans is the high variability in nodule measurement and classification. Therefore we evaluated inter-reader agreement of AI compared to human readers when performing solid (component) nodule classification in a UKLS trial LDCT scan dataset.

Methods: Four manual readers with varying levels of experience (medical researcher to senior radiologist) and AI independently analysed 1253 baseline LDCT scans from the UK lung cancer screening trial. An expert panel reference standard read was performed (blinded from individual results) to serve as a reference standard, against which everything else was judged. In the case of multiple nodules per participant the 'dominant' non-calcified solid component nodule was selected for further analysis. This nodule was categorised based on a 100mm3 threshold, the upper mean threshold for benign nodule growth. Kappa analysis was performed to determine inter-reader agreement between all reads and the reference standard.

Results: From 1253 baseline LDCT scans, the reference standard read categorised 616 (65%) as negative; no nodules or <100mm3. Overall agreement on nodule classification between all human readers, AI, and consensus was moderate (kappa 0.559 [95%CI 0.544-0.573]). An overview of agreement between each read can be seen in Table 1. Substantial inter-reader agreement was only found between readers 3 and 4 (kappa 0.704), and between AI and the reference standard read (kappa 0.757).

Conclusions: Overall inter-reader agreement for the classification of the 'dominant' solid (component) non-calcified lung nodule per participant was moderate, however AI showed potential to have substantial agreement with an experienced expert panel. AI could therefore help standardise lung nodule classification on baseline LDCT scans in a lung cancer screening setting.

Keywords: LDCT lung cancer screening, Artificial intelligence, Workforce

Table 1. *Overview of inter-reader agreement of individuals reads (human readers, AI, and expert reference panel)*

	Reader 1	Reader 2	Reader 3	Reader 4	AI	Reference
Reader 1		0.531	0.537	0.525	0.513	0.600
Reader 2			0.603	0.561	0.465	0.595
Reader 3				**0.704**	0.489	0.525
Reader 4					0.468	0.525
AI						**0.757**
Reference						

**Highlighted are the reads with substantial agreement*

MA02 INNOVATION IN LUNG CANCER SCREENING AND EARLY LUNG CANCER DETECTION
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MA02.07 AI as Primary Reader in 4-IN-THE-LUNG-RUN Lung Cancer Screening Trial: Impact on Negative Misclassification and Referral Rate

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Introduction: Lung cancer screening (LCS) with low-dose computed tomography (LDCT) has shown significant mortality reduction among high-risk individuals. Artificial intelligence (AI) is commonly used as a secondary or concurrent reader in LCS, while its role as the primary reader can primarily reduce radiologist workload by effectively ruling out negative cases. Our study evaluates AI as a primary reader in the European 4-IN-THE-LUNG-RUN (4ITLR) LCS trial, comparing its false-negative (FN) cases to those of experienced radiologists.

Methods: FN cases were extracted from the 4551 baseline LDCTs of the 4ITLR dataset between 13 December 2022 and 22 September 2023. The LDCTs were read independently by both a radiologist and dedicated AI software. A case was designated as FN when nodules >100 mm3 were present and either the radiologist or the AI solely detected nodules <100 mm3 or no nodules (negative). Hereafter, a distinction was made between the indeterminate (100-300 mm3) and positive (>300mm3) cases. The three-month follow-up CT was assessed of all the indeterminate cases to assess the final classification.

Results: 443 FN cases were identified, of which 33 by AI and 410 by radiologists. There was no overlap in FN cases. Among the 33 AI FN cases identified, 9.1% (3 cases) were classified as positive and 90.9% (30 cases) were indeterminate. Upon review of these 30 follow-up scans, 93.3% (28 cases) were reclassified as negative and 6.6% (2 cases) were discontinued from the program. The AI missed 69.7% (23 cases) due to detection errors, and 30.3% (10 cases) due to segmentation errors. Among the 410 radiologist FN cases identified, 1.0% (4 cases) were classified as positive and 99.0% (406 cases) were indeterminate. Upon review of these 406 follow-up scans, 2.2% (9 cases) were positive, 1.7% (7 cases) required a second three-month follow-up CT scan and 90.0% (366 cases) were reclassified as negative. The remaining 5.9% (24 cases) were discontinued from the program.

Conclusions: This study showed the efficacy of independent CT readings by both radiologists and AI in ensuring no FN cases occur at baseline. AI had a lower occurrence of FN cases compared to radiologists, demonstrating potential in effectively ruling out negative cases as the primary reader, without an increased risk of delayed or missed diagnosis due to FN cases.

Keywords: Lung Cancer, Screening, Artificial Intelligence

MA02 INNOVATION IN LUNG CANCER SCREENING AND EARLY LUNG CANCER DETECTION
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MA02.08 Performance of A Blood-based Protein Biomarker Panel in the National Lung Screening Trial

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Introduction: A 4-protein biomarker panel (4MP) has been shown to improve estimation of lung cancer risk and identify individuals who may benefit most from lung cancer screening. In the current study, we evaluated the performance of the 4MP for risk determination of lung cancer in the multicenter National Lung Screening Trial (NLST).

Methods: The 4MP was assessed in two nested case-control cohorts of plasma samples from the NLST. The first cohort consisted of 675 samples from individuals with CT scans without suspicious findings, including 135 eventually diagnosed with lung cancer and 540 matched control samples. The second cohort consisted of 715 samples from individuals with screen-detected pulmonary nodules, including 143 diagnosed with cancer before the next screening timepoint and 572 matched controls. The 4MP was measured using a multiplex bead-based immunoassay using coefficients fixed from a previously developed logistic regression model. Performance was evaluated using receiver operating characteristic analysis, including computing the area under the curve (AUCs) as well as a net reclassification index (NRI) to estimate how well the 4MP improved existing risk prediction models such as the Brock nodule risk calculator.

Results: In the cohort with negative CTs, for those individuals eventually diagnosed with stage II or higher lung cancer, the 4MP showed an AUC of 0.67 (95% CI 0.59-0.74). For all those with advanced (stage III and higher), AUC was 0.71 (95% CI 0.61-0.81). For individuals diagnosed within 1 year of blood draw, the AUC was 0.71 (95% CI 0.51-0.91). In those with indeterminate nodules, the 4MP showed similar performance, with an AUC of 0.64 (95% CI 0.59-0.70) in those eventually diagnosed with stage II or higher lung cancer. The 4MP, added to the Brock model, showed an NRI of 0.26 compared to the Brock model alone.

Conclusions: The 4MP may be a useful adjunct to screening, especially in identifying those who will develop more advanced stage disease in the following year. This could help to identify individuals who may benefit from closer clinical follow-up.

Keywords: lung cancer screening, biomarkers, early detection

MA02 INNOVATION IN LUNG CANCER SCREENING AND EARLY LUNG CANCER DETECTION
SUNDAY, SEPTEMBER 8, 2024 - 15:30 - 16:45

MA02.09 An Effective Multimodel Based on Cell-Free DNA Methylation for Risk Stratification of Pulmonary Nodules

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Introduction: Low-dose computed tomography (LDCT) screening has been used for early detection of lung cancer that led to significant reduction of lung cancer caused mortality. However, only less than 5% pulmonary nodules detected by LDCT are malignant. Most patients with pulmonary nodules are anxious and often overdiagnosed or overtreated in lung cancer screening that may lead to pulmonary injury and fiscal waste. Apparently, more accurate and cost-effective tools are needed to assist nodule diagnosis and management.

Methods: We first performed a genome-wide methylation sequencing in 52 malignant and 76 non-malignant pulmonary nodule tissues and selected a panel of 263 differential DNA methylation regions (DMRs). We then conducted a targeted methylation sequencing on blood cell-free DNA in a prospectively collected and retrospectively analyzed multicenter cohort of 620 participants to develop and optimize a model for risk stratification of pulmonary nodules using machine learning approaches. Forty top-performance markers were finally selected to build a methylation model and risk scores of methylation model were then integrated with age and five CT imaging features to form a combined model. Finally, an independent prospective multicenter cohort with 343 pulmonary-nodule participants were used as an external validation cohort to evaluate the performance of different prediction models.

Results: The performance of the forty-methylation marker model was evaluated in the internal validation cohort (194 malignant and 85 benign) and the external validation cohort (231 malignant vs 112 benign), achieving an ROC AUC of 0.81 (95% CI 0.76- 0.86) in both cohorts, superior to Mayo model (0.66, 0.59-0.72; 0.64, 0.58-0.71) and Brock model (0.72, 0.65-0.78; 0.70, 0.64-0.76). The combined model showed better performance than the methylation model and achieved AUCs of 0.90 (95% CI 0.86-0.94) and 0.89 (95%CI 0.85-0.92) with increases of 0·09 and 0.08 in AUC (95% CI 0.05-0.12, p<0·0001; 95% CI 0.04-0.11, p<0.0001) in internal and external validation cohorts, respectively. We applied two cutoffs (0.22 and 0.94) simultaneously to classify pulmonary nodules into lowrisk (risk score <0.22), intermediaterisk (risk score from ≥0.22 to <0.94), and highrisk (risk score ≥0.94) groups. The combined model could accurately identify high-risk nodules with 90.4% specificity and 93.9% accuracy, as well as low-risk nodules with 98.1% sensitivity and 91.8% accuracy in the combined validation cohorts. The model can reduce 89.9% unnecessary invasive surgeries and avoid 64.8% delayed treatments.

Conclusions: We have developed an integrated model consisting of forty methylation markers, one clinical and five CT imaging features for accurate diagnosis and management of pulmonary nodules.

Keywords: pulmonary nodules, plasma cell-free DNA methylation, risk stratification model

MA02.11 Validation of the Sybil Deep Learning Lung Cancer Risk Prediction Model in Three Independent Screening Studies

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Introduction: Lung cancer is the leading cause of cancer death worldwide. Early diagnosis with low-dose computed tomography (LDCT) can reduce lung cancer morbidity and mortality. However, efficient patient management in LDCT screening programs remains challenging. Sybil is a deep learning model designed to predict future lung cancer risk by analyzing a single whole LDCT image. We aim to validate Sybil using three independent screening studies and evaluate its performance.

Methods: Based on 38 922 LDCT images and 2 010 confirmed lung cancers from the Pan-Canadian Early Detection of Lung Cancer, Pittsburgh Lung Screening Study, and Toronto Screening Program, we used Sybil to estimate lung cancer risk for year 1 to 6 and estimated the area under the receiving operating characteristics curve (AUC). We also evaluated the AUC by nodule diameter, solidity, and nodule presence.

Results: Based on the 3 studies, the AUC for Sybil was 0.93 for lung cancer diagnosed within 1 year, down to 0.79 within 6 years (see Table 1). When restricting the analysis to those with pulmonary nodules, the AUCs of Sybil remained comparable. However, when focusing on individuals with no baseline nodules, the AUC from Sybil reduced to 0.65.

When stratified by nodule diameter, Sybil performs better among larger nodules (maximum diameter > 10 mm), with AUCs of 0.91 for year 1 vs 0.86 in those with small nodules. When stratified by solidity, Sybil performs better in ground glass opacity nodules, with AUC above 0.93 in years 1 and 2, but it performs better in partially solid nodules in years 3 to 6, with AUC above 0.81.

To assess if Sybil can predict lung cancer risk in the absence of nodules, we used LDCT scans for patients with a known lung cancer diagnosis but no apparent nodules at baseline. 91 patients did not have nodules at baseline but were diagnosed with lung cancer between 1 to 6 years. 83 of 91 had low Sybil scores at baseline, which suggests that Sybil's predictive performance may be suboptimal in the absence of nodules.

Conclusions: We evaluated the predictive performance of Sybil in three independent lung cancer screening studies. The performance was best within 1 year. A decline in accuracy was observed for predictions after 3 years. We also found that Sybil may not be able to predict lung cancer risk without the presence of nodules and may have limited clinical use for fast-growing nodules, not present at baseline.

Area under the receiver operating characteristic curve (AUC) values obtained during Sybil evaluation

	Risk of developing cancer within					
	1 year	2 years	3 years	4 years	5 years	6 years
No. LDCT images analyzed	37 609	37 898	38 192	38 459	38 735	38 922
No. confirmed lung cancer	697	986	1 280	1 547	1 823	2 010
AUC	0.93	0.88	0.85	0.83	0.80	0.79

Keywords: Deep learning, Early Detection, CT screening

MA02 INNOVATION IN LUNG CANCER SCREENING AND EARLY LUNG CANCER DETECTION
SUNDAY, SEPTEMBER 8, 2024 - 15:30 - 16:45

MA02.12 UC Screen California: A Statewide Participatory Informatics Approach to Lung Cancer Screening

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Introduction: The US healthcare system is fractured and complicated. Almost one-third of tobacco users do not have a PCP and 84% of eligible individuals are unaware of lung cancer screening (LCS). Despite these challenges, we can leverage widespread cellphone access to connect patients to healthcare, including LCS. In California, 99.0% of households have telephone services and 93.5% have internet access with smartphones being the most common type of computing device. Multiple LCS websites are available in the US, but few offer direct navigation to screening assessment, coordination and scheduling. To address low LCS rates in California, the University of California (UC) Lung Cancer Consortium's Screening and Prevention Taskforce developed a novel web-based screening platform to connect Californians with screening resources and programs. We sought to evaluate public engagement with this tool.

Methods: Taskforce experts collaborated with Chorus Innovations (Long Beach, CA) to develop ucscreenca.org, a participatory informatics platform available in the public domain that can be shared on multimedia devices with web-browsing, voice or text-messaging features. The platform has 3 domains: 1) A user-facing engagement domain, which includes a simplified eligibility assessment module, shared decision-making tools, educational LCS materials, and care navigator connectivity; 2) a secure, interactive dashboard for care navigators; and 3) an analytics dashboard. The modular platform is readily adaptable to different LCS needs. To facilitate dissemination in-person and on social media platforms, a QRFY-generated QR code was linked to ucscreenca.org, and the platform was advertised at UC-sponsored screening events. Using the analytics dashboard, site metrics were tracked from 11/4/23 to 2/29/24. Additional QR code user demographics were captured through QRFY. A 3-question Likert-type survey was also administered via Qualtrics at public LCS awareness events across the UCs in November 2023 to evaluate site usability.

Results: Between November 2023 and February 2024, there were 1077 site visitors, of which 65.6% were in November (n=706), and 8462 individual ucscreenca.org page views. The top 5 pages visited were the homepage, the screening eligibility assessment, the screening assessment results, LCS educational materials (general overview page), and the screening location search function. Site visitors initiated a total of 590 screening assessments and 17.4% (n=101) were eligible for LCS. The average time to screener completion was 102 seconds. Among the 208 users who reported a smoking history, 67 (32.3%) did not complete one or more component questions for the pack-years calculation. Of these 67, the majority (83.6%, n=56) omitted the "packs per day" question. In assessing QR code reach, 223 of the 367 QR codes scanned were from devices registered in Los Angeles and the original languages for these devices were diverse, including Chinese, Spanish, Korean, Bokmal, and French. Finally, amongst 117 Likert-type survey respondents, 95.7% recommended the ucscreenca.org platform and 90.6% found it easy to use.

Conclusions: Mobile and web-based participatory platforms are an important way to reach individuals and families about screening. Our participatory informatics tool demonstrated ease of use and effectiveness. Further dissemination and iterative development of a platform for broader health system-agnostic use in California is ongoing.

Keywords: lung cancer screening, informatics, equity

MA02 INNOVATION IN LUNG CANCER SCREENING AND EARLY LUNG CANCER DETECTION
SUNDAY, SEPTEMBER 8, 2024 - 15:30 - 16:45

MA02.13 Deep Learning-Based Multiomic Model for Lung Cancer Diagnosis

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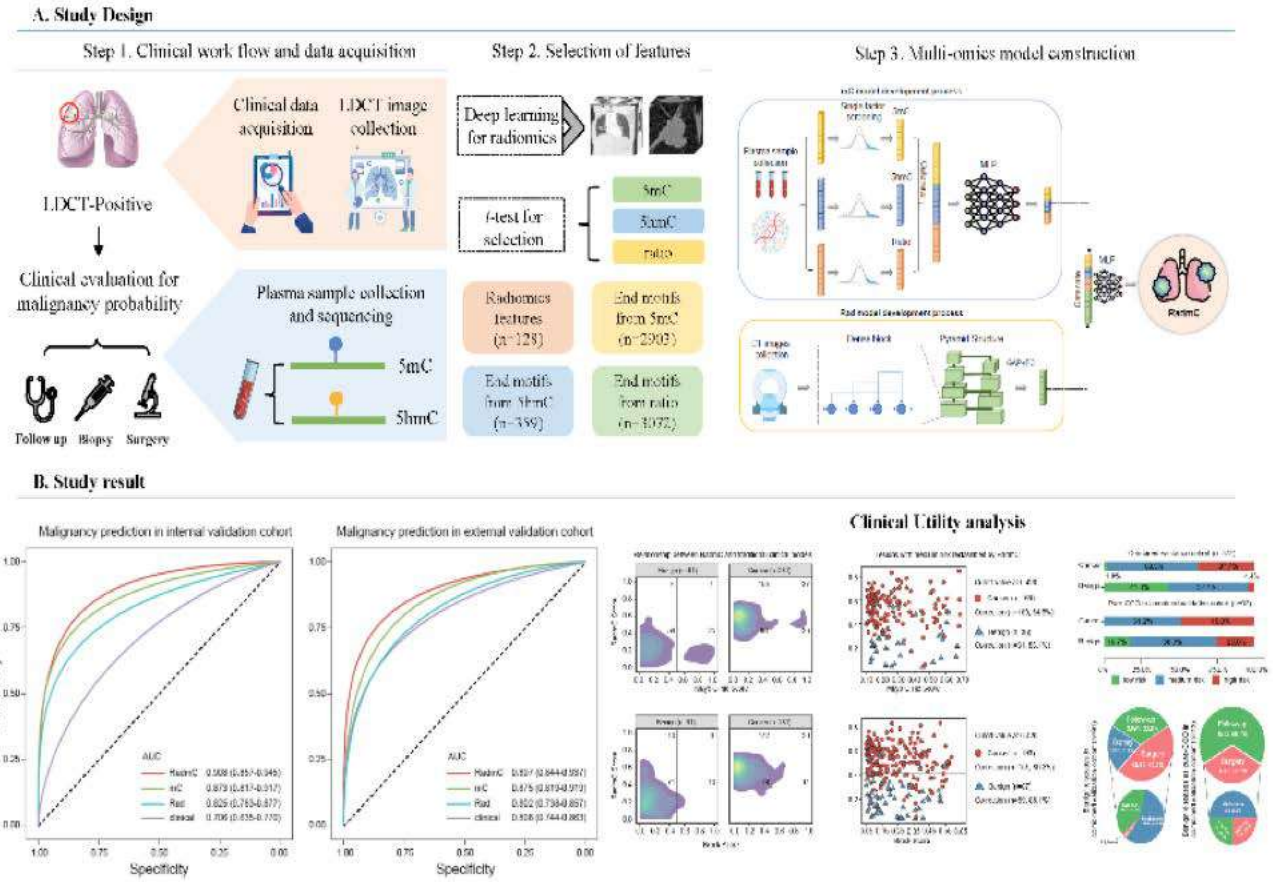
Introduction: Rapid identification of lung cancer from indeterminate pulmonary lesions (IPLs) and avoiding unnecessary invasive biopsies in patients with benign diseases are equally desirable outcomes that are often at odds with one another. A multi-omics deep learning model (RadmC) was proposed in our study to facilitate these outcomes.

Methods: A total of 1236 cfDNA samples and CT images were collected from 1236 participants who carried IPLs in 5 clinical centers. RadmC was constructed by involving radiomics and epigenomics features, including 5-methylcytosines, 5-hydroxymethylcytosines, and the 5-methylcytosines /5-hydroxymethylcytosines ratio in training cohort (n=864), and assessed by area under the curve (AUC), sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy. The net clinical benefit of RadmC in reclassifying IPLs and the biological basis of RadmC were evaluated to enhance the interpretability of RadmC.

Results: RadmC outperformed single-omics model with an improved AUCs of 0.908, 0.897 in the internal (n=187) and external (n=185) validation cohort, maintaining the best sensitivity (0.823, 0.864), specificity (0.870, 0.822), PPV (0.951, 0.938), NPV (0.615, 0.661), and accuracy (0.834, 0.854) in both validation cohorts. Its superiority performance was well maintained in various clinical scenarios, including different ages, sexes, lesion locations, lesion types, sizes, and substages of adenocarcinoma. For IPLs with medium-risk identified by Mayo and Brock models, RadmC could correctly reclassify 64.5% and 80.3% of cancers, 86.1% and 88.1% of benign diseases, respectively, and reduce unnecessary invasive procedures by 96.7% and delayed treatment by 37.7%, providing additionally clinical benefits for IPLs management. Biological exploration analysis revealed that features into RadmC were significantly enriched in cancer proliferation-related pathways, and lower expression of activated-T-cells which indicating a progressed stage of tumor.

Conclusions: RadmC provided a more accurate, robust and noninvasive tool for early diagnosis of lung cancer, showing potential in guiding the clinical management for IPLs.

Keywords: early diagnosis of lung cancer, multi-omics features, deep learning



MA03 THE SCIENCE OF SUBLOBAR RESECTION
MONDAY, SEPTEMBER 9, 2024 - 10:45 - 12:00

MA03.03 The Impact of AI-driven 3D Reconstruction on Pulmonary Surgery Planning (AIR-SURGE): A Multi-Center Multi-Reader Multi-Case Study

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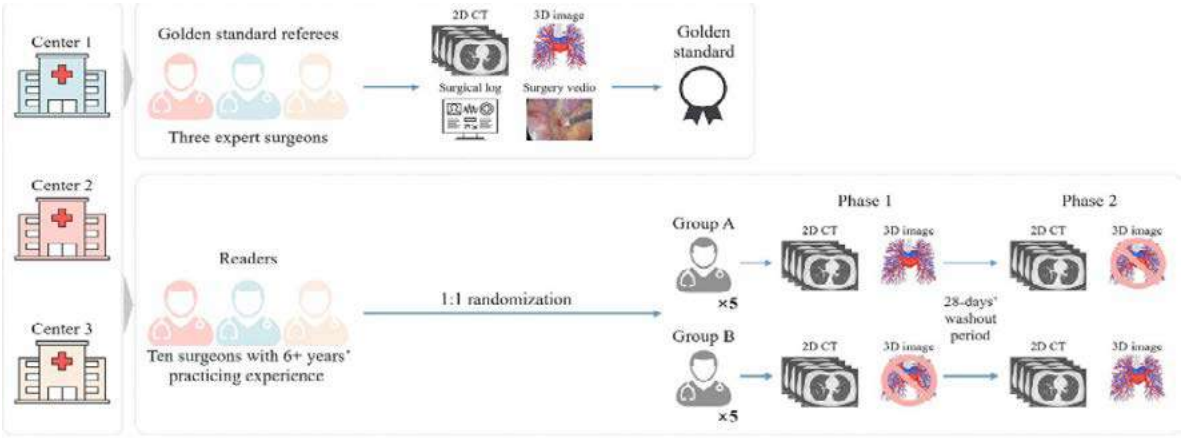
Introduction: The complexity of lung cancer surgery and the global shortage of thoracic surgeons necessitate enhanced efficiency and precision in the management of early-stage lung cancer. The advent of deep learning algorithms presents a promising avenue for efficient transitioning from conventional two-dimensional (2D) chest computed tomography (CT) scans to three-dimensional (3D) reconstructions. However, the clinical impact of these technological advancements remains to be evaluated.

Methods: We conducted a multi-reader, multi-case (MRMC) study, employing a novel two-phase crossover design, to assess the utility of an artificial intelligence (AI) system for preoperative planning. In the initial phase, half of the readers utilized standard 2D CT imaging, while the remainder utilized both 2D CT images and AI-enhanced 3D reconstructions. Following a 28-day washout period, the groups switched methodologies. Each reader was tasked with determining the extent of resection and identifying anatomical variants using a pre-defined surgery planning chart, comprehensively evaluating the system's precision and utility.

Results: The study enrolled 10 thoracic surgeons and 140 cases across three centers. The utilization of the AI system led to a significant 8% improvement in the accuracy of anatomical variant identification and a 41% reduction in error rates. Furthermore, accuracy in selecting the appropriate resection extent increased by 8%, accompanied by a 35% reduction in errors. Notably, the time required for preoperative planning was reduced from 253 to 191 seconds, with an outstanding 99% satisfaction rate among surgeons regarding the model's independent performance.

Conclusions: Our study demonstrates that AI-driven 3D reconstruction enhances preoperative planning in lung cancer surgery by improving accuracy and substantially decreasing error rates in anatomical variant identification and resection extent decision. These initial findings regarding the early role of AI in the thoracic surgery process necessitate further research to fully understand the potential and limitations of integrating AI into thoracic surgical practices

Keywords: Lung surgery, 3D reconstruction, artificial intelligence



The workflow of the MRMC study
A total of 16 thoracic surgeons from three top-tier hospitals in China participated in this clinical trial. Three surgeons collected 400 patients consecutively and enrolled in the study according to inclusion and exclusion criteria. A total of 140 cases were randomly selected from eligible cohorts. Three expert surgeons from three centers established the golden standard based on collected surgical logs, videos, CT scans, and manually constructed 3D reconstructions. The other 10 surgeons were divided into two groups randomly and took part in the MRMC study in which two rounds of fully crossed pre-operative planning simulations were conducted with an interval of 4 weeks, either with or without the aid of AI-derived 3D reconstructions of pulmonary vessels.

Inclusion criteria for readers and golden standard referee

1. Certified attending physician in thoracic surgery department.
2. Practicing thoracoscopic surgery independently for at least one year.
3. Physicians with national license for clinical practicing.
4. Physicians with a good clinical practice certificate.
5. The expert group consists of thoracic surgeons with associate senior clinical titles or above, and their professional direction is lobectomy and segmentectomy.

Upper lobe of right lung	Middle lobe of right lung	Lower lobe of right lung	Upper lobe of left lung	Lower lobe of left lung
S1 ☐	S4 ☐	S6 ☐	S1+2 ☐	S6 ☐
S2 ☐	S5 ☐	S7 ☐	S3 ☐	S8 ☐
S3 ☐		S8 ☐	S4 ☐	S9 ☐
		S9 ☐	S5 ☐	S10☐
		S10☐		

Note 1: The margin should be ≥ 2cm;

Note 2: Segmentectomy is recommended for lesions with solid component <50% and diameter <=2cm.

Note 3: The operation is judged by the segment as the minimum unit, and it is recommended not to consider the combined subsegment.

Upper lobe of right lung	**Arteries**				**Veins**		**Bronchi**	
	Interlobular variant( )	**A^1 ( )**	**A^2 ( )**	**A^3 ( )**	**Interlobular variant ( )**	**V 1+ 2+3 ( )**	**Interlobular variant ( )**	**Intralobular variant ( )**
Type 1	No cross-lobe variant ☐	Both A^1a and A^1b originates from the superior trunk of the pulmonary artery ☐	A^2a arises from the posterior recurrent artery and A^2b from the posterior ascending artery ☐	Both A^3a and A^3b originate from the superior trunk of the pulmonary artery ☐	No cross-lobe Variant ☐	Both the apical vein and the central vein are present, and the apical vein was of type Iab *** Note 2** ☐	No cross-lobe Variant ☐	Three branches: B^1, B^2, B^3 ☐
Type 2	A^2 originates from A^6 ☐	A^1a arises alone and A^1b arises from the superior trunk of the pulmonary artery ☐	Both A^2a and A^2b arise from the posterior ascending artery ☐	A^3a arises from the middle trunk and A^3b from the superior trunk of the pulmonary artery ☐	V^2 drains into the inferior pulmonary vein ☐	Both the apical vein and the central vein are present, and the apical vein was of type Ib *** Note 3** ☐	Upper lobe bronchi originates from the main trachea ☐	Two branches: B^{1+3}, B^2 ☐
Type 3	Other ☐	Other ☐	Both A^2a and A^2b arise from the posterior recurrent artery ☐	A^3a originates from the superior trunk of the pulmonary artery, and A^3b from the middle trunk ☐	Middle lobe vein has a higher draining point *** Note 1** ☐	Central veins only, no apical veins *** Note 4** ☐	Other ☐	Two branches: B^{1+2}, B^3 ☐
Type 4			Other ☐	Other ☐	V^2 and V^6 share the trunk and flow into the pericardium ☐	Apical veins only, no central veins *** Note 5** ☐		Two branches: B^1, B^{2+3} ☐
Type 5					V^2 reflux alone to the left atrium ☐	Other ☐		Four branches B^2 , B^1 , B^{2a} , B^{2b} ☐
Type 6					Other ☐			Other ☐

Other Anatomical Types (text + course diagram) : _____

（Note 1: The middle vein joins the superior lobar vein at the branch of the apical and central veins, and special attention should be paid to it during operation.

Note 2: The apical vein is formed by the confluence of V^1a and V^1b.

Note 3: The apical vein only include V^1b, and V^1a merged into the central vein.

Note 4: Central vein only, no apical vein: The central vein consists of V^1 and V^2. V1 enters the lung radially upward along this route;

Note 5: Apical vein only, no central vein: V^1 and V^2 stem together and enter the hilus from the ventral side. V^2 enters the lung between the posterior ascending artery and the superior trunk of the pulmonary artery along this path.）

A demonstration of a surgical planning chart specifically tailored for lesions in the right upper lobe. A unique chart has been crafted for each lobe to ensure a unified planning format. It also incorporates various metrics such as confidence levels, time consumption, and user satisfaction with the system. To maintain the demonstration's clarity and focus, these additional details are not displayed.

MA03 THE SCIENCE OF SUBLOBAR RESECTION
MONDAY, SEPTEMBER 9, 2024 - 10:45 - 12:00

MA03.04 A Deep Learning Model to Predict Occult Lymphatic Metastasis in Clinical Stage I Non-Small Cell Lung Cancer Based on Chest CT

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Introduction: Surgery and stereotactic body radiation therapy (SBRT) are both major curative local treatments for clinical stage I non-small cell lung cancer (NSCLC), but the choice between the two still needs to be discussed. One of the decisive factors is the correct diagnosis of lymph node staging. About 10% of clinical stage I lung cancer is surgically diagnosed with occult lymphatic metastasis (OLM), so we aimed to develop a deep learning model based on chest CT to predict the OLM of clinical phase I NSCLC and guide individualized precision treatment.

Methods: In this study, patients clinically diagnosed as stage I and pathologically determined as NSCLC who received surgery and lymph node dissection from 2015 to 2017 and 2021 to 2022 in our institution were collected to form a retrospective and prospective cohort, respectively. We extracted deep image representations from preoperative chest CT images of patients in the retrospective cohort by developing an adaptive dense connectivity network and fused them with 13 relevant clinical features by the logistic regression to achieve accurate prediction of OLM. After the model training was completed, its generalization was verified on the prospective cohort. The ROC curve was used to evaluate the predictive performance of the model, and the optimal cut-off value based on the maximum Youden index was used to divide the high and low risk group of OLM and help recommend suitable treatment decisions.

Results: A total of 2489 and 322 patients who met the inclusion criteria were finally enrolled to form the retrospective cohort and prospective cohort, respectively. The retrospective cohort was randomly divided into the training, validation and test sets in an 8:1:1 ratio. Finally, the AUCs of the constructed image-clinical fusion model for predicting OLM in the retrospective and the prospective test set were 0.915 and 0.921, which were significantly higher than those of the clinical model (0.830 and 0.790). The sensitivity, specificity and accuracy were 88.9%, 82.7%, 83.6% and 95.9%, 82.8%, 84.8% in the retrospective and the prospective test set, respectively. Besides, the patients could be significantly divided into the high and low risk group of OLM by the cut-off value of the model as the threshold ($P<0.001$). Among them, radical surgical resection combined with lymph node dissection was first recommended for patients in the high-risk group to avoid probably-missed cure of metastatic lymph nodes, and SBRT could also be another treatment option for patients in the low-risk group especially when they were contraindicated or unwilling to operate.

Conclusions: In our study, a three-dimensional adaptive convolutional neural network model based on chest CT was constructed through deep learning to predict OLM in patients with clinical stage I NSCLC which showed better prediction performance and clinical consistency than the clinical model. It might assist doctors in accurately staging before surgery in patients with early-stage NSCLC and screening the applicable population for surgery or SBRT so as to further improve the level of individualized precision treatment.

Keywords: Non-small cell lung cancer, Occult lymphatic metastasis, Deep learning

MA03 THE SCIENCE OF SUBLOBAR RESECTION
MONDAY, SEPTEMBER 9, 2024 - 10:45 - 12:00

MA03.05 Intraoperative Visualization of Pulmonary Nodules with Indocyanine Green Inhalation Under Near-Infrared Window I and II

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Introduction: Accurate intraoperative location of pulmonary nodules is crucial for precise resection of these lesions. This study aimed to explore the effectiveness and safety of ICG inhalation for intraoperative localization of pulmonary nodules under NIR-I and NIR-II.

Methods: Patients who underwent thoracoscopic surgery with pulmonary nodules ≤ 2 cm in depth and ≤ 2 cm in size were selected. All patients received ICG inhalation after anesthesia. Patients were randomly divided into five groups based on the duration of ICG inhalation: 5, 10, 15, 20, and 25-minutes (doses of 4.7, 9.4, 14.1, 18.75, and 23.4 mg). Intraoperatively, fluorescence visualization of nodules was performed under NIR-I and NIR-II. The primary outcomes were the location rate and background-tumor ratio (BTR) of nodules. The secondary outcomes were the inhalation-related complications.

Results: A total of 140 patients (186 nodules) were enrolled, with 32, 41, 44, 38, and 31 nodules in 5, 10, 15, 20, and 25-minute groups, respectively. Under NIR-I, the nodule localization rates in five groups were 56.3%, 75.6%, 72.1%, 88.9%, and 79.4%, with a significant difference (P=0.038). There were significant differences in BTR between groups (P<0.001), with the highest BTR occurring in 20-min group. Among 120 nodules that could only be located by palpation, the fluorescence localization rate of each group was significantly different (P=0.048), and the 20-min group was the highest (85.7%). Additionally, 18 nodules were unable to be located by palpation, the 20-minute group had the highest rate (66.7%). There were 165 nodules visualized under NIR-II, with 30, 33, 35, 35, and 31 nodules in five groups. Under NIR-II, the location rate in five groups were 70%, 78.8%, 88.6%, 94.3%, and 84.4%, respectively, with no significant difference (P=0.088). There were significant differences in BTR between groups (P<0.001), with the highest BTR occurring in 20 and 25-min groups. Additionally, 15 nodules were unable to be located by palpation, with an average localization rate of 60%, and the 20-minute group demonstrated a 100% rate. Compared to NIR-I, the average localization rate under NIR-II was significantly higher (83.6% vs. 75.2%, P<0.001). Moreover, the localization rates under NIR-II in all groups were significantly higher than those under NIR-I (all P<0.05). During inhalation, 26 patients (18.6%) experienced transient hypoxemia (SpO2≤ 90%). No other complications were observed.

Conclusions: This study demonstrated the feasibility and safety of ICG inhalation for intraoperative localization of pulmonary nodules and verified that NIR-II can further improve the localization of pulmonary nodules.

Keywords: Pulmonary nodule location, Near-infrared fluorescence, Indocyanine green inhalation

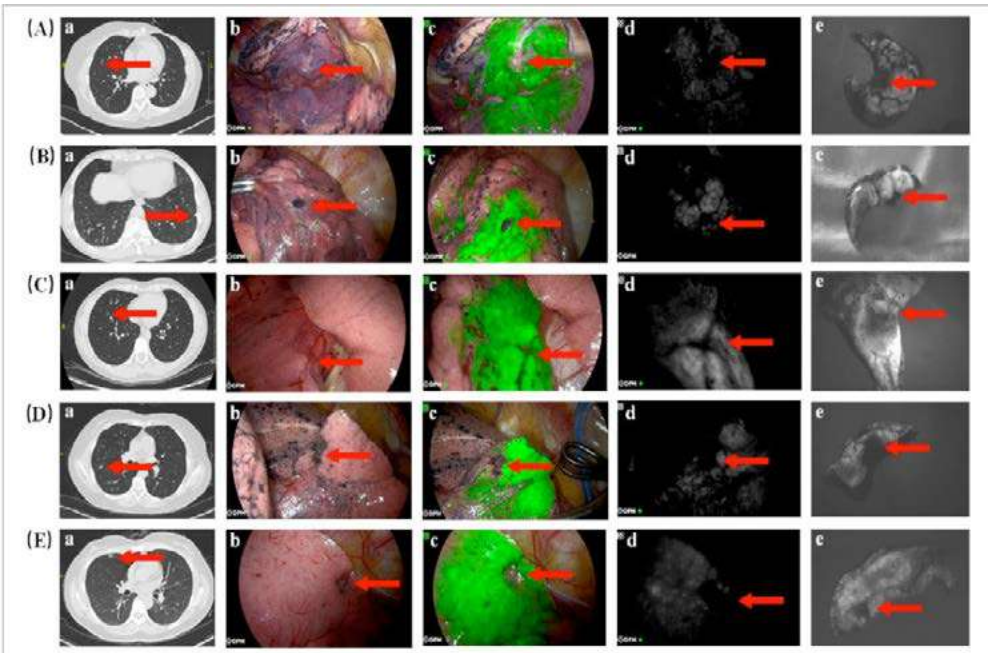

Figure 1. Fluorescence imaging of pulmonary nodules in different time groups. Figures (A) to (E) respectively represent examples of fluorescence imaging of pulmonary nodules in the 5, 10, 15, 20, and 25-minute groups. In each subfigure, a, b, c, d, e represent the chest CT image of the pulmonary nodule, the white-light window image during surgery, the overlap window image, the NIR-I window image, and the NIR-II window image, respectively. The red arrows indicate the location of the pulmonary nodules.

MA03.07 Outcomes of Older Patients in CALGB 140503 (Alliance): Lobar vs Sublobar Resection for Peripheral Stage IA Non-Small Cell Lung Cancer

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Introduction: In the CALGB 140503 trial sublobar resection was not inferior to lobar resection for non-small cell lung cancer (NSCLC) patients with small peripheral tumors. This analysis compares the effect of age on post-operative complications and outcomes with the two surgical approaches.

Methods: Patients enrolled on CALGB 140503 were categorized into three groups based on age: <65 years, 65-75 years and >75 years. Baseline characteristics, surgical approaches, pathological findings, disease-free survival (DFS), overall survival (OS), ≥grade 3 adverse events (AEs) and 90-day mortality were compared. Comparison of continuous variables were tested with Kruskal-Wallis test, and discrete variables were tested with either chi-square or Fisher's exact test. Survival outcomes were compared using the stratified log-rank test.

Results: Of the 697 patients in CALGB 140503, 254 patients were < 65 years old, 314 were 65-75 years, while 129 patients were >75 years. Baseline characteristics were matched between the three cohorts, except for smoking status (57.9%, 32.5% and 27.9% current smokers in the <65, 65-75 and >75 cohorts; p=<.0001) and mean percent predicted FEV1 (82.4, 83.9, 87.9 respectively; p=0.03). There were no differences in the three groups for number of lymph nodes sampled and T-stage, but a higher proportion of patients <65 (5.5%) and >75 (4.7%) had N1 disease, compared to the 65-75 years group (1.6%) (p=0.03). When compared to <65 cohort, patients >75 who underwent lobar resection had a lower DFS [hazard ratio (HR): 1.67; 95% CI, 1.06 – 2.62] and OS (HR: 2.73 95% CI, 1.61 – 4.64). There was no difference in DFS or OS in the group that underwent sublobar resection. There were no differences in DFS or OS between sublobar resection and lobar resection in any of the three age-based cohorts. There was no association between age and ≥grade 3 adverse events and 90-day mortality in either the lobar or the sublobar resection groups. These results are summarized in Table 1.

Conclusions: Older patients tolerated surgical resection in CALGB 140503 well, with similar adverse events and 90-day mortality as younger patients. The reasons for a lower DFS and OS in patients >75 who underwent a lobectomy need to be studied further. Surgical resection for early-stage NSCLC should be offered to all appropriate patients regardless of age.

Keywords: Peripheral Stage IA Non–Small Cell Lung Cancer, older patients, outcomes

		<65 years	65-75 years	>75 years	P-value
5-yr DFS % (95% CI)	Lobar	63.7 (55.6 – 73.1)	71.8 (64.9 – 79.4)	44.8 (33.5 – 59.8)	0.004
	Sublobar	64.8 (56.4 – 74.4)	66.1 (58.7 – 74.4)	54.6 (42.6 – 69.9)	0.19
5-yr OS % (95% CI)	Lobar	83.9 (77.7 – 90.6)	83.1 (77.3 – 89.2)	57.5 (46.1 – 71.7)	<0.001
	Sublobar	83.3 (76.7 – 90.4)	79.9 (73.6 – 86.7)	75.4 (64.9 – 87.6)	0.23
≥grade 3 AE n (%)	Lobar	17 (13%)	27 (16.8%)	11 (16.9%)	0.63
	Sublobar	12 (9.8%)	22 (14.4%)	13 (20.3%)	0.14
90-day mortality n (%)		1 (0.4%)	5 (1.6%)	4 (3.1%)	0.09

MA03 THE SCIENCE OF SUBLOBAR RESECTION
MONDAY, SEPTEMBER 9, 2024 - 10:45 - 12:00

MA03.08 Differential Impact of Sublobar Resection on Visceral Pleural Invasion Classification

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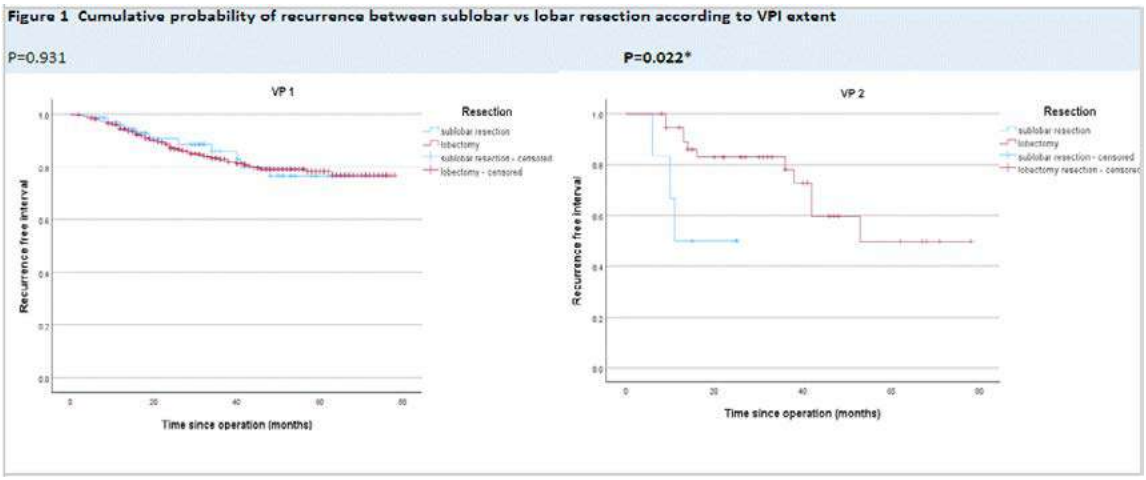
Introduction: Visceral pleural invasion (VPI) is a well-known unfavorable prognostic factor in lung cancer. However, VPI is not always considered when deciding on sublobar resection at the time of surgery for small tumors. Therefore, we aim to evaluate the impact of sublobar resection on small-sized non-small cell lung cancer (NSCLC) according to VPI classification.

Methods: From July 2017 till March 2023, we retrospectively reviewed 4505 of surgically resected NSCLC patients with ≤3cm and VPI (PL1 and PL2) in Seoul National University Hospital. VPI classification was determined by three dedicated pulmonary pathologists based on the elastic layer stain. Relapse free survival (RFS) was evaluated with Kaplan-Meier analysis. Cox-proportional hazards model was employed for prognostic factors.

Results: A total of 509 patients (PL1 = 465 patients and PL2 = 44 patients) were included with a mean follow-up duration of 38.6 ± 20.4 months. Distant metastasis was the dominant pattern of recurrence in both group (PL1 = 74.7% and PL2 = 85.7%). A significant difference was observed between PL1 and PL2 group in RFS (5y-RFS; PL1 vs PL2 = 83.9% vs. 68.2% p = 0.004). There was a trend indicating that the impact of sublobar resection was different according to PL1 or PL2 (p-value=0.057 for interaction). Within PL1 group, there was no difference in RFS between sublobar and lobar resection (5y-RFS; sublobar vs lobar = 85.3% vs. 83.6% p=0.931), whereas PL2 group showed a significant difference between resection types (5y-RFS; sublobar vs lobar = 50% vs. 71.1% p = 0.022) (Figure 1). In a multivariable analysis, sublobar resection did not influence on RFS in PL1 group (p = 0.511, HR = 0.754 [CI 0.325-1.749]. However, sublobar resection was associated with worse RFS compared to lobar resection in PL2 group (p = 0.018, HR = 0.071 [CI 0.008-0.632]).

Conclusions: We revealed that sublobar resection has a differential impact on prognosis according to VPI classification. Sublobar resection should be cautiously utilized in NSCLC with ≤3cm and PL2.

Keywords: Visceral Pleural Invasion, Sublobar resection, Non small cell lung cancer



MA03 THE SCIENCE OF SUBLOBAR RESECTION
MONDAY, SEPTEMBER 9, 2024 - 10:45 - 12:00

MA03.10 Association of Surgical Margin Distance, Locoregional Recurrence, and Survival Among Patients Undergoing Sublobar Resection in CALGB140503

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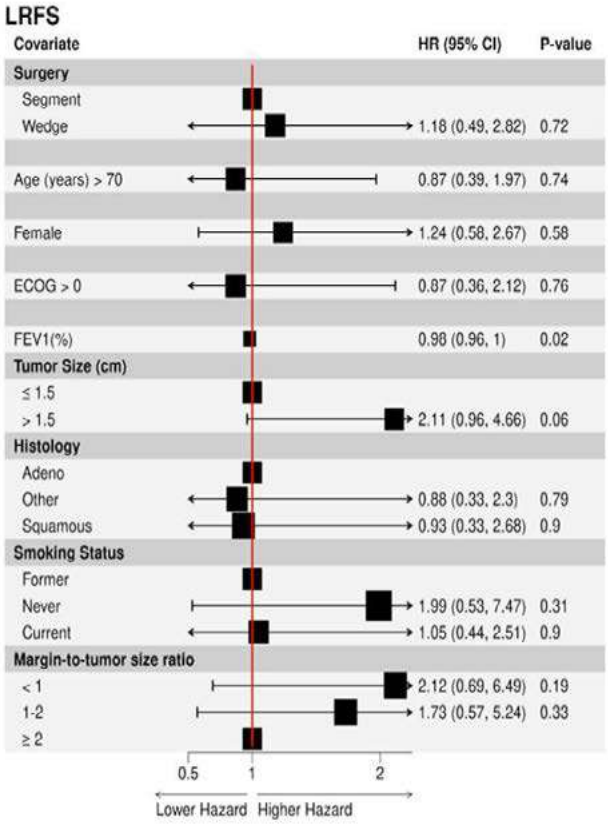
Introduction: In a randomized trial of lobectomy vs sublobar resection (CALGB 140503, NCT00499330) for stage IA (<2cm) lung cancer, sublobar resection was non-inferior to lobectomy for the primary endpoint of disease-free survival (DFS), and secondary endpoint of locoregional recurrence. Despite this, questions remain about adequacy of local control with sublobar resection. In this post-hoc analysis, we evaluate the association between surgical margin distance (SMD) and locoregional-recurrence-free survival (LRFS) and overall survival (OS) within the cohort undergoing sublobar resection.

Methods: Patients who underwent sublobar resection for cT1a-bN0 NSCLC in CALGB 140503 were grouped by presence or absence of locoregional recurrence [LRR]. The SMD, as determined by the operating surgeon, and the ratio between the SMD and tumor size ("margin-to-tumor size ratio") were evaluated. Multivariable Cox proportional hazards modeling was used to evaluate association between SMD and LRFS, OS. The association between margin-to-tumor size ratio and LRFS, OS was similarly analyzed. Patients who died within 90-days of surgery, and patients lost to follow-up were excluded from this analysis.

Results: A total of 329 evaluable patients underwent sublobar resection (201 [61.1%] wedge resection, 128 [37.9%] segmentectomy), of whom 45 (13.7%) developed a LRR during a median follow-up of 7 years. Of these patients, 208 (135 [64.9%] wedge resection, 73 [35.1%] segmentectomy) had known SMD data, of which 29 (13.9%) experienced LRR. There were no significant differences in SMD between patients who did and did not have a LRR (mean SMD in cm [SD]: 1.9 [1.46] vs. 2.0 [1.19], P=0.33). Margin-to-tumor size ratio was similar between patients with and without LRR (mean [SD]: 1.2 [1.0] vs. 1.5 [1.0], P=0.11). There were no independent predictors of LRFS (Figure). Tumor size >1.5 cm (aHR 2.11: 95%CI: 0.96- 4.66, P=0.06) and margin-to-tumor size ratio <1 (aHR: 2.12: 95% CI: 0.69 - 6.94, P=0.19) trended towards but did not achieve statistical significance. There was no association between SMD nor margin-to-tumor size ratio and OS.

Conclusions: In this analysis of the sublobar resection cohort in CALGB 140503, 13.7% experienced LRR. Surprisingly, neither SMD nor margin-to-tumor size ratio were predictive of LRFS or OS.

Keywords: sublobar resection, stage 1 lung cancer, local recurrence



MA03 THE SCIENCE OF SUBLOBAR RESECTION
MONDAY, SEPTEMBER 9, 2024 - 10:45 - 12:00

MA03.11 Postoperative Complications Compromised Disease-Free and Recurrence-Free Survival in CALGB 140503 Trial Patients

D.L. Miller[1], X. Wang[2], B. Damman[3], J. Mentlick[3], R. Landreneau[4], D. Wigle[3], D. Jones[5], M. Conti[6], A. Ashrafi[7], M. Liberman[8], J. Port[9], M. de Perrot[10], J. Mitchell[11], R. Keenan[12], T. Bauer[13], T. Stinchcombe[2], N. Altorki[9], [1]Medical College of Georgia, Augusta/GA/USA ,[2]Duke Cancer Institute, Durham/NC/USA ,[3]Mayo Clinic, Rochester/MN/USA ,[4]University of Pittsburg, Pittsburgh/PA/USA ,[5]Memorial Sloan Kettering, New York/NY/USA ,[6]University of Delaval Quebec, Montreal/QC/CA ,[7]University of British Columbia, Surrey/BC/CA ,[8]University of Montreal, Montreal/QC/CA ,[9]Cornell Medicine, New York/NY/USA ,[10]University of Toronto, Toronto/ON/CA ,[11]University of Colorado, Denver/CO/USA ,[12]Moffitt Cancer Center, Tampa/FL/USA ,[13]Hackensack Meridan Health, Neptune City/NJ/USA

Introduction: The CALGB/Alliance 140503 phase III trial revealed that sublobar resection (SLR) had non-inferior disease-free survival (DFS) and similar recurrence-free survival (RFS) and overall survival (OS) compared to lobar resection (LR) in patients with peripheral cT1a,bN0 NSCLC. Adverse events (AEs) grade ≥ 3 occurred in less than 15% of patients. The influence of these more severe complications on the patients' cancer-related survivals have not been analyzed. We investigated the impact of AEs grade ≥ 3 on cancer recurrence, cancer-specific survivals and overall survival.

Methods: Between 6/2007 and 3/2017, 697 patients were randomized to LR (357) or SLR (340); 80.2% of the resections were via VATS approach. Adverse events were graded using the AEs version 4.0 and were grouped into a Low-Grade (LG) group (AEs ≤ 2) and a High-Grade group (HG) (AEs ≥ 3); Grade 5 AE (Death) was excluded from survival analyses. Survival endpoints were estimated by the Kaplan-Meier estimator and tested by stratified Log-rank test. The Chi-square test was used to compare the distribution of LG AEs vs HG AEs among various groups. Locoregional recurrence (LRR) and distant recurrence (DR) - free survivals were also calculated.

Results: High-Grade AEs occurred in 102 patients (14.6%) in the study population, 15.4% of the LR patients and 13.8% of SLR patients.(Chi-square, p = 0.555) The three most common HG AEs were pulmonary (8.0%), infection (6.7%), and cardiovascular (2.7%) related. There was no difference in the association of HG AEs and type of surgical procedure (Chi-square, p = 0.159) or the site volume.(Chi-square, p = 0.119) Five-year OS was 81.1% after LG AEs and 75.5% after HG AEs.(Log rank, p = 0.205) Five-year DFS was 66.9% after LG AEs and 49.6% after HG AEs.(Log rank, p = 0.006) Five-year RFS was 72.9% after LG AEs and 56.9% after HG AEs.(Log rank, p = 0.006) Five-year LRRFS was 88.9% after LG AEs and 76.4% after HG AEs (Log rank, p = 0.054) and five-year DRFS was 85.1% after LG AEs and 80.4% after HG AEs (Log rank, p = 0.109). Multivariate analysis showed that age > 70 years, male gender, and decreased %FEV1 increased HG AEs and significantly affected disease-free, recurrence-free and locoregional recurrence-free survivals.

Conclusions: In this large, prospective randomized trial, HG AEs negatively influenced DF and RF survival, but not overall survival. LRR and DR survivals were also affected, but not significantly. This analysis shows that even in patients who undergo resection for the smallest (< 2 cm) of NSCLCs, postoperative HG AEs can decrease cancer-specific survivals. Prevention of postoperative HG AEs is mandatory in patients undergoing surgical treatment for early-stage NSCLC to reduce recurrence and maximize survival.

Keywords: Lung Cancer, Surgical Complication, Survival

MA04 REAL-WORLD IMPLEMENTATION OF EARLY LUNG CANCER DETECTION
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MA04.03 Bringing Equity to the Community: The Dana-Farber Cancer Care Equity Program's Lung Cancer Screening Initiative

N. Florez, S. Pohl, Z. Wei, L. Kiel, T. Patwary, E. Mazzola, L. Garber, E. Harding, L. Svoboda, C. Lathan, Dana-Farber Cancer Institute, Boston/MA/USA

Introduction: Disparities in lung cancer (LC) screening and survival persist among Black and Hispanic communities. The Dana-Farber Cancer Institute (DFCI) Cancer Care Equity Program (CCEP) diagnostic clinic was established in 2012 to reduce cancer health disparities through facilitating access to screening, treatment, prevention, and survivorship services in Greater Boston.

Methods: We evaluated lung cancer-focused CCEP services at two federally qualified community health centers in underserved Boston areas. Data included single-patient visits since CCEP began LC screening in 2014 among 391 patients who consented to a larger cohort study. Descriptive statistics summarized demographics and experiences from patients' CCEP initial consults.

Results: 101 patients had at least one CCEP consult for LC screening between January 22, 2014, and May 10, 2023. The mean age was 61 years; 44% were female. Most (69%) identified as Black or African American and 47% as Hispanic; 54% spoke English, 33% spoke only Spanish, and 13% spoke both languages. Nearly all had Medicare or Medicaid as primary insurance (47% and 41%). Among 101 patients referred for LC screening, 97% (98) reported current or past tobacco use, 52% (50) reported smoking ≥20 cigarettes daily, and 30% (29) reported smoking 11-20 cigarettes daily. The mean pack-years smoked was ≥29 years (range: ≥1-50+ years, among 96 patients). Most (79%, 80) identified as active tobacco users at the time of consultation, and a large majority (91%, 73) received CCEP smoking cessation counseling; smoking cessation materials were provided to 96% (70) of these patients, with 93% reporting wanting to participate in a smoking cessation program. Though most patients (80%, 81) were referred to CCEP for LC screening, a notable 20% underwent recommended LC screening despite being referred for another reason; 60 additional patients were referred for LC screening but did not consent to the larger cohort study. Following their consult, 80% (81) of patients had a radiology test ordered, including low-dose CT (LDCT; 79%, 64) or standard chest CT scans (21%, 17). CT scans were often ordered as follow-up to prior abnormal scans (11) or due to symptoms such as cough or shortness of breath (6). A median of 3 CT and 7 LDCT scans were ordered annually, though 21 LDCT scans were distinctly ordered in 2015, the year that LDCT scans were approved through Medicare. LDCT scans were ordered for 87% (39) of the patients who smoked ≥20 cigarettes daily (mean smoking time: 41 years), including 80% (56) of active tobacco users. LDCT and CT scans were ordered for 80% (45) and 20% (11) of Black patients and 85% (22) and 15% (4) of the patients who solely spoke Spanish. Notably, 85% (69) of patients completed their LDCT/CT scans; reasons for missing the appointment included not wanting to go (6) or forgetting (3). Three of the 101 patients were diagnosed with lung cancer.

Conclusions: The DFCI CCEP aims to improve access to cancer care for local marginalized communities. CCEP's integration of LC screening and smoking cessation services among vulnerable populations demonstrates that tailored interventions can be impactful in promoting equity.

Keywords: Lung Cancer Screening, Cancer Health Disparities, Smoking Cessation

MA04 REAL-WORLD IMPLEMENTATION OF EARLY LUNG CANCER DETECTION
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MA04.04 Treatment Patterns and Survival of Screen-Detected Lung Cancer in the Real World Versus the National Lung Screening Trial

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Introduction: While lung cancer screening has been shown to increase the detection of early-stage lung cancers amenable to curative treatment in clinical trial settings, concerns about the efficacy of screening in the real world remain. Outside of clinical trials, patients often have more comorbid conditions and face greater difficulty accessing cancer care, which may prevent patients with screen-detected lung cancer from receiving curative treatment. We evaluated treatment patterns and outcomes for stage I lung cancer detected via screening using a US national sample from SEER-Medicare and compared these treatment patterns and outcomes to that in the National Lung Screening Trial (NLST).

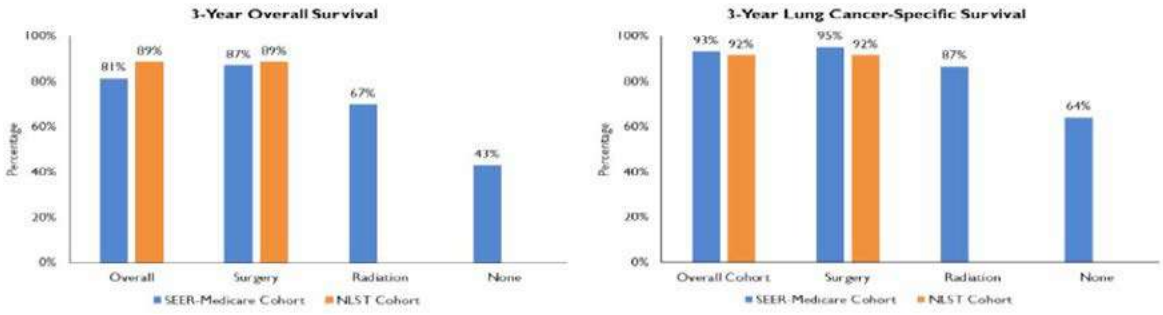
Methods: Patients aged 65-78 with stage I non-small-cell lung cancer (NSCLC) detected via low-dose computed tomography (LDCT) screening from 2015-2017, with follow-up through 2019, in the SEER-Medicare database ("SEER-Medicare cohort") and patients aged 65-78 with stage I NSCLC detected via LDCT screening in the NLST ("NLST Cohort") were identified for analysis. In the SEER-Medicare cohort, patients who received >1 LDCT scans during the 18 months before their lung cancer diagnosis were considered to have screen-detected lung cancer. The proportions of patients who received surgery, radiation, other or no treatment in the SEER-Medicare cohort were compared to those proportions in the NLST cohort. Three-year overall and lung cancer-specific survival in each cohort were evaluated.

Results: A total of 461 patients in the SEER-Medicare cohort and 168 patients in the NLST cohort met inclusion criteria. Among patients in the SEER-Medicare cohort, 73.8% (n=340) underwent surgery, 21.0% (n=97) underwent radiation, and 3.3% (n=15) underwent other treatments; only 2.8% (n=13) received no treatment. In comparison, in the NLST cohort, 94.6% (n=159) underwent surgery, 2.4% (n=4) underwent radiation, 1.8% (n=4) underwent other treatments, and 1.2% (n=2) received no treatment (Figure). Three-year overall and lung cancer-specific survival in the SEER-Medicare and NLST cohorts are shown in the Figure. Both patients in the SEER-Medicare and NLST cohorts had excellent 3-year lungcancer-specific survival at 93.1% (95% CI:90.1-95.2%) and 91.6% (95% CI:86.2-94.9%), respectively.

Conclusions: In this US national analysis of patients diagnosed with screen-detected stage I NSCLC, nearly all patients received either surgery or radiation, only 3% of patients received no treatment, and 3-year lung cancer-specific survival was 93%. These findings suggest that—even outside of rigorous clinical trial conditions—a very high proportion of patients with screen-detected lung cancers can receive curative treatment and can achieve survival outcomes comparable to that observed in the NLST.

Keywords: Lung cancer, Lung cancer screening, Early-stage

Figure. Three-year overall and lung cancer-specific survival among all patients and stratified by treatment type in the SEER-Medicare cohort and NLST cohort.



MA04 REAL-WORLD IMPLEMENTATION OF EARLY LUNG CANCER DETECTION
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MA04.05 An Evolution and Expanding Engagement to Excel in Lung Cancer Screening

M.R. Gieske[1], I.A. Budhani[2], D.A. Alkapalan[2], J.A. Ries[2], [1]St Elizabeth HealthCare, Edgewood/KY/USA ,[2]St. Elizabeth Healthcare, Edgewood/KY/USA

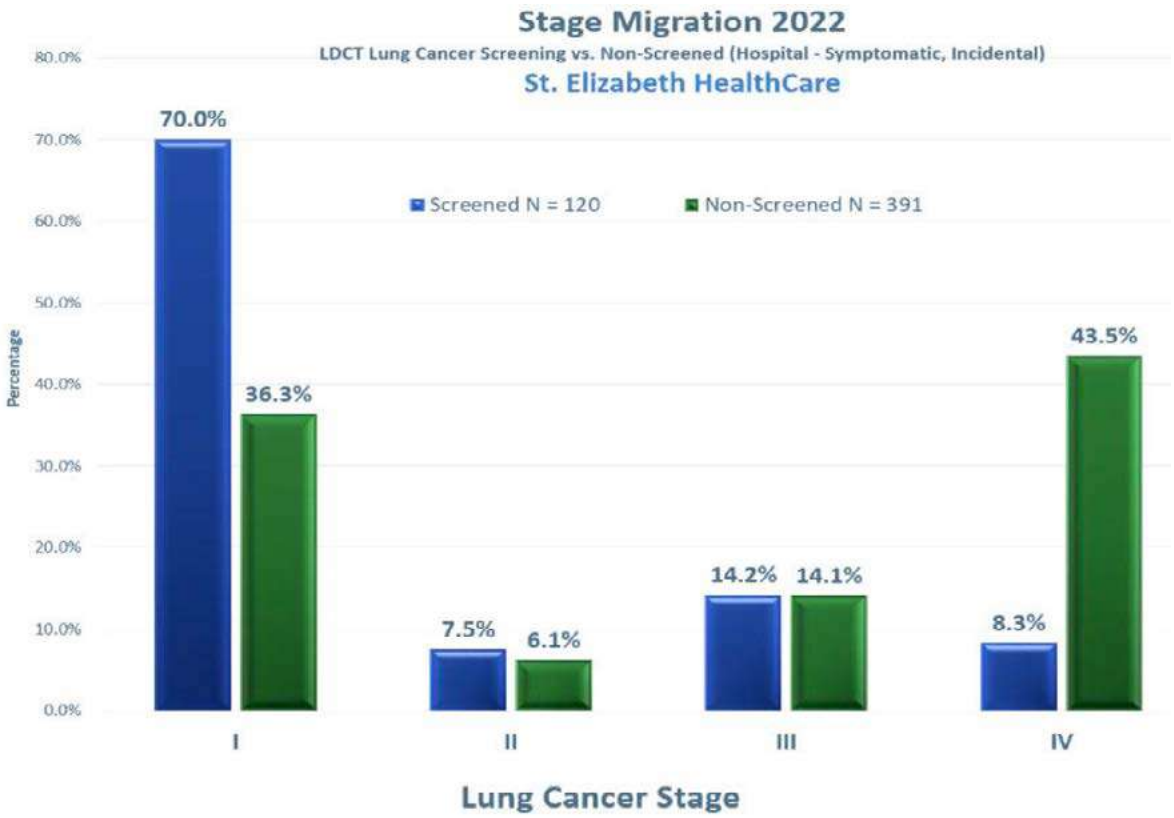
Introduction: St. Elizabeth Healthcare, a community-based hospital system serving Northern Kentucky and Southeastern Indiana, initiated its Lung Cancer Screening Program (LCSP) in 2013. Over the past decade, our program has evolved and expanded, exceeding initial benchmarks and showcasing the transformative power of collaboration and outreach efforts. With a commitment to continual improvement, we have achieved significant advancements in early detection and stage migration, workup, and treatment, positively impacting patient outcomes, improving year over year.

Methods: With over 40,000 LDCT lung cancer screens conducted to date, our program employs a comprehensive approach to screening and care coordination. We have discovered 638 lung cancers (LCs), one for every 28 unique patients screened, over 400 in stage I (62.7%). Uptake of United States Preventive Services Task Force 2021 screening eligible individuals attributed to our primary care providers is 46.8%. Lung-RADS category 4 nodules undergo weekly review by our dedicated nodule review board, ensuring timely and efficient management. Our team of three LCS nurse navigators plays a pivotal role in facilitating communication and streamlining patient care. Data tracking through a centralized Compendium enables ongoing evaluation and conveyance of our results. Regular reporting and collaboration with our 41 primary care sites network and 191 providers enhances program performance and accountability. Our Population Health Support Services team of twelve RN outreach specialists follows up on outstanding orders and monitors their completion of orders and screens.

Results: There has been a notable rise in stage I diagnoses over recent years. Stage migration analysis illustrates a progressive shift towards earlier stages of disease, with stage I diagnoses comprising 50.8% in 2021 (n 33), 70.0% 2022 (n 84) as illustrated in the stage migration chart below), 71.6% 2023 (n101), and thus far this year 79.4% (n 27). Overall, our healthcare system has seen a 23.1% decline in late-stage lung cancers from 2015 to 2022, with early-stage LCs surpassing late-stage in 2022. With an adherence rate exceeding 60% over the past three years, emphasis on annual follow-up has contributed to long-term screening success.

Conclusions: Despite inherent challenges, our experience underscores the value of a programmatic approach and interdisciplinary collaboration in optimizing LCS outcomes. As evidenced by our evolving results and continued stage migration, the maturation of a well-coordinated screening program yields tangible benefits in early detection and improved patient prognosis. We remain steadfast in advancing our efforts, leveraging innovation and partnership to further enhance the effectiveness and reach of LCS initiatives.

Keywords: lung cancer screening, stage migration, collaboration



MA04.07 Low-Dose Computed Tomography Lung Cancer Screening Participants Live Longer Than Matched Controls, A Case-Control Study

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Introduction: The current evidence from randomized controlled trials has supported a reduction in mortality caused by LDCT lung cancer screening. There is limited data on the impact of screening on mortality in observational trials. The study aims to assess the 10-year overall survival of the lung cancer LDCT screened group compared to a propensity matched unscreened control group.

Methods: In this observational case-control study, the data of 43,686 patients from the database of the National Health Fund (NFZ) aged 50-75 were analyzed. The study group consisted of 7281 individuals who underwent LDCT lung cancer screening in Pilot Pomeranian Lung Cancer Screening Program (PPLCSPP) between 2009-2011 and matched controls from a general Polish population. Data on comorbidities and survival of program participants and the general population were collected and analyzed from the NFZ registry covering medical services for almost all Polish citizens. This registry contains the data on all medical events provided both in hospital and outpatient settings. The survival and comorbidities of 7281 participants of PPLCSPP and 36,405 matched controls selected from the population of 9.81 million people from the NFZ registry were analyzed and compared. The control group was randomly selected from among 9.81 million people from the NFZ database using the 1:5 propensity score matching method. For each screened person, 5 people were matched using the following variables: age, sex, chronic and acute diseases, neoplasm, demographic indicators regarding the number of physicians per 10,000 inhabitants, and the average monthly salary in the place of residence. The former two variables were selected to diminish the potential effect of disparities in access to the health care system in Poland. Patients were followed for at least 10 years for events requiring treatment and diseases, and for death.

Results: During over 10 years of follow-up, hypertension, chronic coronary artery disease, hypercholesterolemia, diabetes, unstable coronary artery disease, COPD, atrial fibrillation and heart failure was diagnosed in 52.2%, 20.5%, 13.2%, 13.0%, 11.4%, 5.6%, 2.8%, 2.0%, respectively. A multivariate analysis showed a beneficial effect on long-term survival of participation in the screening study HR=0.653, occurrence of hypertension HR=0.882, hypercholesterolemia HR=0.567, female gender HR=0.527. Factors negatively affecting survival are lung cancer diagnosis HR=5.141, stroke HR=2.451, colorectal cancer HR=2.166, heart failure HR=2.061, chronic kidney disease HR=2.044, breast cancer HR=1.837, COPD HR= 1.766, atherosclerosis HR=1.503, diabetes HR=1.471. The 10-year survival of the screening group was statistically more favorable and amounted to 86.9%, the control group 81.3%, $p<0.001$.

Conclusions: Participants of LDCT lung cancer screening have reduced all-cause mortality compared to the general population of people at the age 50-75.

Keywords: Lung cancer screening, Early detection, Lung cancer secondary prevention

MA04.08 High Recruitment Rate and Performance of a National Lung Cancer Screening Network Implementing Web-Based Instruments

M. Balbi[1], C. Battiloro[2], G. Besutti[3], M. Caterino[4], F. Caumo[5], E. Cavigli[6], A.F. De Filippis[7], G. Di Nardo[8], D. Galetta[9], C.M.S. Ierna[10], E. Mercadante[11], G. Milanese[12], G.L. Pariscenti[13], U. Pastorino[14], S. Sironi[15], [1]Radiology Unit, San Luigi Gonzaga Hospital, Department of Oncology, University of Turin, Orbassano, Italy, Turin/IT ,[2]azienda Ospedaliera Specialistica dei Colli Monaldi, Napoli, Napoli/IT ,[3]IRCCS in Tecnologie Avanzate e Modelli Assistenziali in opncologia, Reggio Emilia, Italy, Reggio Emilia/IT ,[4]Istituto Nazionale Tumori Regina Elena, Roma/IT ,[5]IRCCS Istituto Oncologico Veneto, Padova, Italy, Padova/IT ,[6]Azienda Ospedaliera Universitaria Careggi, Firenze, Italy, Firenze/IT ,[7]Presidio Ospedaliero Santo Spirito, Pescara, Italy, Pescara/IT ,[8]IRCCS CROB Istituto di Ricovero e Cura a Carattere Scientifico, Potenza, Italy, Potenza/IT ,[9]IRCCS Istituto dei Tumori Giovanni Paolo II, Bari, Italy, Bari/IT ,[10]Azienda Ospedaliera Cannizzaro, Catania, Italy, Catania/IT ,[11]IRCCS Istituto Nazionale dei Tumori Fondazione G. Pascale, Napoli, Italy, Napoli/IT ,[12]Section of Radiology, Department of Medicine and Surgery (DiMeC), University Hospital of Parma, Parma, Italy, Parma/IT ,[13]IRCCS Ospedale Policlinico San Martino, Genova, Italy, Genova/IT ,[14]Fondazione IRCCS Istituto Nazionale dei Tumori, Milano/IT ,[15]ASST Ospedale Papa Giovanni XXIII, Bergamo, Italy, Bergamo/IT

Introduction: Lung cancer screening (LCS) can reduce mortality in high-risk individuals, but recruitment of heavy smokers to repeated low dose computed tomography (LDCT) examinations has proven critical, particularly in the most deprived subset of the population at higher lung cancer (LC) risk. The RISP national network represents a unique experience of web-based screening with accelerated recruitment and randomized design.

Methods: The RISP program (acronim for Italian Lung Screening Network) was funded in 2021 by the Ministry of Health, that selected 18 highly specialized clinical centers across the country with the aim of proving the feasibility and cost/effectiveness of a national LCS network, by the implementation of centralized web-based recruitment facilities and automated second reading of all LDCT images with the same software for artificial intelligence (AI) analysis (Coreline, AVIEW). Eligible participants were also randomized to annual vs. biennial LDCT interval. Approval by the ethics committees and administrative boards of participating centers was obtained by July 2022.

Results: From October 2022 to March 2024, a total of 20,704 volunteers individually registered in the national RISP web site, 10,582 (51%) proved to be eligible for LDCT screening (age 55-75 years, ≥ 35 pack/year or PLCOm12 ≥ 2.6% at 6 years), and 8,747 (83%) received baseline LDCT. The analysis of the first 8747 LDCTs showed 80% global concordance in LungRADS classification of local radiologists vs. AI second reading. AI analysis also revealed a similar quantification of the individual risk profile obtained with the top 192-slice LDCT scanners compared to all other scanners: 4% vs. 5% Brock score ≥10 and 14% vs. 16% coronary artery calcification (CAC score) ≥400, respectively. After a median follow-up of 12 months, 91 (1.0%) LCs were detected, of which 50 (54.9%) were stage I and 70 (76.9%) resected.

Conclusions: The present data show the feasibility, high 18-months recruitment, early LC detection and resectability rates of a national web based LCS network. Further data on the cost/efficacy evaluation by site and LDCT scanner will be presented.

		RISP volunteers N=8747
Age	Median (IQR)	62 (59-67)
Female	N(%)	3522 (40.3%)
Pack-years	Median (IQR)	43.8 (36.3-53)
Current smokers	N(%)	6688 (76.5%)
Median Follow-up time		12.1 (9.2-14.6)
Lung Cancers		91 (1.0%)
	Stage I	*50 (54.9%)*
	resected	*70 (76.9%)*

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MA04.09 An International Qualitative Study of Healthcare Provider Perspectives of the Psychosocial Impacts and Barriers to Lung Cancer Screening

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Introduction: Many countries are (or are considering) implementing lung cancer screening (LCS) following landmark trials demonstrating the effectiveness of screening with low-dose computed tomography for reducing lung cancer mortality. Psychosocial outcomes are a key consideration for LCS programs, ranging from harm to individuals to impacts on screening participation, and downstream effects on medical help-seeking generally. This study aimed to investigate the psychosocial aspects of LCS for participants from the perspective of healthcare providers from a diverse range of trial and service designs across the globe.

Methods: We conducted semi-structured interviews between August and December 2023 with (1) health professionals involved in delivering or designing LCS including physicians, nurses, trial assistants/coordinators, and researchers, and (2) primary care practitioners not previously involved in LCS. Participants were recruited internationally to include experiences across programs, jurisdictions, and policy landscapes. Interviews were recorded and transcribed verbatim and the study authors participated in coding data and developing themes. Data were analysed thematically.

Results: Twenty-seven healthcare providers were interviewed. Most (n=20) had experience in providing LCS. Participants were from England (n=11), Australia (n=10), Canada (n=3), Ireland (n=2) and New Zealand (n=1), representing six established LCS trials/programs. Themes generated included: (1) anxiety, worry, and fear are central harms and barriers to uptake; (b) positive psychological responses to LCS are common; (c) lung cancer fatalism is ingrained and underpins anxiety; (d) smoking stigma is pervasive and interacts with LCS invitation; (e) family, community, and other social influences (e.g., reduced psychological harm during LCS from social network support); and (f) issues specific to LCS-eligible populations (e.g., correlated disadvantage, comorbidities). Each theme was associated with psychosocial barriers to appropriate engagement (e.g., fear of cancer, nihilism - “what’s the point?”, avoiding judgement or lecturing about smoking, lack of social support). Key considerations for LCS service design for managing psychosocial outcomes and barriers were also identified. These were aggregated across countries, trials and programs, and included both purposeful, top-down aspects of program design, as well as self-taught or unmandated strategies patient-facing providers used in practice. Example considerations included: public awareness/education to reduce lung cancer fear and fatalism, program navigation and continuity of care throughout the LCS pathway, cultural safety and support for different participant groups, and designed wording for reducing stigma, communicating risk, and delivering results.

Conclusions: We identified similarities in provider perspectives about the psychosocial aspects of LCS across countries and trial/programs designs. This suggests that international best-practice guidance could be developed for LCS programs to manage participants psychosocial outcomes and potentially reduce barriers to screening uptake. Further work investigating communication methods specific to managing stigma and communicating lung cancer risk is needed. Additionally, LCS programs should consider sociocultural influences for LCS participants, and how these may be leveraged in recruitment and managing psychological burden.

Keywords: psychosocial, lung cancer screening

MA04.11 Women Enrolled in Lung Screening as a Result of Direct Outreach Are More Likely to be Cancer Survivors

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Introduction: Lung cancer screening (LCS) with low-dose CT (LDCT) reduces mortality. Randomized controlled trials have suggested that the mortality benefits may be greater in women than men, and research has shown that women with a prior history of any cancer are at greater risk for developing a primary lung cancer. LCS is underutilized compared to screening mammography. The CALM study (Coordinate A Lung Screening with Mammography) successfully enrolled women in LCS through outreach at the time of breast cancer screening. Here we compare the demographic characteristics of women enrolled in CALM with those who underwent LDCT without direct outreach.

Methods: A retrospective cohort study of women enrolled in LCS from September 2021 to October 2022 was performed. This included women who enrolled because of direct outreach from the CALM study and those who enrolled without this intervention. Direct outreach consisted of generating a monthly list of women undergoing screening mammography and notifying referring providers of their patients' lung screening eligibility based on USPSTF guidelines. Demographic characteristics of screening participants were collected at the time of the shared decision-making visit (SDMV), including those needed to calculate lung cancer risk using the PLCOm2012 model. Differences in the two groups' demographics and lung cancer risk were assessed with Pearson's Chi-Square test and two-sample t-test, respectively.

Results: Screening was initiated in 459 women: 113 after provider outreach (CALM participants) and 346 without outreach. Race and ethnicity between the two groups were similar (81% white in the outreach group and 85% non-outreach group (p=0.35)). Adherence rates were similar (55% outreach group and 53% non-outreach group (p=0.77)). Women responding after outreach had a non-statistically significantly lower baseline lung cancer risk, but a higher personal history of cancer (34.5% vs 14.2%; p<0.001) (Table 1).

Conclusions: Women who enrolled in LCS as part of the CALM study had a statistically significantly higher likelihood of having a prior cancer. This suggests that women who are cancer survivors are receptive to undergoing lung screening, though they may not have been aware of their eligibility prior to the CALM intervention. We plan to design future intervention strategies to improve lung screening enrollment for women as part of cancer survivorship.

Keywords: Lung cancer, Screening, Mammography

	Women Enrolled without Outreach	Women Enrolled with Outreach (CALM)	P-value
	N=346	N=113	
Average PLCO Risk Score	3.3%	2.8%	p=0.396
Personal History of Cancer	14.2%	34.5%	p<0.001

MA04 REAL-WORLD IMPLEMENTATION OF EARLY LUNG CANCER DETECTION
MONDAY, SEPTEMBER 9, 2024 - 14:00 - 15:15

MA04.12 Uncovering Disparities and Trends in Lung Cancer Screening Based on Patient Race and Insurance Status

E.J. Zolfaghari[1], R. Tseng[2], P. Sather[2], T. Ermer[2], V. Mase[2], F. Detterbeck[2], L. Tanoue[3], G.A. Woodard[2], [1]Yale New Haven Hospital, New Haven/CT/USA ,[2]Yale New Haven Hopsital, New Haven/CT/USA ,[3]Yale New Haven Hopsital, Division of Pulmonology, Yale School of Medicine/CT/USA

Introduction: Recognizing disparities in lung cancer screening by patient race and insurance status is crucial for advancing public health equity. This enables targeted interventions, addressing disproportionate risks and access barriers faced by certain demographic groups. Understanding differences in access facilitates tailored lung cancer screening programs, optimizing resource allocation and outcomes. Identifying patterns in screening across different racial and insurance groups helps providers implement strategies to ensure equitable access to detection and treatment.

Methods: A prospectively collected and maintained Lung Cancer Screening Dashboard from a large Northeast hospital system electronic-medical record database retrospective review was performed. Patient insurance status (Medicare, Private Insurance, Medicaid, self-pay or worker's compensation, Other) and race (White, Black/African American, Asian, Other, None of the Above) for all adult screening chest computed tomography (CT) scans ordered between Jan 1st, 2018 to March 9th, 2024 were collected and evaluated for growth trends. Predictive measures were used to estimate projections for the remainder of 2024, whereas growth calculations used 2023 data as that was the most recent full calendar year.

Results: Overall growth and increased lung cancer screening adoption was seen over the study period with a total of 1,317 scans in 2018 verses 5,014 scans in 2023. Most screening CT scans are performed through Medicare (57.3% in 2023), followed by Private Insurance (21.38%) and Medicaid (19.6%). In the study period, White patients with Medicare were more likely to be screened for lung cancer than other ethnicities (77.5% Medicare in 2023). Interestingly, Black Medicare patients experienced the greatest increase in screening scans with a 4.5-fold increase between 2018 and 2023 vs 3.5-fold increase among White Medicare patients. Increases in screening were similar among Medicaid patients, White (3.9-fold increase) and Black (3.8-fold increase), whereas Black Private Insurance patients saw a notable increase in screening scans (6.7-fold increase) vs White (3.3-fold increase). Since 2020, an increasing number of African Americans have received lung CT screenings.

Conclusions: Increased lung cancer screening among White patients accounts for a disproportionate share of the increases in lung cancer screening. Screening outreach efforts should focus on Black and other patient populations for more equitable use of this important health service. Recognizing trends in lung cancer screening informs policymaking, driving initiatives to address systemic inequities in healthcare delivery. Acknowledging and addressing disparities in lung cancer screening empowers healthcare systems to deliver more equitable and effective care, reducing the burden of disease on vulnerable populations.

Keywords: racial disparities, health equity, insurance coverage

MA05 TREATMENT TARGETS AND MONITORING MARKERS FOR MESOTHELIOMA AND THYMIC TUMORS
MONDAY, SEPTEMBER 9, 2024 - 15:30 - 16:45

MA05.03 A Phase II Study of Tislelizumab Combined with Chemotherapy in Patients with Thymic Carcinoma

L. Wu, J. Li, Y. Kong, B. Chen, Y. Zhou, X. Pu, Y. Luo, L. Xu, Q. Wang, Hunan Cancer Hospital/The Affiliated Cancer Hospital of Xiangya School of Medicine, Changsha/CN

Introduction: Thymic carcinomas are rare malignancies that in general arise in the prevascular (anterior) mediastinum. Studies are hampered by the paucity of these tumors, the large variety of carcinoma subtypes, and the lack of unique morphologic and immunophenotypic features. The standard diagnosis and treatment mode of thymic carcinoma has not been established. At present, most scholars prefer systemic treatment for primary thymic carcinoma .

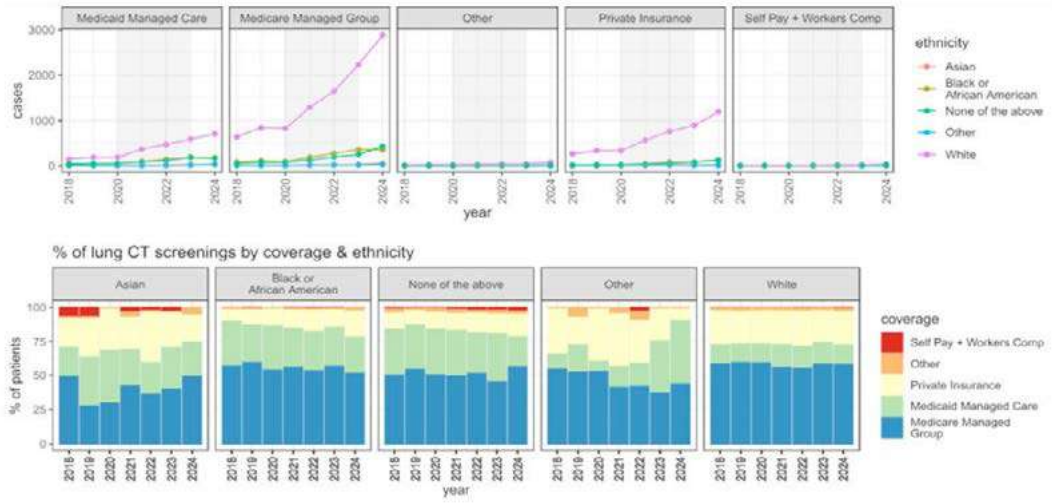
Methods: From Sep 2022 till Dec 2023, We included all patients diagnosed with thymic carcinoma who had never received systemic treatment. Patients received tislelizumab 200 mg IV Q3W in combination with paclitaxel 175mg/m2 IV Q3W and carboplatin AUC 5 IV Q3W . The primary objective of the study was to assess the objective response rate (ORR). Secondary objectives included assessments of safety and progression-free survival (PFS); exploratory objectives included the disease control rate (DCR), overall survival (OS). Tumor response was assessed by investigators per RECIST v1.1. All adverse events (AEs) were monitored and recorded.

Results: 17 patients were enrolled; the median age was 61.0 years (range 41-67). At data cutoff (Jan 31, 2024), 14 patients (82.3%) were undergoing treatment. Discontinuations occurred in 3 patients (17.6%)—2 (11.8%) primarily due to disease progression, 1 (5.8%) due to an AE. Efficacy analyses included 17 patients. The ORR of tislelizumab in combination with chemotherapy was 41.7% (7/17) in the evaluable population; the DCR was 100% (17/17). Median PFS and OS was not reached (95% CI not estimable). Treatment-emergent (TE)AEs of any grade and of grade ≥3 severity occurred in 47.1% (8/17) and 5.8% (1/17) of the 17 enrolled patients, respectively; the most common treatment-related AE was leukopenia (any grade: 29.4% [5/17]; grade ≥3: 5.8% [1/17]) and thrombopenia(any grade: 17.6% [3/17]; grade ≥3: 5.8% [1/17]).1 patient (5.8%)occurred immune related myocarditis and hepatitis.

Conclusions: In the first-line systemic treatment of malignant thymic carcinoma, the combination of PD-1 monoclonal antibody and chemotherapy has a obviously anti-tumor therapeutic response.The safety is mainly similar to chemotherapy. It provides a new therapeutic option for clinical practice.

Keywords: Thymic carcinoma, Tislelizumab, chemotherapy

Table 1: Characteristics of Patient Race & Insurance Coverage



MA05 TREATMENT TARGETS AND MONITORING MARKERS FOR MESOTHELIOMA AND THYMIC TUMORS
MONDAY, SEPTEMBER 9, 2024 - 15:30 - 16:45

MA05.04 Targeting TROP-2 In Diffuse Pleural Mesothelioma

M.D. Offin, S. Tischfield, P. Manoj, P. Agrawal, S. Tendler, E.C. Pratt, W. Travis, A. Rimner, C.B. Simone, E. de Stanchina, J. Qiu, V. Markov, M. Donoghue, J.S. Lewis, M.G. Kris, J.L. Sauter, P.S. Adusumilli, C.M. Rudin, A. Quintanal Villalonga, M.G. Zauderer, Memorial Sloan Kettering Cancer Center, New York City/NY/USA

Introduction: Diffuse pleural mesothelioma (DPM) is a nearly universally fatal malignancy with limited treatment options. There is a lack of validated biomarkers, other than histology, and no approved targeted strategies. Utilizing our patient derived xenograft (PDX) library, we identified TROP-2 as a candidate target. TROP-2 expression has been shown to correlate with tumorigenesis in several solid tumors but has not been adequately assessed in DPM.

Methods: TROP-2 expression was evaluated by flow cytometry (PE anti-human) in PDX and by immunohistochemistry (IHC; ENZ-ABS380) in a DPM patient tumor microarray (TMA). Transcriptomic analysis of publicly available datasets (MESOMICS and TCGA) was performed and correlated with TROP-2 expression. The oncogenicity (colony formation, proliferation, migration/invasion) of TROP-2 overexpression and knockout (KO) was evaluated in isogenic cell lines derived from epithelioid (H2452, H28) and biphasic (MSTO-211H) DPM. RNAseq was performed to identify pathways altered by TROP-2 expression. The metastatic potential of TROP-2 was evaluated via intracardiac injection. The efficacy of the TROP-2 antibody drug conjugate (ADC) Sacituzumab Govitecan (SG) was assessed in PDXs with high (MSK_LX307) and intermediate/low (MSK_LX707, MSK-LX606, MSK_LX13) TROP-2 expression (n=10/cohort): vehicle, chemotherapy (gemcitabine; 40 mg/kg/week), and SG (0.5 mg/mouse/twice a week). ImmunoPET was performed with a novel tracer ([89Zr]Zr-DFO-SG) on MSK-_LX13 and MSK_LX606 to evaluate TROP-2 expression.

Results: 73% (8/11) of PDXs expressed TROP-2 by flow cytometry and 54% (34/63) of TMA samples expressed TROP-2 by IHC. Transcriptomic analyses of publicly available DPM cohorts correlated high TROP-2 expression with a pro-metastatic, stem-like phenotype. TROP-2 overexpression increased tumorigenicity in vitro (proliferation, colony formation, migration and invasion) in all cell lines, whereas TROP-2 KO exerted the opposite effects. TROP-2 expression induced pro-oncogenic pathways including MAPK and AKT signaling, as well as stemness and metastasis markers. Intracardiac injection of DPM cell lines associated TROP-2 overexpression with increased metastatic colonization, while TROP-2 KO led to abrogation of metastasis. immunoPET showed avidity for both PDXs and was confirmed with a terminal biodistribution study. Treatment of PDXs with SG was well tolerated, and tumor growth was significantly slowed in PDXs treated with the TROP-2 ADC compared to gemcitabine.

Conclusions: TROP-2 exerts pro-oncogenic effects in DPM by increasing oncogenic signaling and metastatic potential. The TROP-2 ADC, SG, blunted tumor growth in PDX models. These data confirm TROP-2 as a therapeutic target in mesothelioma. Based on these findings, we are opening an investigator initiated single arm phase 2 trial to assess the overall response rate of SG in patients with previously treated recurrent/metastatic DPM.

Keywords: Mesothelioma, TROP-2, ADC

MA05 TREATMENT TARGETS AND MONITORING MARKERS FOR MESOTHELIOMA AND THYMIC TUMORS
MONDAY, SEPTEMBER 9, 2024 - 15:30 - 16:45

MA05.05 External Validation of Proposed 9th Edition of TNM Classification for Thymic Epithelial Tumours: Institutional Series of 436 Cases

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Introduction: The 9th Edition of TNM classification (TNM9) for thymic epithelial tumours has been proposed as an improvement to the 8th edition (TNM8) by introducing a size descriptor for pT1 category and re-classification of lung or phrenic nerve invasion as pT2. We aim to perform an independent validation of the proposed TNM9 classification, with a comparison of the prognostic characteristics with TNM8 and the Masaoka-Koga (M-K) classifications.

Methods: This is a single institutional, retrospective study including all thymic epithelial tumours underwent surgical resection with curative intent during a 31-year period (1991-2022), irrespective of resection status. Clinical and pathological variables, as well as recurrence and survival data were retrieved from an institutional thymoma database. Survival analysis was performed using univariate Cox regression, Statistical significance was defined as P<0.05.

Results: This study includes a total of 436 cases, with a documented recurrence rate of 12.6% (55/436). Thymoma, thymic neuroendocrine tumour and thymic carcinoma comprise 90.8% (396/436), 3.4% (15/436), 5.7% (25/436) of cases respectively. The overall stage re-assignment rate of TNM9 from TNM8 was 5.3%. Prognostic significance was observed with proposed TNM9 in terms of recurrence free survival (RFS), although only borderline statistical significance was seen with proposed pT1b category (pT1a vs pT1b, P = 0.057). No prognostic relevance was seen with overall survival (OS). No statistical significance in RFS was observed between T2 N0 M0 tumours and T3 N0 M0 tumours with lung invasion only (TNM8), therefore our data supported re-classifying the latter as pT2 in TNM9. We were unable to assess the prognostic impact of phrenic nerve invasion independent of N and M status, as all six cases in our study population were stage IV. In comparison with TNM8 and M-K classifications, TNM9 showed similar prognostic characteristics by identifying a single favourable prognostic group (stage I), with less pronounced differences between stage II-IV. M-K classification, on the other hand, identified two relatively distinct prognostic groups (favourable: I-IIb, unfavourable: III-IVb) with less pronounced difference within each group.

Conclusions: The findings from our study generally supported the proposed TNM9 classification for thymic epithelial tumours in relation to RFS. The lack of prognostic significance with the proposed pT1b category may be due to the limited sample size of our study. Furthermore, our data suggested TNM9 and M-K classifications are complementary to each other. Provision of both staging parameters is therefore recommended over TNM9 as the sole staging parameter for surgically resected thymic epithelial tumours.

Keywords: Thymoma, Staging

MA05.08 Follow-Up after First-Line Nivolumab Plus Ipilimumab in Patients with Pleural Mesothelioma: A Real-World Dutch Cohort Study (FLORA-Study)

L.H. Douma[1], M.M. Hofman[2], F. Zwierenga[3], A.I.G. Buma[4], J.H. Schouwink[5], J.A. Burgers[6], I. Smesseim[6], D.W. Dumoulin[2], J.G.J.V. Aerts[2], C.J. de Gooijer[6], [1]Netherlands Cancer Institute - Antoni van Leeuwenhoek, Amsterdam/NL ,[2]Erasmus MC Cancer Institute, Rotterdam/NL ,[3]University of Groningen, Groningen/NL ,[4]Radboud University Medical Center, Nijmegen/NL ,[5]Medisch Spectrum Twente, Enschede/NL ,[6]Netherlands Cancer Institute, Amsterdam/NL

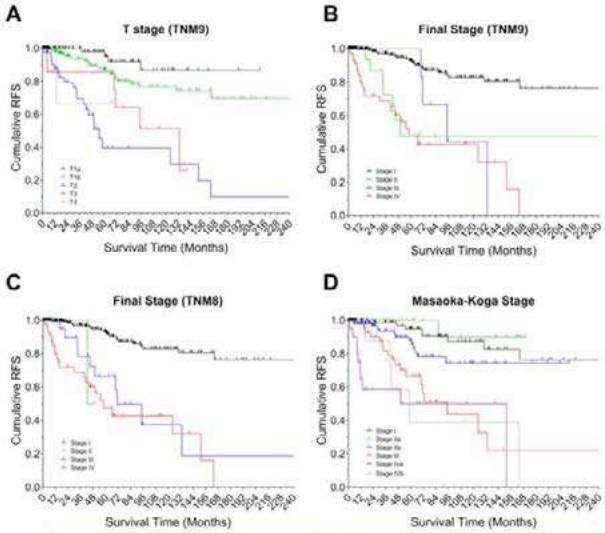
Introduction: Pleural mesothelioma (PM) is an aggressive malignancy, with treatment options limited to palliative systemic therapy (platinum-based/pemetrexed combination). The registration of nivolumab/ipilimumab (nivo/ipi) in 2022 has replaced chemotherapy as the standard of care in the first-line for most patients. For second-line treatment, chemotherapy remains a rational option after nearly 20 years of experience. After first-line chemotherapy, approximately 37-47% of patients may be candidates for additional treatment, while after nivo/ipi in the Checkmate 743 trial, this was 44.9%. The proportion of patients who receive second-line treatment after nivo/ipi is unknown in real-world. The aim of this study is to provide an overview of subsequent therapy in patients with PM who progressed on nivo/ipi, based on real-world data, and to evaluate the efficacy of second-line platinum-based/pemetrexed combination treatment in this patient cohort.

Methods: FLORA is an observational, multicenter cohort study in five Dutch medical centers. Clinical data from patients with PM treated with first-line nivo/ipi were obtained from the medical records. The primary endpoint was median overall survival (mOS) of patients receiving second-line platinum-based/pemetrexed treatment. Secondary endpoints included mOS of first-line nivo/ipi, objective response rate (ORR) and median progression-free survival (mPFS) of second-line chemotherapy and subgroup analyses (non-responders and responders to first-line treatment and histological subtype).

Results: Between May 2021 and July 2023, 267 patients with PM who received first-line nivo/ipi were included (Figure 1). Of these patients, 227 were male (85%), with a median age of 72 (IQR 67-77) years. The histological subtypes were epithelioid (n=167, 62%), sarcomatoid (n=59, 22%), mixed (n=34, 13%), and unknown (n=7, 3%). Ninety-one (49%) patients received a second-line treatment, of which 73 (39%) patients received second-line platinum-based/pemetrexed chemotherapy (Figure 1). Among these 73 patients, 55 (75%) had a WHO performance score of 0-1, and 9 patients had a score of 2 (12%), while data for 9 patients were unavailable. mOS for second-line chemotherapy was 8.1 months (95% CI 7.7-8.5). Secondary endpoints will be presented at the congress.

Conclusions: This study provides the first real-world data on subsequent treatment options for patients with PM who progressed on nivoipi, with a mOS of 8.2 months after second-line chemotherapy

Keywords: immunotherapy, second-line treatment, mesothelioma



Variable	Event/N	Est. 5-Year RFS rate	Est. 10-Year RFS rate	P
T stage (TNM9)				
T1a	4/138 (2.9%)	98.0%	86.7%	Ref.
T1b	23/225 (10.2%)	87.0%	76.6%	0.057
T2	21/55 (38.2%)	39.6%	39.6%	**1.2×10^{-9}**
T3	6/14 (42.9%)	85.7%	51.4%	**0.001**
T4	1/4 (25.0%)	66.7%	-	0.062
Final stage (TNM9)				
I	21/346 (6.1%)	93.1%	82.9%	Ref.
II	7/28 (25.0%)	47.6%	47.6%	**2.0×10^{-6}**
III	4/8 (50.0%)	100%	44.4%	**0.004**
IV	23/54 (42.6%)	47.5%	42.8%	**1.1×10^{-16}**
Final stage (TNM8)				
I	21/346 (6.1%)	93.1%	82.9%	Ref.
II	1/5 (20.0%)	50.0%	-	**0.007**
III	10/31 (32.3%)	66.4%	37.4%	**1.0×10^{-6}**
IV	23/54 (42.6%)	47.5%	42.8%	**1.1×10^{-16}**
Masaoka-Koga stage				
I	8/139 (5.8%)	94.9%	87.3%	Ref.
IIa	1/41 (2.4%)	90.0%	90.0%	0.438
IIb	13/160 (8.1%)	87.8%	74.3%	0.107
III	18/62 (29.0%)	66.3%	43.7%	**4.1×10^{-7}**
IVa	10/22 (45.5%)	50.1%	50.1%	**6.1×10^{-9}**
IVb	5/12 (41.7%)	38.9%	38.9%	**1.0×10^{-6}**

MA05 TREATMENT TARGETS AND MONITORING MARKERS FOR MESOTHELIOMA AND THYMIC TUMORS
MONDAY, SEPTEMBER 9, 2024 - 15:30 - 16:45

MA05.07 Pretreatment with Cisplatin or Radiation Therapy Enhances CAR T-Cell Therapy Efficacy

R. Bellis, M.S. Skovgard, H.T. Quach, A. De Biasi, J. Villena-Vargas, P.S. Adusumilli, Memorial Sloan Kettering Cancer Center, New York/NY/USA

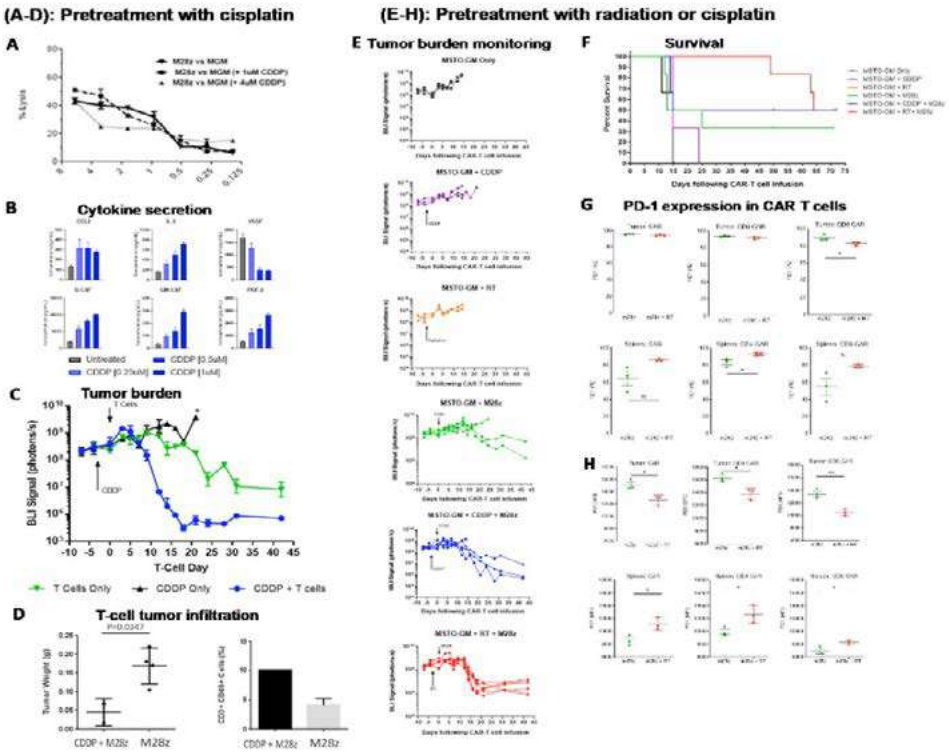
Introduction: With recent advances in immunotherapy for thoracic cancers, including malignant pleural mesothelioma (MPM), we sought to evaluate the feasibility and efficacy of combination therapy of pretreatment with cisplatin or tumor-targeted, non-ablative radiation with mesothelin (MSLN)-targeted CAR T cells (M28z) in an orthotopic mouse model of MPM.

Methods: In vitro, the effects of pretreatment with cisplatin or radiation on mesothelioma cells (MSTO-211H) were assessed by cytokine analysis (multiplex bead-based enzyme-linked immunosorbent assay) and cytotoxicity (chromium release assay). In vivo, in mice established with orthotopic MPM using MSTO-211H cells transduced to express green fluorescent protein (GFP) and MSLN (MGM), a single dose of cisplatin or low-dose, tumor-targeted radiation was administered 3 days prior to intravenous administration of a single, low-dose of M28z CAR T cells. Tumor burden was assessed via bioluminescent imaging (BLI). Safety and efficacy of the combination therapies was evaluated by overall survival (OS), flow cytometry quantification of tumor-infiltrating T cells, and serum cytokine/chemokines.

Results: Pretreatment with either cisplatin (0.25uM-1uM) or radiation (2Gy, 4Gy, 10Gy) of mesothelioma cells (MSTO-211H) did not effect cytotoxicity (Fig. 1A), increased chemokines/cytokines, including GM-CSF, FGF-2, IL-6, and VEGF in a dose-dependent manner (Fig. 1B), reduced tumor burden significantly (Fig. 1C&D), and augmented tumor infiltration of T cells (Fig. 1D). Tumor-bearing mice treated with combination of cisplatin or radiation followed by 1 x 105 M28z CAR T cells had improved median OS (not reached and 67 days, respectively, Fig. 1E&F) compared to cisplatin alone (15 days), radiation alone (15 days), and M28z alone (40 days). Even with a low dose of M28z CAR T cells (5 x 104 cells), tumor eradication was observed in mice pretreated with 4Gy tumor-targeted radiation (Fig. 1F). Serum of tumor-bearing mice showed an increase in multiple cytokines, including FGF-2, IL-10, and VEG-F in mice pretreated with cisplatin or radiation followed by M28z compared to mice receiving M28z CAR T cells only. PD-1 expression in CAR T cells by percentage and intensity of expression is lower compared to in spleen of mice that received combination therapy (Fig. 1G&H).

Conclusions: Our results demonstrate increased survival of mice pretreated with cisplatin or tumor-targeted radiation in combination with M28z CAR T cells even with a low dose of CAR T cells compared to single treatments alone (cisplatin alone, radiation alone, or M28z alone). Our results provide strong rationale to translate combination therapy regimen to treat patients with MPM.

Keywords: Chemotherapy, CAR T cell therapy, Radiation therapy



Cisplatin or radiation has the potential to enhance M28z efficacy both in vitro and in vivo.

(A) M28z showed no increase in cytotoxicity when cocultured with MGM tumor cells that had been pretreated with cisplatin (1uM or 4uM) as measured by cytotoxicity assay (chromium release assay). **(B)** Supernatant of MSTO-211H cells 72hrs after treatment with varying doses of cisplatin (CDDP) show increases in cytokines/chemokines in a dose-dependent manner. **(C)** Tumor burden as assessed by bioluminescence imaging of mice inoculated with 1 x 10^6 MGM cells received either no treatment, M28z only, or a single dose of CDDP via intraperitoneal injection 3 days prior to M28z injection. **(D)** Mice inoculated with MGM followed by either 2 x 10^6 M28z or pretreatment with a single dose of CDDP 3 days prior to M28z CAR T cell injection were euthanized 7 days after CAR T cell injection. Tumor weights and percentage of CD3+ CD45+ tumor infiltrating T cells was assessed with flow cytometry. **(E-F)** Tumor burden as assessed by BLI and survival curves of mice inoculated with 1 x 10^6 MGM cells followed by no treatment, M28z only, treatment with either CDDP or RT alone, or combination treatment of either CDDP or RT 3 days prior to M28z injection. **(G-H)** PD-1 percentage and MFI of M28z CAR T cells in both tumor and spleen of mice who received intra-pleural injection of 1 x 10^6 MGM cells showed increased infiltration and less exhaustion in mice who received pretreatment RT compared to M28z alone.

MA05.08 Follow-Up after First-Line Nivolumab Plus Ipilimumab in Patients with Pleural Mesothelioma: A Real-World Dutch Cohort Study (FLORA-Study)

L.H. Douma[1], M.M. Hofman[2], F. Zwierenga[3], A.I.G. Buma[4], J.H. Schouwink[5], J.A. Burgers[6], I. Smesseim[6], D.W. Dumoulin[2], J.G.J.V. Aerts[2], C.J. de Gooijer[6], [1]Netherlands Cancer Institute - Antoni van Leeuwenhoek, Amsterdam/NL ,[2]Erasmus MC Cancer Institute, Rotterdam/NL ,[3]University of Groningen, Groningen/NL ,[4]Radboud University Medical Center, Nijmegen/NL ,[5]Medisch Spectrum Twente, Enschede/NL ,[6]Netherlands Cancer Institute, Amsterdam/NL

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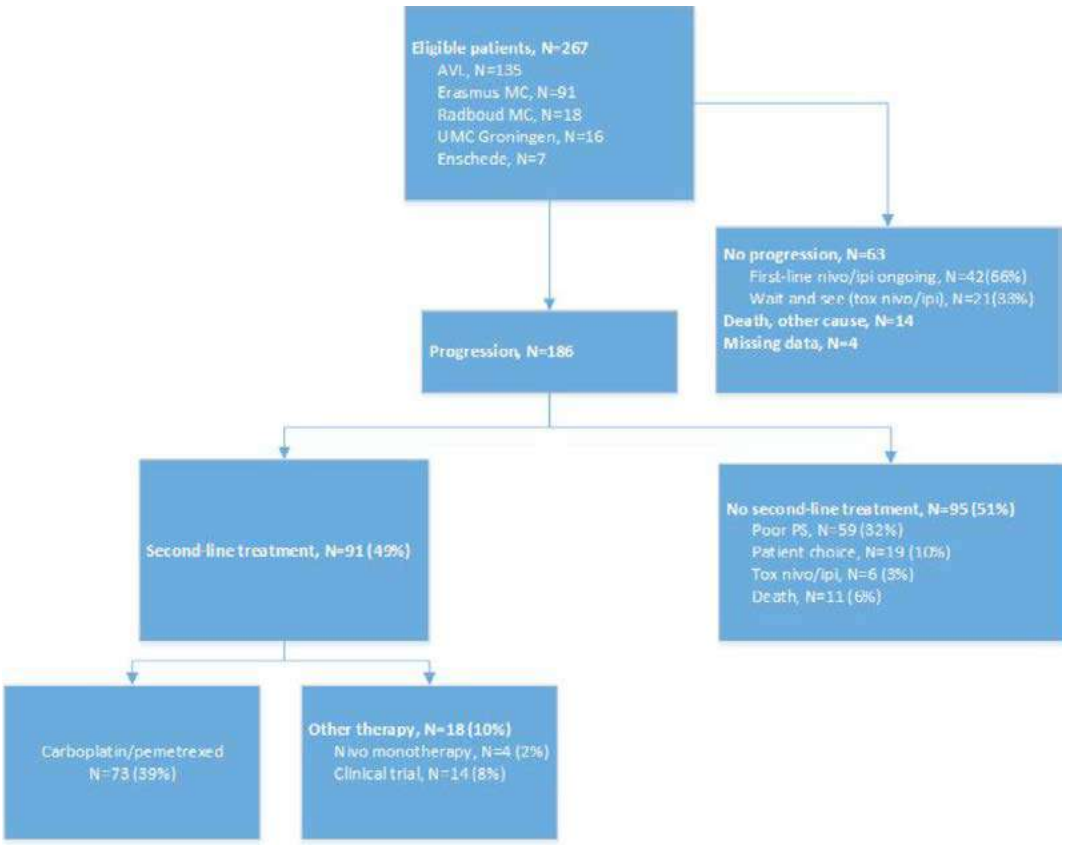
Conclusions: This study provides the first real-world data on subsequent treatment options for patients with PM who progressed on nivo/ipi, with a mOS of 8.2 months after second-line chemotherapy

Keywords: immunotherapy, second-line treatment, mesothelioma



MA05 TREATMENT TARGETS AND MONITORING MARKERS FOR MESOTHELIOMA AND THYMIC TUMORS
MONDAY, SEPTEMBER 9, 2024 - 15:30 - 16:45

MA05.10 Presenting Features and Diagnostic Delays of NUT Carcinoma: A Report from the NUT Carcinoma Registry

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Introduction: Diagnostic delays are common for patients with NUT Carcinoma (NC), an aggressive poorly differentiated/squamous cell cancer of lung/head and neck origin driven by the NUT fusion oncoprotein. Rapid diagnosis is essential for treatment initiation and trial consideration in a disease with a mOS in metastatic disease of 6.7 mo and no approved targeted therapies. We investigated presenting features of NC and associations with time-to-diagnosis.

Methods: We included U.S. participants enrolled in the NC registry from 2007-2024 with adequate records. Medical records and pathology reports were manually reviewed. Time from symptom to diagnosis (TSD) was defined as time from initial symptom onset until NC diagnosis (NCDx). Time from biopsy to diagnosis (TBD) was defined as time from initial biopsy until NCDx. We examined associations between age, gender, or race with TSD/TBD as dichotomized outcomes in separate models, using univariable logistic regression.

Results: We analyzed 100 patients with median age 37 (range 7-81) years; 49.0% were female, 82.7% (n=62/75) were White, 5.3% (n=4/75) were Black/African American, 6.7% (n=5/75) were Asian, and 3.4% were Hispanic (n=3/87). Initial cancer diagnosis was at an academic center in 37.0%. At presentation, 54.0% had metastatic disease, 68.0% had a thoracic primary, and 28.0% had a head and neck primary. The most common presenting symptoms for patients with thoracic primary were cough (48.5%, n=33/68) and dyspnea/fatigue (42.6%, n=29/68); for those with a non-thoracic primary, swelling/mass (40.6%, n=13/32) and congestion (34.4%, n=11/32). Infection (48.0%, n=48/100) was most common initial clinical diagnosis. TSD was an average of 4.3 months (median 3.0, range 0.3-32.5); TBD was an average of 41 days (median 20 days, range 1-919). Overall, 87.0% of initial biopsies had malignant cells; 28.0% needed a second biopsy. The first finalized pathology report showing cancer was NC in only 23.0% (n=20/87); the most common other diagnoses were poorly differentiated/squamous cell cancer 86.6% (n=58/67) and carcinoma 10.4% (n=7/67). Of pertinent IHC, 86.1% (n=62/72) were keratin (+), 83.3% (n=30/36) were p63 (+), and 88.9% (n=32/36) were p40 (+), 81.5% (n=22/27) had Ki-67 ≥50%. NC was diagnosed via NUT IHC in 85.0%, NUT FISH in 7.0%, and RNA fusion testing in 8.0%. For the TSD outcome, non-White race (OR=4.17, 95%CI 1.05-14.81) was associated with longer interval to NC diagnosis; age ≥50 (OR=2.79, 95%CI 0.99-8.05) and female sex (TSD: OR=0.65, 95%CI 0.28-1.51) were not. In contrast, for the TBD outcome, age ≥50 (OR=3.33, 95% CI 1.23-9.43) was associated with longer interval to NC diagnosis; non-White race (OR=0.57, 95%CI 0.18-1.76) and female sex (OR=0.84, 95% CI 0.38-1.83) were not. Of 24 patients who started treatment before a NC diagnosis, 83.3% were on a regimen used in NC. After a diagnosis of NC, 37.2% (n=35/94) participated in a clinical trial.

Conclusions: NUT carcinoma almost always presents as a squamous/poorly differentiated non-small cell lung (NSCLC) or head and neck cancer. Overall, 77% of NC diagnoses were initially missed, and 28% needed a second biopsy. After a diagnosis of NC, only 37% participated in a clinical trial. Results suggest widespread education on diagnosing NC is needed.

Keywords: NSCLC, fusion oncogene, diagnosis

MA05 TREATMENT TARGETS AND MONITORING MARKERS FOR MESOTHELIOMA AND THYMIC TUMORS
MONDAY, SEPTEMBER 9, 2024 - 15:30 - 16:45

MA05.11 Phase 3 Trial of Pleurodesis for Malignant Pleurisy: Sterile Graded Talc vs. OK-432 WJOG8415L (J-PLEURA)

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Introduction: WJOG8415L (J-PLEURA), was designed to evaluate the effectiveness and safety of sterile graded talc for pleurodesis in treating malignant pleural effusion, against OK-432, a lyophilized substance derived from group A Streptococcus pyogenes, which has been inactivated and processed with penicillin, the standard in Japan.

Methods: The primary endpoint was the success rate of pleurodesis effectiveness 30 days after the procedure, specifically looking at the absence of pleural fluid reaccumulation. Secondary endpoints included the duration until the reaccumulation of pleural effusion, the quarterly rate of patients remaining free of pleural effusion, assessments of quality of life (QoL), and the recording of side effects.

Participants included patients diagnosed with malignant pleural effusion associated with lung or gastrointestinal cancers, presenting symptoms such as dyspnea. The study consisted of two groups: Group A received intrathoracic OK-432, dosed at 0.2 KE/kg up to 10 KE, and Group B received 4g of sterile graded talc intrathoracically. Both groups had the therapeutic agents suspended in saline and injected into the chest cavity, followed by saline flushes to aid distribution. Fluid was then drained until daily volumes were at or below 150mL before drain removal. A secondary administration could be considered after seven days if necessary.

Candidates were eligible if they had a confirmed diagnosis through tissue or cytology, exhibited symptoms of respiratory distress due to pleural effusion, were expected to survive beyond 30 days post-procedure, and were over the age of 20 at consent. The study aimed to enroll 300 patients over two years, with a subsequent year of follow-up, and a final year dedicated to analysis.

Efficacy was gauged by the percentage of patients free from pleural effusion recurrence at 30 days and at subsequent time points. Safety was monitored by the incidence and grade of adverse events as per the CTCAE v4.0.

Results: 43.9% in the OK-432 group and 29.6% in the talc group met the primary endpoint, though without statistical significance (p=0.9965). A marginal benefit was noted for OK-432 in terms of three-month non-recurrence survival (p=0.0319). Safety profiles were similar across both treatments, and no significant difference in QoL was observed. However, there was one instance of treatment-related mortality in the OK-432 group due to pneumonia.

Conclusions: The trial determined no substantial difference between talc and OK-432 regarding pleurodesis efficacy in malignant pleural effusion. Both treatments had equivalent safety outcomes and similar impacts on QoL. While OK-432's insignificant advantage in non-recurrence survival rates over three months positions it as a viable option, the singular treatment-related death necessitates cautious interpretation, although it does not undermine its overall efficacy comparable to that of talc.

Keywords: Malignant Pleural Effusion, Pleurodesis, OK-432

MA06 NEW STRATEGIES IN ALK, ROS1, NTRK, BRAF, AND MET NSCLC
TUESDAY, SEPTEMBER 10, 2024 - 11:15 - 12:30

MA06.03 Efficacy and Safety of Taletrectinib in Patients with ROS1+ Non-Small Cell Lung Cancer: The Global TRUST-II Study

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This abstract is under embargo until September 10 at 11:35.

MA06 NEW STRATEGIES IN ALK, ROS1, NTRK, BRAF, AND MET NSCLC
TUESDAY, SEPTEMBER 10, 2024 - 11:15 - 12:30

MA06.04 Unecritinib in Patients with ROS1 Positive Advanced Non-Small Cell Lung Cancer: Updated Results from a Phase II Trial

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Introduction: Unecritinib (TQ-B3101), a novel multi-tyrosine kinase inhibitor targeting ROS1, ALK, and c-MET, had shown promising antitumor activity and acceptable safety profile in ROS1 inhibitor-naive patients with ROS1-positive advanced NSCLC from the phase II TQ-B3101-II-01 study (NCT03972189): objective response rate (ORR) was 80.2% and the median progression-free survival (PFS) was 16.5 months (data cut-off: Dec 20, 2021). Here we report updated data.

Methods: ROS1 inhibitor-naive patients with histologically confirmed locally advanced or metastatic NSCLC with ROS1 rearrangements received unecritinib 300 mg BID orally in continuous 28-day cycles until disease progression or unacceptable toxicity. The primary endpoint was ORR assessed by independent review committee (IRC) per RECIST 1.1. Secondary endpoints included duration of response (DOR), disease control rate (DCR), PFS, intracranial ORR, intracranial DOR, intracranial time to progression (TTP), intracranial PFS, overall survival (OS) and safety.

Results: The cutoff date for this analysis was Jun 20, 2022. Among 111 efficacy evaluable patients, ORR was 81.08% (95% CI, 72.55-87.89), the median PFS and DOR were 17.25 months (95% CI, 11.86-26.71) and 20.30 months (95% CI, 12.88-26.12), respectively. The median OS was not reached. Among 33 patients with baseline brain metastases, ORR was 72.73% (95% CI, 54.48-86.70), the median PFS, DOR and OS were 10.09 months (95% CI, 5.52-11.89), 9.23 months (95% CI, 7.36-11.04) and 28.22 months (95% CI, 19.25-36.53), respectively. Among 48 patients who had previously received chemotherapy, ORR was 79.17% (95% CI, 65.01-89.53), the median PFS and DOR were 19.32 months (95% CI, 10.12-not evaluable [NE]) and 20.30 months (95% CI, 11.04-NE), respectively. Among 11 patients with intracranial target lesions at baseline, the median intracranial DOR and intracranial TTP per RANO-BM were 9.36 months (95% CI, 7.39-26.12) and 17.25 months (95% CI, 8.25-NE), respectively. In the safety population (n=113), grade ≥3 treatment-related adverse events (TRAEs) occurred in 51.33% of patients. Treatment-related dose interruption, reduction and discontinuation occurred in 40.71%, 20.35% and 1.77% of patients, respectively. No patients died due to TRAEs. No grade ≥3 ocular disorders and neurotoxicity occurred.

Conclusions: In this updated analysis with longer follow-up, unecritinib continued to show the clinical benefit and manageable toxicities in ROS1-positive advanced NSCLC patients. Further analysis of OS will be performed as survival data mature.

Keywords: Unecritinib, ROS1, NSCLC

	Overall efficacy-evaluable patients (n= 111)	Baseline brain metastases (n=33)	Previous chemotherapy (n=48)
ORR, % (95% CI)	81.08 (72.55,87.89)	72.73 (54.48,86.70)	79.17 (65.01,89.53)
CR, n (%)	2 (1.80)	-	-
PR, n (%)	88 (79.28)	-	-
SD, n (%)	8 (7.21)	-	-
PD, n (%)	11 (9.91)	-	-
NE, n (%)	2 (1.80)	-	-
DOR, m (95% CI)	20.30 (12.88,26.12)	9.23 (7.36,11.04)	20.30 (11.04,NE)
PFS, m (95% CI)	17.25 (11.86,26.71)	10.09 (5.52,11.89)	19.32 (10.12,NE)
6 months, % (95% CI)	83.17 (74.62,89.05)	-	-
12 months, % (95% CI)	55.04 (44.64,64.27)	-	-
OS, m (95% CI)	NE (36.53, NE)	28.22 (19.25,36.53)	NE (30.39,NE)
12 months, % (95% CI)	96.35 (90.55,98.61)	-	-
24 months, % (95% CI)	82.18 (73.12,88.42)	-	-

MA06 NEW STRATEGIES IN ALK, ROS1, NTRK, BRAF, AND MET NSCLC
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MA06.05 A Phase II Study of Lorlatinib in Advanced ROS1+ NSCLC Pre-Treated with Crizotinib and Platinum-Based Chemotherapy

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Introduction: Early-generation ROS1 tyrosine kinase inhibitors (TKIs) approved for the treatment of ROS1-positive (ROS1+) non-small cell lung cancer (NSCLC) exhibit antitumor activity, but resistance commonly develops, and their intracranial activity is suboptimal. Lorlatinib, a ROS1 and anaplastic lymphoma kinase (ALK) inhibitor, demonstrates properties of brain-penetration and overcoming resistance to crizotinib driven by ROS1 mutations. Robust antitumor activity of lorlatinib was observed among patients with ROS1+ NSCLC, including those with central nervous system (CNS) metastases, in a global Phase I/II study (B7461001). Herein, we present the efficacy and safety results from a Phase II, multi-center, single-arm study in China (NCT05297890) investigating lorlatinib in patients with locally advanced or metastatic ROS1+ NSCLC.

Methods: Adult patients with advanced ROS1+ NSCLC pre-treated with crizotinib and platinum-based chemotherapy were enrolled in the study. All patients received lorlatinib 100 mg QD continuously. The primary endpoint was objective response rate (ORR) assessed by independent central radiology (ICR) per RECIST v1.1. Secondary endpoints included ICR-assessed parameters, such as duration of response (DoR), intracranial ORR (IC-ORR), IC-DoR, progression-free survival (PFS), as well as overall survival (OS) and safety. Adverse events (AEs) were graded per NCI-CTCAE v5.0.

Results: As of the data cutoff date (26 December 2023), 70 patients were enrolled. Median age was 55.0 years (range 32-80). Other characteristics included: female (61.4%); brain metastasis (62.9%); adenocarcinoma (94.3%). Median treatment duration was 7.4 months (range 0.2-19.0). The study met its primary objective by demonstrating a clinically meaningful and statistically significant improvement in ICR-assessed ORR. Among evaluable participants (n=65), the ICR-assessed ORR was 44.6%. Among 37 participants with baseline intracranial lesions, the IC-ORR was 43.2% and 8 (21.6%) participants achieved CR. Detailed efficacy results are shown in the table. All 70 patients experienced at least one all-causality treatment-emergent AE (TEAE); the most common TEAEs (by cluster term*/PT) were hypercholesterolemia* (95.7%) and hypertriglyceridemia* (85.7%). Grade ≥3 treatment-related AEs (TRAEs) occurred in 30 (42.9%) patients; the most common Grade ≥3 TRAEs were hypertriglyceridemia* (27.1%) and hypercholesterolemia* (15.7%). TRAEs leading to dose reduction were reported in 12 (17.1%) patients. No TRAE leading to permanent treatment discontinuation or TRAE leading to death was reported.

Conclusions: Lorlatinib demonstrated robust and durable objective response and notable intracranial activity in patients with advanced ROS1+ NSCLC pre-treated with crizotinib and chemotherapy. Lorlatinib was well-tolerated, and safety data from this study was consistent with the known safety profile of lorlatinib.

Table: Lorlatinib Efficacy in Patients with Advanced ROS1+ NSCLC (Assessed by ICR)

Best overall response (ERAS[a])	
No. of patients in analysis	N=65
ORR (CR+PR) (%)	29 (44.6)
95% exact CI[b]	(32.3, 57.5)
PR	29 (44.6%)
Duration of objective response	
No. of patients in analysis	N=29
Number (%) of Patients with Events	5 (17.2)
Median (months) (95% CI[c])	NR(13.8, NR)
6-mo estimate(95% CI[d])	88.4%(68.0%, 96.1%)
Progression-free survival (SA)	
No. of patients in analysis	N=70
Number (%) of Patients with Events	27 (38.6%)
Median (months)(95% CI[c])	17.9(6.9, NR)
Best intracranial overall response (SA[e])	
No. of patients in analysis	N=37
IC-ORR (CR+PR) (%)	16 (43.2)
95% exact CI[b]	(27.1, 60.5)
CR	8 (21.6%)
PR	8 (21.6%)
Duration of intra-cranial objective response	
No. of patients in analysis	N=16
Number (%) of patients with Events	3 (18.8)
Median (months)(95% CI[c])	13.8 (6.8,NR)

CI: confidence interval; CR: complete response; ERAS: evaluable for response analysis set; ICR: independent central radiology; IC-ORR: intracranial objective response rate; NSCLC: non-small cell lung cancer; NR: not reached; PR: partial response; SA: safety analysis set. a. The analysis was assessed in evaluable for response analysis set includes all patients who have received at least one dose of lorlatinib and have measurable disease at baseline according to the ICR confirmation.b. Using exact method based on binomial distribution.c. Using Brookmeyer Crowley method.d. Using Greenwood's formular with log (-log) method.e. The analysis was assessed in safety analysis set with baseline intracranial lesion assessed by ICR.

Keywords: Lorlatinib, ROS1, NSCLC

MA06 NEW STRATEGIES IN ALK, ROS1, NTRK, BRAF, AND MET NSCLC
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MA06.07 Patterns of Progression with Lorlatinib and Insights into Subsequent Anticancer Therapy Efficacy in Advanced ALK+ NSCLC

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Introduction: Lorlatinib, a brain-penetrant, third-generation anaplastic lymphoma kinase (ALK) tyrosine kinase inhibitor (TKI), demonstrated statistically significant and clinically meaningful improvement in progression-free survival (PFS) vs crizotinib in the phase 3 CROWN study in patients with previously untreated advanced ALK+ non-small cell lung cancer (NSCLC; NCT03052608). This study investigated the efficacy of subsequent treatments following discontinuation of lorlatinib or crizotinib in the CROWN study after 5 years of follow-up and different characteristics of early progressors to lorlatinib and patients who remained progression free after 5 years.

Methods: Patients were randomized 1:1 to receive oral lorlatinib 100 mg once daily or crizotinib 250 mg twice daily. The primary endpoint was PFS by blinded independent central review. Secondary endpoints included time from randomization to the date of disease progression with first subsequent systemic anticancer therapy or death (PFS2).

Results: As of October 31, 2023, after 5 years of follow-up, first-line lorlatinib showed prolonged benefit, with median PFS not reached (NR) and 60% of patients being progression free. At the time of data cutoff, 75 of 149 (50%) and 135 of 142 (95%) patients had discontinued lorlatinib and crizotinib, respectively. Among patients who discontinued lorlatinib, only 8 progressed intracranially. Of the 38 patients in the lorlatinib group and 109 in the crizotinib group who received ≥1 subsequent systemic anticancer therapy, ALK TKIs were the first subsequent treatment in 23 (61%) and 101 (93%), respectively, and chemotherapy was the first subsequent treatment in 15 (39%) and 4 (4%). Median duration of the first subsequent treatment was 9.3 months (IQR, 2.6-22.6) with lorlatinib and 14.9 months (IQR, 5.3-38.4) with crizotinib. Objective response rates with the first subsequent systemic anticancer therapy were higher in patients previously treated with lorlatinib than with crizotinib (Table). With a median follow-up for PFS2 of 61.4 months (95% CI, 59.2-62.5) with lorlatinib and 58.4 months (95% CI, 56.8-61.9) with crizotinib, median PFS2 was NR (95% CI, NR-NR) with lorlatinib and 37.9 months (95% CI, 27.4-50.1) with crizotinib (HR, 0.43; 95% CI, 0.30-0.62). Additional analyses are ongoing to assess different clinical and molecular characteristics of patients who progressed during the first year of treatment vs those who remained progression free after 5 years.

Conclusions: In patients who discontinued lorlatinib due to any reason, subsequent systemic treatments appeared to offer additional benefit demonstrated by clinical outcomes and prolonged PFS2.

Keywords: non-small cell lung cancer, lorlatinib

Study treatment	Lorlatinib			Crizotinib		
First Subsequent Therapy	Any ALK TKI (n=23)[a]	Any non-ALK TKI (n=15)[b]	Overall (n=38)	Any ALK TKI (n=101)[a]	Any non-ALK TKI (n=8)[b]	Overall (n=109)
Objective response rate (95% CI), %[c]	26.1 (10.2-48.4)	20.0 (4.3-48.1)	23.7 (11.4-40.2)	17.8 (10.9-26.7)	12.5 (0.3-52.7)	17.4 (10.8-25.9)
Best overall response, n (%)						
Complete response	2 (9)	1 (7)	3 (8)	1 (1)	0	1 (1)
Partial response	4 (17)	2 (13)	6 (16)	17 (17)	1 (13)	18 (17)
Stable disease	1 (4)	3 (20)	4 (11)	23 (23)	0	23 (21)
Progressive disease	6 (26)	3 (20)	9 (24)	10 (10)	2 (25)	12 (11)
Unknown	3 (13)	5 (33)	8 (21)	9 (9)	4 (50)	13 (12)
Not reported, therapy ongoing	7 (30)	1 (7)	8 (21)	41 (41)	1 (13)	42 (39)

[a]Includes alectinib, brigatinib, ceritinib, crizotinib, and lorlatinib. [b]Includes chemotherapy ± anti-angiogenic, chemotherapy/immunotherapy, chemotherapy/immunotherapy/anti-angiogenic, or other (investigational drug, cabozantinib, osimertinib). [c]Using the Clopper-Pearson method.

MA06.08 Kinetics and Management of Adverse Events Associated with Lorlatinib after 5 Years of Follow-Up in the CROWN Study

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Introduction: Lorlatinib is approved for the treatment of patients with metastatic ALK+ non-small cell lung cancer (NSCLC). Because lorlatinib has a unique safety profile, in this post hoc analysis, we present kinetics of selected adverse events (AEs) from the CROWN study after 5 years of follow-up to suggest optimized therapy management strategies.

Methods: In the CROWN study, patients with previously untreated advanced ALK+ NSCLC were randomized 1:1 to receive oral lorlatinib 100 mg once daily or crizotinib 250 mg twice daily. Safety analyses include incidence, prevalence, time to onset, and duration for selected AEs associated with lorlatinib that led to dose reduction or interruption.

Results: As of October 31, 2023, with a median duration of follow-up for progression-free survival (PFS) of 60.2 months (95% CI, 57.4-61.6 months), median PFS was not reached (95% CI, 64.3 months-not reached) with lorlatinib (n=149). All-cause AEs led to lorlatinib dose reduction in 23% of patients, temporary discontinuation in 62%, and permanent discontinuation in 11%. Dose reduction within the first 16 weeks did not impact PFS or time to intracranial progression. Most common AEs leading to dose reduction (in ≥3% of patients) were edema (7%), hypertriglyceridemia (4%), cognitive effects (3%), mood effects (3%), and peripheral neuropathy (3%); AEs leading to temporary discontinuation (in ≥5% of patients) were hypertriglyceridemia (8%), pneumonia (8%), cognitive effects (6%), SARS-CoV-2 test positive (6%), edema (5%), peripheral neuropathy (5%), and mood effects (5%); and AEs leading to permanent discontinuation (in >1% of patients) were cognitive effects (1%) and cardiac failure (1%). Median time to onset and duration of most common lorlatinib-related AEs leading to dose reduction or interruption are shown in Table. Additional analyses to explore the outcomes of selected AEs following therapy management is ongoing.

Conclusions: This post hoc analysis after 5 years of follow-up suggests that with long exposure to lorlatinib, treatment discontinuation due to AEs remained low, and most AEs were effectively managed with dose modifications. Systemic and intracranial outcomes in patients who underwent dose reduction were similar to those in patients who did not undergo dose reduction, indicating that dose reductions may be an effective strategy to mitigate toxicity without compromising efficacy of lorlatinib. ClinicalTrials.gov NCT03052608

Keywords: non-small cell lung cancer, lorlatinib, long-term safety

Incidence and prevalence of CNS AEs			
Time interval	**n**	**Incidence, n (%)**	**Prevalence, n (%)**
0-6 months	149	37 (25)	37 (25)
6 months-1 year	129	14 (11)	28 (22)
1-2 years	117	17 (15)	32 (27)
2-3 years	98	12 (12)	26 (27)
3-4 years	90	7 (8)	23 (26)
4-5 years	84	9 (11)	22 (26)
≥5 years	79	1 (1)	9 (11)
Time to onset and duration of most common AEs that led to dose reduction or interruption			
AEs	**n**	**Time to onset, median (range), days**	**Duration of AE, median (range), days**
Hypercholesterolemia	108	14 (1-1205)	1093 (14-2256)
Hypertriglyceridemia	99	15 (6-973)	1151 (23-2247)
Edema	85	54 (1-1503)	366 (4-2045)
Peripheral neuropathy	65	113 (2-1784)	546 (7-1990)
CNS AEs	63	116 (1-1657)	237 (2-2071)

MA06 NEW STRATEGIES IN ALK, ROS1, NTRK, BRAF, AND MET NSCLC
TUESDAY, SEPTEMBER 10, 2024 - 11:15 - 12:30

MA06.09 Predictors of Long-Term Ensartinib Response from the eXalt3 Trial

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Introduction: We profiled enrollment samples from patients in the eXalt3 Phase 3 trial and have continued to follow patient outcomes to assess biomarker predictive value. Here we profile three patients who, as of December 2023, have continued to respond to ensartinib, despite showing biomarkers of resistance to other ALK inhibitors.

Methods: We obtained 13 clinical samples (FFPE) before treatment with ALKi and performed spatial transcriptomics using the Visium CytAssist platform. We followed three patients who continued to respond to ensartinib for at least 72 cycles or five years. The REvolution system nominated biomarkers of resistance and response to ensartinib, using long-term (>3 months) culture of cells without the need for passaging and conserving resistance pathways over time. We cultured two ALK-dependent, NSCLC cell lines in the presence of ensartinib. H3122 cells became resistant within 14 days, while H2228 cells remained sensitive to ensartinib for over 42 days, despite becoming resistant to alectinib, lorlatinib, and crizotinib in a parallel experiment. We used the H3122 and H2228 evolved populations to nominate ensartinib resistance and response biomarkers, respectively.

Results: 3 patients were found to continue to respond to ensartinib despite displaying clinically validated ALK inhibitor resistance mechanisms, including sub-populations with EGFR, YAP1, and MET activation. Analysis of enrollment biopsy samples showed these mechanisms were present intrinsically, prior to treatment. We identified eight potential biomarkers of ensartinib long-term response using cells evolved in REvolution. We found that these biomarkers were activated (>4.3 Log2FC) in susceptible H2228 evolved cells and not changed or deactivated (up to -4.7 Log2FC) in resistant H3122 resistant evolved cells. The three long-term responding patients exhibited between one and four of the ensartinib response biomarkers. The sub-populations expressing general ALK inhibitor resistance mechanisms tended to coexpress ensartinib response biomarkers in these patients.

Conclusions: We profiled three patients who have continued to respond to ensartinib for over 70 cycles, despite exhibiting clinically validated resistance mechanisms to other ALK inhibitors at enrollment. The REvolution, long-term evolution system, identified biomarkers which predicted response to ensartinib.

Keywords: ALK, NSCLC, resistance

MA06 NEW STRATEGIES IN ALK, ROS1, NTRK, BRAF, AND MET NSCLC
TUESDAY, SEPTEMBER 10, 2024 - 11:15 - 12:30

MA06.11 Phase II Trial of Ensartinib for Advanced or Metastatic Non-Small-Cell Lung Cancer with MET Exon 14 Skipping Mutations

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Introduction: Met proto-oncogene exon 14 skipping (METex14) mutations have been identified as treatable non-small cell lung cancer (NSCLC) tumor driver genes. Ensartinib is originally considered as a second-generation ALK inhibitor, our pre-clinical and pilot clinical data have exhibited the potential of ensartinib as a MET inhibitor. Current study aimed to evaluate the efficacy and safety of ensartinib for advanced or metastatic NSCLC with METex14 mutations.

Methods: This is a single-arm, multi-center, phase II study (ChiCTR2100048767). Eligible patients (aged ≥18 years) were histologically/ cytologically confirmed advanced or metastatic NSCLC with METex14 mutations, wild type EGFR/ALK/ROS1, TKI-naïve, with ≥1 measurable lesion, and had disease progression or intolerance after ≥1 cycle of platinum-based chemotherapy, ECOG PS ≤2 and the predicted survival time was ≥3 months. Patients received oral ensartinib 225 mg once daily until disease progression or intolerance. The primary endpoint was objective response rate (ORR). Secondary endpoints were duration of response (DOR), disease control rate (DCR), progression-free survival (PFS), and safety.

Results: From July 2021 to February 2024, 31 patients (15 males, median age, 72 years [range, 47-84]) were enrolled and received ensartinib therapy; of whom, the majority was adenocarcinoma (28/31, 90.3%), TNM stage IV (25/31, 80.6%), and ECOG PS ≤1 (20/31, 64.5%). In 30 evaluable patients, the median follow-up time was 11.1 months (range, 4.1-18.1). 23 patients (76.7%) had a decrease in tumor burden compared with baseline, the ORR was 53.3% (16/30; 95% CI, 36.1%-69.8%) and the DCR was 86.7% (26/30; 95% CI, 70.3%-94.7%). The median time to first response was 0.93 months (95% CI, 0.87-0.99 months) and the median DOR was 7.9 months (95% CI, 2.9-12.9 months). Median PFS was 6.0 months (95% CI, 4.4-7.6 months). 4 of 5 patients with brain metastases at baseline had achieved partial response. Adverse events (AEs) were reported in 24 patients (80%), with 7 (23.3%) of grade 3. The most common AEs were rash (14/30, 46.7%), anemia (7/30, 23.3%), ALT increased (7/30, 23.3%), AST increased (7/30, 23.3%), and pruritus (6/30, 20%). No serious events and treatment-related death occurred. In addition, we estimated the association between ctDNA clearance(baseline, V0; after 4 weeks treatment, V1) and therapeutic efficacy in 17 patients, showing that complete clearance (ctDNA positive at V0 and negative at V1) was corelated with best ORR (80%; 95% CI, 37.6%-96.4%), followed by patients with ctDNA negative at both V0 and V1 was 42.9% (95% CI, 15.8%-75.0%), the response rate was worst in patients with non-clearance (ctDNA positive at both V0 and V1; 20%; 95% CI, 3.6%-62.5%).

Conclusions: This phase II study demonstrated that ensartinib had an encouraging anti-tumor activity and manageable safety profile in patients with advanced or metastatic NSCLC harboring METex14 mutations. This regimen is expected to provide a promising treatment option for this population.

Keywords: ensartinib, non-small-cell lung cancer, MET exon 14 skipping mutations

MA06 NEW STRATEGIES IN ALK, ROS1, NTRK, BRAF, AND MET NSCLC
TUESDAY, SEPTEMBER 10, 2024 - 11:15 - 12:30

MA06.12 Updated Efficacy, Safety, and Biomarker Analysis in Patients with TRK Fusion Lung Cancer Treated with Larotrectinib

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Introduction: NTRK gene fusions are oncogenic drivers in a variety of cancers including lung cancer. Larotrectinib is the first-in-class, highly selective, CNS-active TRK inhibitor approved in the tumor-agnostic setting for patients with TRK fusion cancer based on a robust and durable efficacy demonstrated in patients with various tumor types. Here, we report updated efficacy and safety data along with biomarker analysis in patients with TRK fusion lung cancer treated with larotrectinib.

Methods: Patients with TRK fusion lung cancer treated with larotrectinib in 2 clinical trials (NCT02122913 and NCT02576431) were included. Larotrectinib was administered at 100 mg twice daily. Response was assessed by an independent review committee (IRC) per Response Evaluation Criteria in Solid Tumors version 1.1. The data cutoff was July 20, 2023.

Results: As of the data cutoff, 32 patients with a median age of 55.5 years (range 25-81) with TRK fusion lung cancer were enrolled, including 12 with CNS metastases at baseline. NTRK gene fusions were identified locally by next-generation sequencing (NGS) in all patients. The gene fusions involved NTRK1 (n=24; 75%) and NTRK3 (n=8; 25%). Patients had received a median of 2 prior lines of systemic therapies; 1 patient was treatment-naïve. The overall response rate per IRC was 66% (95% confidence interval [CI] 47-81): 4 complete responses, 17 partial responses, 7 stable disease, 2 progressive disease, and 2 not evaluable. The median time to first response was 1.8 months (range 1.5-7.3). The median duration of response was 34 months (95% CI 10-not estimable [NE]) with a median follow-up of 26 months. The median progression-free survival was 22 months (95% CI 10-NE) with a median follow-up of 28 months. The median overall survival was 39 months (95% CI 17-NE) with a median follow-up of 33 months. The duration of treatment ranged from 2 to 75+ months. At the time of data cutoff, 11 patients had progressed, of whom 6 continued treatment post-progression for ≥4 weeks due to continued clinical benefit. Treatment-related adverse events (TRAEs) were predominantly Grade 1/2. Grade 3/4 TRAEs were reported in 9 patients. One patient discontinued treatment due to TRAEs (increased alanine aminotransferase, aspartate aminotransferase, and gamma-glutamyltransferase). Baseline genomic data derived from either circulating tumor DNA (ctDNA; n=15 patients) or tissue DNA (n=13 patients) were available for a total of 16 patients. Baseline ctDNA analysis detected NTRK gene fusions in 6 of 15 patients. Additional baseline NTRK and known or likely oncogenic co-occurring mutations were identified in 6 of the 16 patients. Post-baseline potential oncogenic mutations were identified in 7 of 13 patients that had available DNA samples. Five patients had acquired potential resistance mutations: 2 patients had on-target mutations, 2 patients had off-target mutations and 1 patient had both.

Conclusions: Larotrectinib continues to demonstrate rapid and durable responses, extended survival benefit, and a favorable safety profile in patients with advanced TRK fusion lung cancer. These results support the use of NGS panels, including ctDNA, to detect NTRK gene fusions in patients with lung cancer to identify those who may benefit from targeted treatment.

Keywords: lung cancer, larotrectinib, NTRK gene fusion

MA06 NEW STRATEGIES IN ALK, ROS1, NTRK, BRAF, AND MET NSCLC
TUESDAY, SEPTEMBER 10, 2024 - 11:15 - 12:30

MA06.13 Updated Safety Analysis of Encorafenib Plus Binimetinib in Patients with BRAF V600e-Mutant Metastatic NSCLC from PHAROS Study

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Introduction: The combination of encorafenib (BRAF inhibitor) and binimetinib (MEK inhibitor) showed meaningful clinical benefit and a manageable safety profile in the phase 2 PHAROS study (NCT03915951) in patients with BRAF V600E-mutant metastatic non-small cell lung cancer (mNSCLC). This updated analysis reports the safety profile of the combination after an additional 10 months of follow-up since the primary analysis.

Methods: PHAROS is an ongoing study evaluating encorafenib 450 mg once daily plus binimetinib 45 mg twice daily in patients with BRAF V600E-mutant mNSCLC who were either treatment-naïve or had received 1 prior therapy for metastatic disease. We investigated the treatment-related adverse event (TRAE) profile by treatment line and time to onset of specific clusters of TRAEs, which were selected based on prior clinical trial experience.

Results: As of July 19, 2023, encorafenib plus binimetinib treatment was ongoing in 19 (32%) treatment-naïve (n=59) and 4 (10%) previously treated patients (n=39). Median duration of treatment was 16.3 months for treatment-naïve and 5.5 months for previously treated patients; 41% and 10% of patients have received >2 years of treatment, respectively. The most common (>30% in either arm) TRAEs were similar in treatment-naïve and previously treated patients: nausea (59% and 41%), diarrhea (41% and 49%), fatigue (31% and 33%), and vomiting (31% and 28%) (TRAEs in ≥10%; Table). All treatment-related pyrexia events were Grade 1 or 2 in treatment-naïve (10% and 2%) and previously treated patients (3% and 0%). In previously treated patients with (n=24) and without (n=15) prior immunotherapy, the most common (>30%) TRAEs were diarrhea (50% and 47%), fatigue (50% and 7%), nausea (46% and 33%), and vomiting (33% and 20%). In the overall population, the most common specific TRAE clusters were retinopathy excluding retinal vein occlusion (26%), rash (24%), and liver function test abnormalities (16%), with median times to onset of 0.1, 2.0, and 1.8 months, respectively. In the overall population, TRAEs led to dose interruptions, reductions, and permanent discontinuations of encorafenib in 48%, 31%, and 18% of patients, respectively, and of binimetinib in 54%, 33%, and 19% of patients, respectively.

Conclusions: This updated safety analysis after 10 months of additional follow-up of encorafenib plus binimetinib in patients with BRAF V600E-mutant mNSCLC showed similar TRAE profiles in treatment-naïve and previously treated patients. The safety profile remained manageable and generally consistent with that seen in the earlier analysis and that established for patients with BRAF V600E/K-mutant metastatic melanoma.

Table. Treatment-Related Adverse Events in ≥10% of Patients in Either Group

	Treatment-naïve (n=59)	Previously treated (n=39)				
	Grade 1	Grade 2	Grade 3/4	Grade 1	Grade 2	Grade 3/4
Any event, n (%)[a]	3 (5)	22 (37)	32 (54)	6 (15)	15 (39)	13 (33)
Nausea	20 (34)	12 (20)	3 (5)	5 (13)	10 (26)	1 (3)
Diarrhea	11 (19)	10 (17)	3 (5)	9 (23)	9 (23)	1 (3)
Fatigue	8 (14)	10 (17)	0	5 (13)	6 (15)	2 (5)
Vomiting	10 (17)	7 (12)	1 (2)	9 (23)	2 (5)	0
Vision blurred	9 (15)	2 (3)	1(2)	6 (15)	0	0
Alanine aminotransferase increased	2 (3)	5 (8)	4 (7)	1 (3)	0	1 (3)
Asparate aminotransferase increased	5 (8)	0	6 (10)	1 (3)	0	1 (3)
Anemia	1 (2)	7 (12)	2 (3)	3 (8)	3 (8)	1 (3)
Constipation	6 (10)	3 (5)	0	4 (10)	1 (3)	0
Abdominal pain	4 (7)	4 (7)	0	1 (3)	1 (3)	0
Blood alkaline phosphatase increased	3 (5)	3 (5)	2 (3)	0	0	0
Blood creatine phosphokinase increased	3 (5)	4 (7)	1 (2)	2 (5)	1 (3)	0
Dry skin	8 (14)	0	0	3 (8)	0	0
Lipase increased	0	1 (2)	7 (12)	1 (3)	0	0
Alopecia	7 (12)	0	0	3 (8)	0	0
Decreased appetite	4 (7)	3 (5)	0	0	1 (3)	1 (3)
Pyrexia	6 (10)	1 (2)	0	1 (3)	0	0
Dizziness	4 (7)	2 (3)	0	4 (10)	0	1 (3)
Myalgia	1 (2)	3 (5)	2 (3)	4 (10)	0	0
Peripheral edema	4 (7)	2 (3)	0	3 (8)	2 (5)	0
Pruritus	5 (8)	1 (2)	0	5 (13)	1 (3)	0
Rash	6 (10)	0	0	2 (5)	0	1 (3)
Rash maculopapular	4 (7)	1 (2)	1 (2)	2 (5)	2 (5)	0
Asthenia	1 (2)	1 (2)	1 (2)	4 (10)	1 (3)	2 (5)
Ejection fraction decreased	0	2 (3)	2 (3)	1 (3)	2 (5)	1 (3)

[a] Arranged in decreasing incidence of total number of patients across Grades 1-4 in the treatment-naïve group.

Keywords: non-small cell lung cancer, encorafenib, binimetinib

MA07 NOVEL TARGETS TO OVERCOME RESISTANCE TO THERAPY
TUESDAY, SEPTEMBER 10, 2024 - 11:15 - 12:30

MA07.03 Systematic Engineering of TROP2 CAR T Cell Therapy to Overcome Resistance Pathways in EGFRmutant NSCLC

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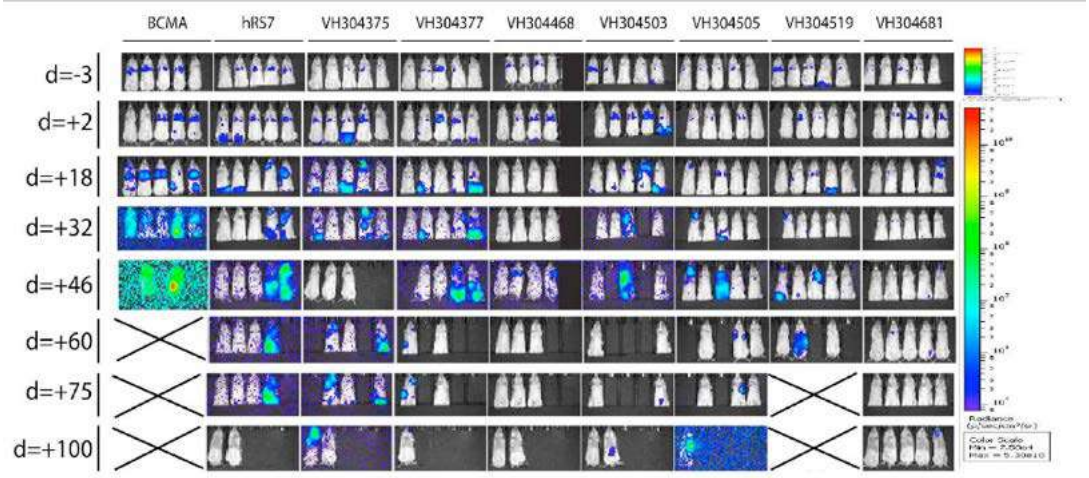
Introduction: While tyrosine kinase inhibitors in EGFR mutant (EGFRm) NSCLC have shown excellent response rates, durable responses are rare in the advanced/metastatic setting. After the development of acquired resistance, second line therapies have low response rates. Immune checkpoint inhibitors have not demonstrated any benefit in patients harboring EGFRm NSCLC. There is an unmet need for therapies which can lead to durable activity in patients with EGFRm NSCLC. Antibody drug conjugates (ADC) have shown activity in the second line setting in NSCLC, though durable responses are rare. We propose utilizing TROP2 directed CAR T to treat EGFRm NSCLC including in the setting of resistance to EGFR inhibitors and ADC.

Methods: We developed a novel approach to treat EGFRm NSCLC by targeting the protein TROP2 using CAR T. We also developed novel fully humanized VH binders against TROP2 in CAR T constructs. We evaluated our CAR utilizing in vitro and in vivo models of EGFRm NSCLC including in patient derived xenografts.

Results: We show that CAR T cell therapy has a high degree of cytotoxicity in pre-clinical models of EGFRm NSCLC such as cell lines (93% cytotoxicity at 1:1 E:T against PC9 at 24 h compared to control CAR $p < 0.01$), in patient derived samples, and in the setting of acquired resistance to EGFRi. We also demonstrate that in the setting of resistance to TROP2 ADC due to low epitope expression such as TROP2 T256R mutation and mutations in the topoisomerase pathway, CAR T based killing is maintained (TROP2 T256Rm TROP2 CAR 61% cytotoxicity vs 19% in TROP2 ADC $p<0.01$). We developed novel fully human VH CAR T constructs that are highly active against EGFRm NSCLC models including prolonged survival compared to our benchmark sacitizumab based CAR T (Median survival 83 days vs not reached at day 122; p-value 0.049). We map the epitopes of our novel TROP2 VH CAR T constructs which revealed ability to target novel epitopes not accessible to traditional antibody based single chain variable fragment (scFv) based approaches.

Conclusions: We evaluated the activity of TROP2 CAR T in EGFRm NSCLC including in EGFRi resistant and TROP2 ADC resistant setting. We demonstrate a high degree of in vivo activity of our TROP2 CAR T against multiple in vivo models of EGFRm NSCLC. We map the epitopes targeted by scFv based TROP2 ADC as well as developed novel TROP2 fully human VH based CAR T that target novel epitopes of TROP2.

Keywords: Immunotherapy, EGFR, Cellular Therapy



In vivo activity of novel TROP2 VH based CAR T. Mice were injected with PC9 ffLuc+ and after engraftment confirmed given control BCMA CAR-T or TROP2 CAR-T at 0.3E6 CAR+/mouse. Tumor was measured subsequently by BLI.

MA07 NOVEL TARGETS TO OVERCOME RESISTANCE TO THERAPY
TUESDAY, SEPTEMBER 10, 2024 - 11:15 - 12:30

MA07.04 Targeting CD24 Enhances the Response to Third-Generation Tyrosine Kinase Inhibitors in EGFR-Mutant Non-Small Cell Lung Cancer

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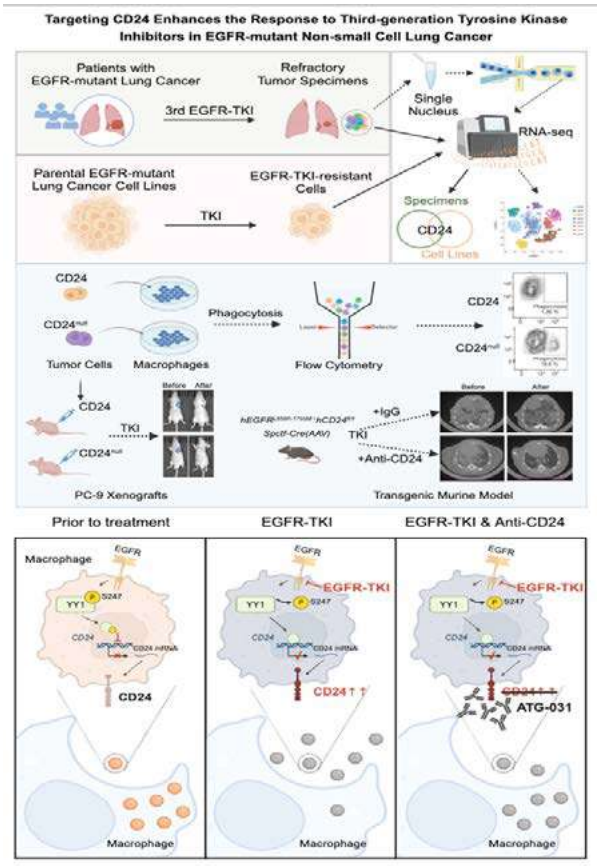
Introduction: Approximately 10-20% of NSCLC patients have EGFR activating mutations. Osimertinib, a third-generation EGFR TKI, selectively inhibits both EGFR-TKI sensitizing and resistant mutations, making it the first-line treatment for EGFR-mutant advanced NSCLC. Several other third-generation EGFR TKIs, such as almonertinib and furmonertinib, have been developed and approved in China. However, these treatments hardly eliminate disease, and most patients develop tumor resistance and disease progression. While the addition of platinum-based chemotherapy or immunotherapy to osimertinib showed superior efficacy in advanced or recurrent EGFR-mutant NSCLC patients, there are currently no promising treatments for cases with TKI-refractory diseases. This emphasizes the need for new EGFR TKI-refractory NSCLC treatments.

Methods: Three acquired resistant cell models with cross-resistance to third-generation EGFR TKIs were generated from three patient-derived EGFR-mutant NSCLC cell lines. Cell models were used to examine drug responsiveness, tolerance, and resistance expression changes during TKI-resistance evolution using RNA sequencing. RNA or single-nucleus RNA sequencings were performed on tumor specimens from 17 patients with EGFR-mutant NSCLC, including nine who had received TKIs for locally advanced disease with incomplete response. Transgenic mouse models were used using Cre/LoxP-inducible expression of L858R/T790M mutant human EGFR, which developed lung adenocarcinomas after induction with AAV. Mass spectrometry-based phospho-proteomics and 3C-sequencing were conducted to investigate the transcriptomic expression changes in cells with TKI-resistance.

Results: We investigate cell surface proteins that could be targeted and identify CD24 as being consistently heightened in responsive, tolerant, and resistant cells in response to TKI compared to their parental cells according to RNA profiling. Single-nucleus RNA sequencing data of clinical tumors indicates elevated CD24 expression in cancer cell cluster in the TKI-refractory tumors compared to the TKI-naïve group. Moreover, high CD24 expression was associated with increased risk of tumor relapse compared with the low-CD24 group in patients who have received adjuvant osimertinib. CD24 promotes cell survival and phagocytic resistance by macrophages in TKI-refractory tumor cells. Knock out of CD24 gene or anti-CD24 antibody enhances the PC9 xenograft eradication by osimertinib. In transgenic mouse models, anti-CD24 and osimertinib synergistically suppresses the growth of EGFR-mutant tumor expressing humanized CD24. Finally, we demonstrate that EGFR TKI suppresses YY1 phosphorylation at the S247 site, which increases CD24 gene transactivation via an enhancer-promoter structural interaction.

Conclusions: Enhanced CD24 expression in response to third-generation TKI treatment plays a critical role in surviving during the initial treatment in EGFR-mutant NSCLC. Targeting of CD24 in combination with third-generation TKI synergizes to eradicate EGFR-mutant NSCLC.

Keywords: EGFR tyrosine kinase inhibitor, Drug resistance, CD24



MA07 NOVEL TARGETS TO OVERCOME RESISTANCE TO THERAPY
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MA07.05 Unbiased Functional Genomics Screen Identifies Unique Therapeutic Vulnerabilities in Osimertinib-Resistant NSCLCs

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Introduction: Osimertinib is a third-generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) with marked clinical efficacy in early- and late-stage non-small cell lung cancer (NSCLC) patients harboring EGFR mutant tumors, particularly exon 19 deletions or L858R mutations. Despite a significant survival advantage conferred by osimertinib monotherapy, most late-stage patients will develop progressive, osimertinib-resistant disease that is only marginally responsive to currently available salvage therapies. Mounting evidence suggests that the evolutionary pressures exerted on malignant cells during their acquired resistance to molecularly targeted therapies often lead to the acquisition of common and exploitable cellular traits, so-called 'collateral sensitivities,' that arise irrespective of the genomic changes that engender resistance. We hypothesize that osimertinib-resistant NSCLCs are functionally dependent upon convergent, actionable, and EGFR-independent cellular processes which can be therapeutically targeted to overcome the diversity of osimertinib-resistant cellular populations present among EGFR-mutant NSCLC patients.

Methods: We generated models of osimertinib resistance using a diverse series of patient-derived EGFR-mutant NSCLC cell lines, including several derived from the tumors of patients who were either EGFR TKI-naïve (e.g., MGH-119 and MGH-1109) or who had disease progression while on EGFR TKI therapy (e.g., MGH-134 and MGH-141), as well as multiple prototypic EGFR-mutant NSCLC cell lines (e.g., PC9, HCC827, and H1975). These cell lines were rendered osimertinib-resistant via long-term propagation (~10-14 weeks) in escalating concentrations of osimertinib until a durable >10-fold increase in GI50 was obtained. We then performed whole-genome (i.e., MinLib sgRNA library) CRISPR-Cas9 loss-of-function screens on a subset of these parental and osimertinib-resistant NSCLC derivatives. Following pooled library deep sequencing at >500x coverage and subsequent deconvolution, gene-level 'essentiality scores' were derived from differentially enriched or depleted sgRNAs to allow for the identification of differentially essential genes in parental and osimertinib-resistant populations.

Results: Of the top 500 differentially essential genes within each patient-derived cell line (e.g., genes most essential to the outgrowth of osimertinib-resistant cells but most dispensable to drug-sensitive cells), 8 genes were commonly represented among all 6 cell lines screened to date and a further 85 genes commonly represented among permutations of 4 screened cell lines, quantities significantly exceeding that which would be expected by chance. Interestingly, these overlapping essential genes were highly enriched for members of the heme biosynthesis pathway (e.g., CPOX, PPOX, and ALAD), as well as other candidate collateral sensitivities involving the unfolded protein response and ubiquitin-proteasome system. Accordingly, genetic and pharmacologic inhibition of heme synthesis not only reduces clonogenic colony formation in osimertinib-resistant NSCLC derivatives to a significantly greater extent than in their respective parental derivatives, but also partially restores osimertinib sensitivity in osimertinib-resistant cells.

Conclusions: Our findings suggest that diverse populations of osimertinib-resistant NSCLCs are uniquely and convergently vulnerable to perturbations in heme synthesis and homeostasis, a candidate EGFR-independent collateral sensitivity which is known to impact cellular metabolism, ROS production, apoptosis, and sensitivity to ionizing radiation, thereby warranting further preclinical investigations into modulating heme homeostasis as a means to overcoming osimertinib resistance.

Keywords: Osimertinib, Resistance, EGFR

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MA07.06 Eradicating Drug Tolerant Persisters (DTPs) In EGFR-Mutated Non Small Cell Lung Cancer (NSCLC) By Targeting TROP2

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Introduction: EGFR tyrosine kinase inhibitors (TKI) have dramatically impacted the outcome of EGFR-mutated NSCLC patients, but relapse frequently occurs due to incomplete eradication of all tumor cells and the establishment of DTP cells which can evolve into develop diverse mechanisms of drug resistance. Eradicating EGFR-TKI-DTPs induced therapeutically may thus enhance initial durable responses. By systematically evaluating cell surface proteins upregulated by osimertinib in DTPs, we identified TROP2 as a potential target for antibody-drug conjugate (ADC) or CAR T-cell-based approaches.

Methods: We evaluated TROP2 expression after osimertinib treatment in EGFR-mutated NSCLC cell lines in vitro (Western blots, surface cytometry, quantitative-PCR) and patient derived xenografts (PDXs) in vivo (single cell RNA-sequencing (scRNAseq), immunofluorescence). We further assessed TROP2 expression at the mRNA (quantitative-PCR) and protein levels (immunohistochemistry (IHC)) in tumor samples from patients with EGFR-mutated NSCLC, at diagnosis or EGFR TKI minimal residual disease (MRD) state. We then performed in vitro assays and in vivo studies to assess the efficacy of sacituzumab-govitecan (SG), an FDA approved anti-TROP2 ADC, or a sacituzumab scFV-based CAR T-cell targeting TROP2 to eradicate DTPs and prevent relapse following osimertinib therapy.

Results: We performed scRNAseq of DTPs following osimertinib treatment of EGFR-mutant NSCLC cell line xenografts and PDXs in vivo, which identified significant induction of TROP2 (TACSTD2) gene expression. We confirmed high levels of TROP2 cell surface protein expression in vitro and in vivo in these models and further TROP2 induction in the osimertinib induced DTP state. In diagnostic tumor samples from patients with EGFR-mutated NSCLC, TROP2 IHC expression was also elevated compared with EGFR wild type NSCLC, including patients with EGFR-mutated NSCLC treated with neoadjuvant EGFR TKI followed by surgery. We treated a novel in vivo EGFR TKI DTP model (EGFR-mutated NSCLC PDX DFCI243) with the TROP2 ADC SG after achieving MRD with osimertinib, which slightly improved relapse free survival, but all mice relapsed. We therefore evaluated whether immune-based strategies to eliminate DTP could be more effective. Osimertinib induced DTP were completely eradicated by sacituzumab scFV-based anti-TROP2 CAR T-cells in vitro. Furthermore, treatment with a single dose of TROP2 CAR T-cells was significantly more effective than repeated dose SG at administered during osimertinib induced MRD in the DFCI243 PDX model. Median relapse free survival was significantly longer in mice treated with anti-TROP2 CAR T-cells compared to osimertinib alone (210 days vs. 99 days; $p<0.0001$) and compared to the administration of SG (210 days vs. 130 days; $p=0.0014$). Importantly, no tumor regrowth was observed in half (5/10) of the PDX in the osimertinib-TROP2 CAR T group, while 100% (10/10) of the PDX in the osimertinib-SG group experienced regrowth.

Conclusions: Our findings provide a preclinical rationale for targeting TROP2 in DTP of EGFR-mutated NSCLC. In an aggressive PDX model which recapitulates the clinical phenomenon of DTP, targeting of TROP2 with CAR T-cells leads to extended and complete tumor responses. This work demonstrates that immune-based targeting of DTP is a viable strategy to pursue with immune effector cellular therapies that cannot be achieved with chemotherapy or ADC-based approaches.

Keywords: Cellular Therapy, Drug Tolerant Persisters, EGFR mutated NSCLC

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MA07.08 Proteogenomic Analysis of CSF Reveals Distinct Molecular Patterns of Leptomeningeal Metastases in EGFR-Mutated NSCLC

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Introduction: Leptomeningeal metastases (LM) is becoming frequent in EGFR-mutated advanced NSCLC and causes dismal prognosis due to limited treatment options. Previous studies prove that cerebrospinal fluid (CSF) ctDNA indicates poor prognosis. However, a deeper understanding of the molecular phenotypes of LM is lacking, hindering the exploration of potential therapeutic targets.

Methods: Using Data-independent Acquisition and ctDNA next-generation sequencing, we characterized 135 CSF from 120 patients with advanced EGFR-mutated NSCLC and LM (n=69), or brain metastases (BM, n=43), or non LM/BM (n=8). Proteomic data was available for 135 samples and genomic data available for 86 smaples. We established mouse model of LM: iterative in vivo selection of leptomeningeal adaptive cancer cell by injection into the cisterna magna; and next identifying leptomeningeal metastatic cells following hematogenous dissemination. ELISA, qPCR and WB were applied to test protein expressions.

Results: To explore the proteomic correlates of CSF ctDNA detection which represented an aggressive cancer phenotype, we compared the proteomic profiles between positive and negative CSF ctDNA. We found genes (MUC1, SUSD2, RNPEP, SETPB, PDCD6IP, AMY2B, and etc) and gene sets (cell cycle, metabolic and inflammatory response) significantly up-regulated in ctDNA-positive CSF. We then looked further into the molecular patterns using quantitatice proteomic data. CSF in the LM group was distinct from those in the BM or non LM/BM group: a significantly higher number of proteins were detected in the LM group; upregulated proteins of LM fell in 5 functional categories: disruption of blood brain barrier, increased tumour growth and migration, endocytosis and dysregulated immune response. Differential expression of proteins compared to BM and non LM/BM group were selected as LM-specific and highlighted the molecular heterogeneity in LM: we used LM-specific proteomics to stratify LM into two subtypes, each of which was related to different clinical features and survival outcomes. Subtype I, which was characterized by disrupted extracellular matrix and increased endocytosis, was associated with significantly shorter overall survival. Patients of subtype I had higher rate of positive CSF cytology and concurrent TP53 alterations detected by CSF ctDNA. By integrating a comparison between pre- and post-LM in two more cases, we found 18 LM-associated proteins, high expression of which constituted a signature specific to LM. Among them, the increased expression of polymeric immunoglobulin receptor (pIgR) might be correlated to higher propensity to LM development, attested by the external datasets of single cell RNA sequencing of CSF from patients with NSCLC and LM and bulk RNA sequencing of cell lines; the higher expression of pIgR also indicated poor prognosis. ELISA testing indicated elevated expression of pIgR in the CSF from LM in a cohort of 30 patients. PIgR was upregulated in leptomeningeal metastatic models. Mechanistically, we found that pIgR enhanced the stemness of cancer cell to sustain cancer growth within the leptomeningeal space.

Conclusions: We connected genomic aberration to proteomics which consistently revealed a more aggressive cancer phenotype. More importantly, we revealed the proteomic stratification of LM which provided insight into the underlying biology of this deadly complication, and suggested the opportunity for a therapeutic target.

Keywords: leptomeningeal metastases, cerebrospinal fluid, proteogenomic

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MA07.09 Genome-Wide CRISPR Screen Identifies SFRP2 as a Novel Stromal Target to Enhance Abscopal Effect of Radioimmunotherapy

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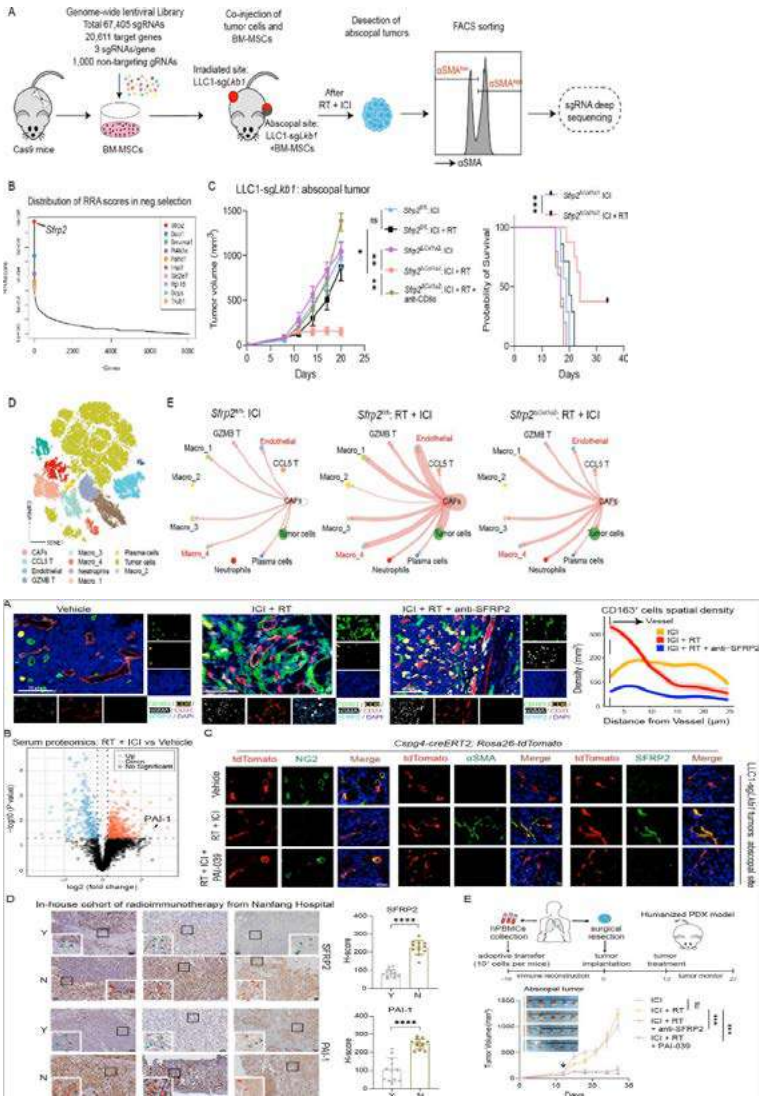
Introduction: The abscopal effect of radiotherapy, where tumor shrinkage occurs beyond the irradiated field, can be enhanced by immune checkpoint blockade and holds great promise. Nevertheless, the abscopal effect following radioimmunotherapy remains clinically infrequent, and mechanisms underlying this effect are neither fully appreciated nor therapeutically leveraged.

Methods: In vivo genome-wide CRISPR-Cas9 screening were performed in the bilateral LLC1-sgLkb1 murine lung cancer model to identify the key regulator of abscopal effect, validated by a genetically engineered mouse strain. Single-cell multi-omics technique and genetic lineage-tracing assays were integrated to interrogate the underlying mechanisms. An immune system-tumor double humanized lung cancer patient-derived xenograft (PDX) models were established to evaluate the efficacy of targeting this signaling cascade.

Results: In vivo genome-wide CRISPR-Cas9 screens and MAGeCK analyses identified Sfrp2 as a pivotal stromal regulator of abscopal effect, specifically expressed in cancer-associated fibroblasts (CAFs). Depleting Sfrp2 in CAFs using transgenic mice could promote this effect of radioimmunotherapy. Spatial profiling analyses indicated that SFRP2+ CAFs wrapped around the vessels and were accompanied by a substantial number of immunosuppressive macrophages and sparse cytotoxic cells, whereas blockade of SFRP2 resulted in a resurgence of CD8+T cell infiltration. Single-cell transcriptomic and serum proteomics analyses uncovered that irradiated tumor-derived PAI-1 triggered cell-fate transition of pericytes into SFRP2+ CAFs, leading to impaired cytokine and cell adhesion signaling and hindering the trafficking of CD8+T cells. Furthermore, low expression of SFRP2 or PAI-1 was associated with the occurrence of abscopal effect in an in-house cohort of radioimmunotherapy. Notably, targeting SFRP2 or PAI-1 could effectively diminish tumor burden and enhance abscopal effect of radioimmunotherapy in both syngeneic and humanized PDX models.

Conclusions: This study performed a large-scale unbiased genomic investigation to demonstrate SFRP2 as a stromal setpoint that dictates the abscopal effect, providing a potential predictive marker and therapeutic target for radioimmunotherapy of lung cancer.

Keywords: radioimmunotherapy, abscopal effect, tumour stroma



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MA07.11 AGRN-Positive Tumor Cells Promoting Immunotherapy Resistance in Lung Adenocarcinoma by Reshaping the Immune Microenvironment

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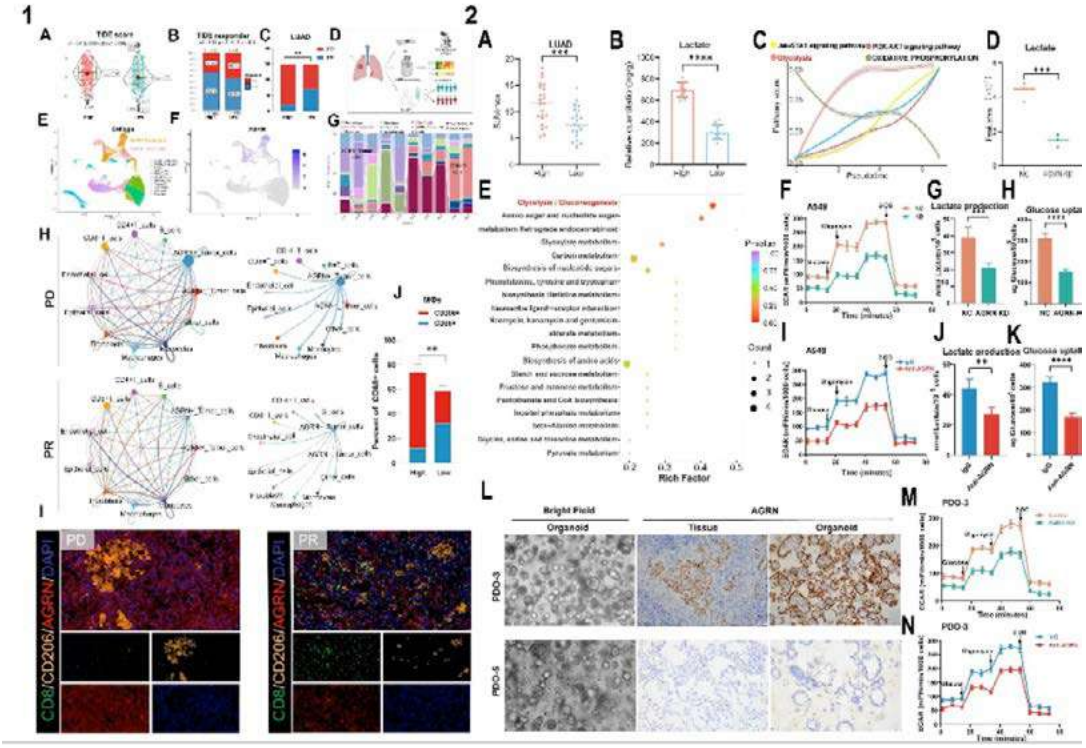
Introduction: Lung adenocarcinoma (LUAD) is one of the most common tumor types worldwide, which brings a great burden to society and the economy. Immunotherapy is a promising area in treating LUAD, however drug resistance poses a formidable challenge. Thus, exploring targets to improve the efficacy of immunotherapy is a research hotspot.

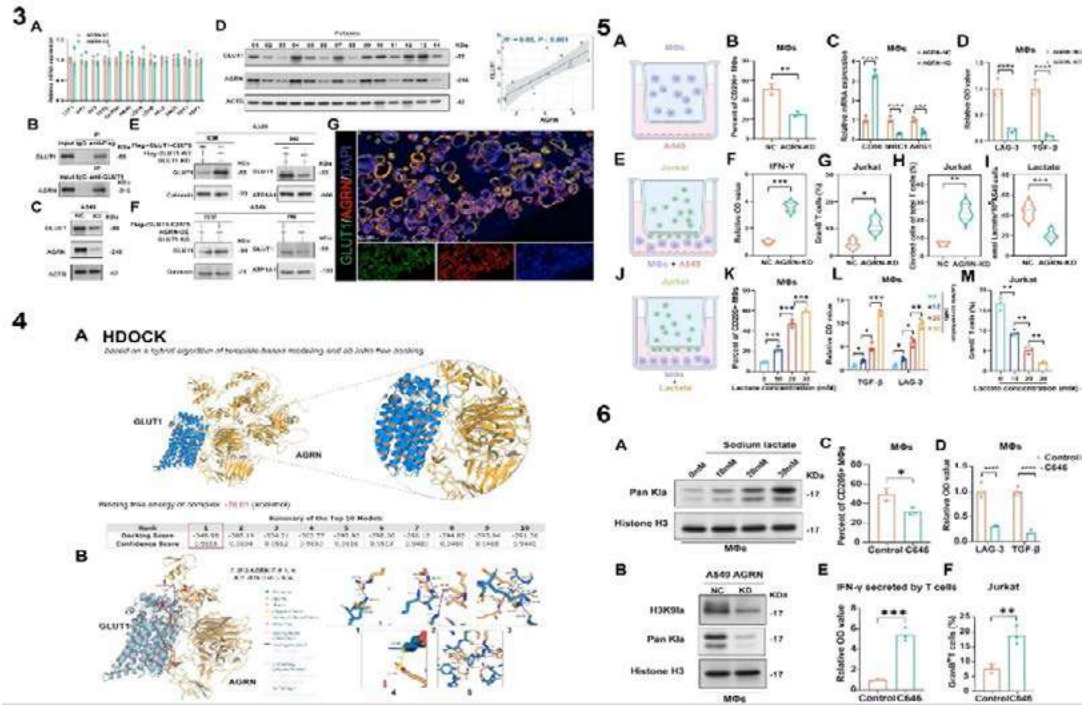
Methods: We performed single-cell RNA sequencing and multiplex immunofluorescence to identify the key gene associated with anti-PD1 tolerance. Organoid model, in vitro coculture system, metabolomics, transcriptomics, Lactation modification omics, and multiplex immunofluorescence were used to explore the biological function of agrin (AGRN) on tumor glycolysis and immune escape. Molecular and biochemical strategies like RNA-sequencing, CoIP-MS, mass spectrometry, and CUT&Tag were used to gain insight into the underlying mechanisms of AGRN.

Results: We revealed that the proportion of AGRN-positive tumor cells significantly increased in tumor tissues from patients with anti-PD1-resistant LUAD. AGRN upregulates GLUT1 expression on LUAD cell membranes by interacting with GLUT1, thereby promoting glycolysis and lactate accumulation. These changes subsequently induce histone lactylation modification in macrophages, leading to M2-like polarization and CD8+ T cell suppression, eventually resulting in an immunosuppressive microenvironment and immunotherapy resistance. Notably, we synthesized a monoclonal antibody targeting AGRN, and verified that the antibody can reset the tumor microenvironment and restore sensitivity to anti-PD1 by blocking the AGRN/GLUT1/lactate axis.

Conclusions: We found that AGRN can induce macrophage lactate modification by promoting glycolysis and lactate secretion in LUAD cells, leading to an immunosuppressive tumor microenvironment. We also propose that the AGRN/GLUT1/lactate axis is critical for triggering immune evasion and anti-PD1 tolerance. Inhibiting this axis with antibody overcomes anti PD1 resistance in LUAD.

Keywords: Lung adenocarcinoma, Glycolysis, Immunotherapy





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MA07.12 Unleashing the Potential of the Probiotic F.prausnitzii to Optimize PD-1 Inhibitor Efficacy in NSCLC Treatment

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Introduction: Lung cancer, specifically Non-Small-Cell Lung Cancer (NSCLC), remains a primary contributor to cancer mortality rates worldwide, with limited efficacious treatment strategies available. While PD-1 inhibitors have gained regulatory approval for NSCLC treatment, their effectiveness is hindered by individual immune response differences. Existing research elucidates the significant role of gut microbiota in modulating the efficacy of immunotherapy. However, these studies principally identified deleterious bacteria, posing specific targets for clinical application and feasibility into question due to the non-specificity associated with eradicating harmful bacteria. In an innovative divergence from this established focus, our study pioneers in identifying a beneficial probiotic, Faecalibacterium<F.> prausnitzii, aiming to expand the utilities of PD-1 inhibitors in NSCLC treatment. The possibility of clinical application through supplementation of this probiotic, rather than elimination of harmful ones, instils a realistic optimism for achieving enhanced treatment outcomes in NSCLC patients.

Methods: We analyzed fecal samples from nine NSCLC patients pre-treatment to identify F.prausnitzii concentration via metagenomic sequencing. Utilizing an animal model, we examined PD-1 inhibitors' impact on tumor growth in the presence of F.prausnitzii and its supernatant. Through flow cytometry, we studied CD8+ T cell activation, exhaustion, and production of IFN-γ and Granzyme B. Using RNA-seq, we explored metabolic changes after F.prausnitzii exposure. High-throughput sequencing and bioinformatics were used to investigate F.prausnitzii's impact on immunotherapy.

Results: Upon prospective collection of fecal samples from 9 NSCLC patients undergoing neoadjuvant immunotherapy, we observed that 6 patients achieved a major pathological response (MPR) while 3 did not. Metagenomic sequencing indicated a higher abundance of F.prausnitzii in responders. Our animal model indicated that PD-1 monoclonal antibody inhibited tumor growth; this effect augmented upon gavage with either F.prausnitzii or its supernatant (F.prausnitzii sp.). Flow cytometry results showed an increase in CD8+ T cell infiltration in tumor tissues and a decrease in CD8+ T cell exhaustion upon using F.prausnitzii sp. with PD-1 monoclonal antibody. Further, the combination enhanced secretion of effector molecules (IFN-γ and Granzyme B). RNA-seq differential analysis revealed a decrease in tryptophan decomposition metabolic pathway and IL4I1 expression post-intervention with F.prausnitzii sp. UPLC-MS demonstrated a decrease in the levels of tryptophan metabolites (KYNA and I3A) in mouse serum when treated with F.prausnitzii sp. in combination with PD-1 monoclonal antibody. Lastly, upon integrating high-throughput sequencing and bioinformatics analysis, it was discovered that F.prausnitzii sp. activated transcription factor RUNX3, thereby inhibiting the transcriptional activity of IL4I1 promoter. Knocking down RUNX3 in NSCLC cells completely reversed the inhibitory effect of F.prausnitzii sp. on IL4I1.

Conclusions: The tentative findings emphasize the promise of probiotics and F.prausnitzii, in particular, in refining NSCLC immunotherapy outcomes. Future research must prioritize uncovering the specific microbial and functional metabolites that enhance PD-1 inhibitor response. The supplementation of probiotics, specifically F.prausnitzii, is a pivotal innovation in boosting immunotherapy efficacy and is anticipated to contribute to personalized NSCLC treatment strategies.

Keywords: Probiotic, Immunotherapy, PD-1 Inhibitor Efficacy

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MA07.13 Neoadjuvant Chemotherapy Is Associated with Optimized Spatial Landscape of Tissue-Resident Memory T Cells in Non-Small Cell Lung Cancer

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Introduction: Neoadjuvant chemotherapy (NAC) combined with immunotherapy is increasingly used in non-small cell lung cancer (NSCLC). Tissue-resident memory T (TRM) cells are the primary immune subset in response to immunotherapy. However, the immunomodulating effect of NAC on TRM cells remains unknown.

Methods: We established two NSCLC cohorts including patients who underwent upfront surgery (US) or NAC followed by surgery. Beyond unpaired comparison between US cohort (n=122) and NAC cohort (n=141) with resection samples, 58 post-NAC resection samples with matched pre-NAC biopsy samples were available for paired comparison. Using multiplex immunofluorescence, we characterized CD103+CD8+ TRM cells and four TRM subsets, including naive TRM1 (PD-1-Tim-3-), pre-exhausted TRM2 (PD-1-Tim-3-) and TRM3 (PD-1-Tim-3-), and terminally exhausted TRM4 (PD-1-Tim-3-). Cell density, cytotoxicity (GZMB positive rate) and two spatial features (infiltration score and cancer-cell proximity score) were defined to evaluate the effect of NAC on TRM subsets.

Results: Cell densities, infiltration scores and cancer-cell proximity scores of TRM cells, especially TRM1&2 subsets, were increased after NAC, which were associated with longer disease-free survival (DFS). Contrarily, no significant change was observed in TRM4 subset, which were associated with shorter DFS. Besides, cytotoxicity of TRM subsets was unaltered after NAC. Patients achieving major pathologic response (MPRs) have higher cell density of TRM1&2 and higher cancer-cell proximity score of TRM2&3 compared with non-MPRs.

Conclusions: NAC may remodel an anti-tumorigenic landscape of TRM cells by increasing cell density and promoting spatial distribution of immunoreactive TRM subsets.

Keywords: Neoadjuvant chemotherapy, Tissue-resident memory T cell, non-small cell lung cancer

MA08 PULMONARY NODES AND NODULES
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MA08.03 Survival Validation and Gene Mutations of N Descriptors in the Ninth Edition of the TNM Classification for Lung Cancer

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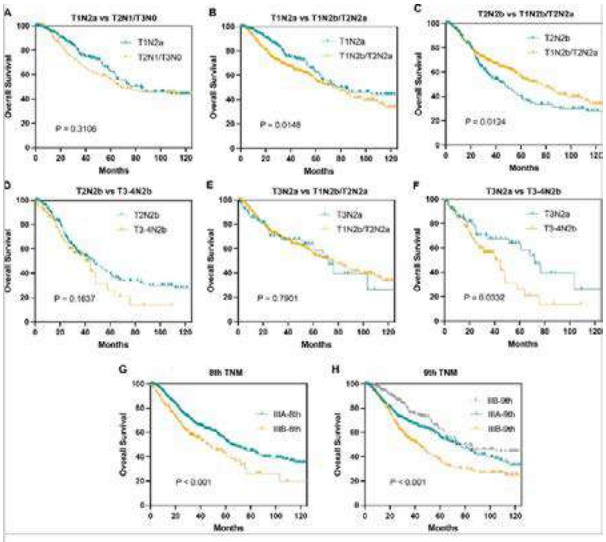
Introduction: The IASLC Staging Committee recently unveiled the ninth edition of TNM staging system for lung cancer. This study aims to investigate survival, stage grouping, as well as gene mutation of N descriptors in this new classification system.

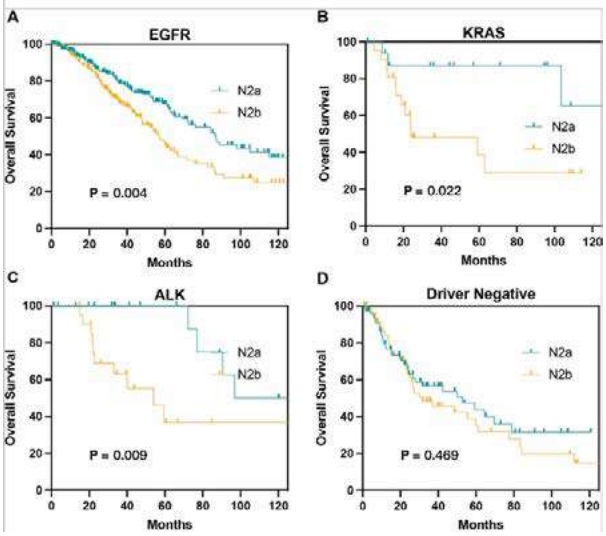
Methods: Data were extracted from the lung cancer database of Fudan University Shanghai Cancer Center spanning from 2008 to 2020. Patients, who underwent radical resections and had a pathology of N2, were collected. Subsequently, cases were further categorized into N2a (single-station N2) and N2b (multiple-station N2) based on the N descriptors from the ninth edition of lung cancer TNM staging system.

Results: Among the 1263 cases with pN2, 711 were classified as pN2a, and 552 as pN2b. Patients with pN2a exhibited statistically higher overall survival (OS) compared to patients with pN2b (P<0.001). The survival rate for individuals classified as T1N2a was comparable to those categorized as T2N1/T3N0 (IIB) and notably better than those identified as T1N2b/T2N2b (IIIA). Conversely, the survival rate for T2N2b was lower than T1N2b/T2N2a (IIIA) and akin to T3-4N2b (IIIB). Furthermore, the survival rate for T3N2a was similar to T1N2b/T2N2a (IIIA) and significantly better than T3-4N2b (IIIB). The incorporation of single and multiple N2 in the ninth TNM staging system improved its ability to stratify the survival of N2 patients compared to the eighth TNM system. In patients who possess common driver mutations such as EGFR mutation, KRAS mutation, and ALK fusion, a significant survival difference between N2a and N2b has been observed. However, this distinction is not apparent in patients without common driver mutations.

Conclusions: This study represents the first external validation confirming the prognostic accuracy of N descriptors and staging groups in the ninth edition of the TNM classification for lung cancer, which provides significant evidence for the clinical application of this classification system.

Keywords: the ninth TNM classification, survival validation, gene mutation





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MA08.04 Exploration on the Prognostic Heterogenicity in Stage IIB (the 9th Edition of TNM Classification) NSCLC Patients with Different Nodal Statuses

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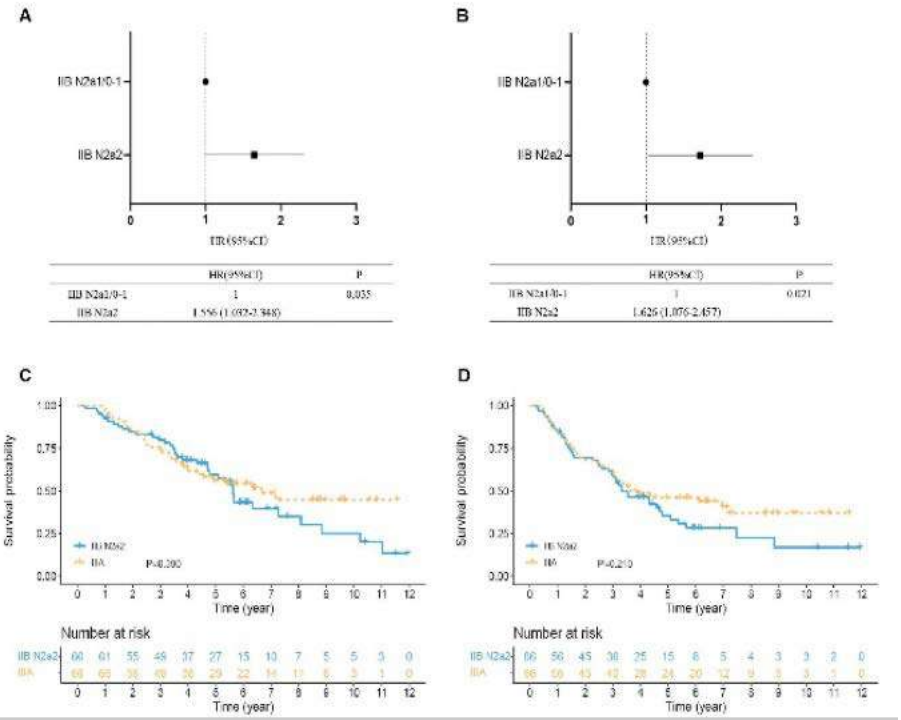
Introduction: The latest 9th edition of the lung cancer tumor-node-metastasis (TNM) staging system downgrades certain stage IIIA patients from stage IIIA (N2a) to IIB. This study aims to investigate potential prognostic differences among IIB patients with different nodal statuses.

Methods: Consecutive stage IIB and IIIA non-small cell lung cancer (NSCLC) patients who underwent lobectomy with systematic lymph node dissection were included. Staging was reassigned according to the 9th edition of the lung cancer TNM classification. Subgrouping was done based on lymph node involvements: IIB N2a1 (single-station N2 without N1 involvement), IIB N2a2 (single-station N2 with N1 involvements) and IIB N0-1. Survival analysis was conducted using the Kaplan-Meier method, with propensity score matching (PSM) employed to mitigate potential biases. COX regression models were utilized to assess prognostic differences.

Results: A total of 224 patients with stage IIB NSCLC was evaluated. Among them, there were 38, 66 and 120 patients in the IIB N2a1, IIB N2a2 and IIB N0-1 subgroups, respectively. Univariate COX analysis indicated comparable prognoses between the stage IIB N0-1 and stage IIB N2a1 patients, whereas stage IIB N2a2 patients exhibited poorer outcomes. Upon combining the IIB N2a1 and IIB N0-1 subgroups, multivariate COX analysis demonstrated a significantly worse prognosis for stage IIB N2a2 patients compared to those with stage IIB N2a1/0-1 tumors (OS HR: IIB N2a1/0-1 vs. IIB N2a2 = 1 vs. 1.556, P=0.035; DFS HR: IIB N2a1/0-1 vs. IIB N2a2 = 1 vs 1.626, P=0.021). Further comparison between stage IIB N2a2 and stage IIIA patients, following PSM analysis, indicated similar survivals (5-year OS survival rate: 59.5% vs. 56.4%, P=0.390; 5-year DFS survival rate: 35.5% vs. 46.2%; P=0.210). Multivariate COX analysis further confirmed no significant difference in prognosis between the two groups (OS HR: IIB N2a2 vs. IIIA = 1 vs. 0.775, P=0.294; DFS HR: IIB N2a2 vs. IIIA = 1 vs. 0.770, P=0.254).

Conclusions: The prognosis of stage IIB N2a2 patients was worse than that of remaining stage IIB patients but comparable to that of stage IIIA patients. We proposed that stage IIB N2a2 patients should be reclassified as stage IIIA. However, further validation with a larger dataset is necessary to confirm these observations.

Keywords: non-small cell lung cancer, The 9th edition of the lung cancer TNM staging sys, stage IIB



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MA08.05 Lung Cancer in Young Adults is Associated with Advanced Disease at Diagnosis and Increased Frequency of Targetable Mutations

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Introduction: Most patients diagnosed with lung cancer are 65 years or older with an increased risk above the age of 55 in the smoking population, as reflected in most screening cohorts. Risk factors for younger patients ≤ 45 years of age remain largely undefined and only smaller cohorts have been described in the literature. Here, we report the largest European cohort of young adults with lung cancer to date, diagnosed at the West German Cancer Center from 2019 to 2023.

Methods: All patients diagnosed with lung cancer at the West German Cancer Center between 2019 and 2023 were included (n = 3561). Electronic medical records of patients ≤ 45 years (a) (n = 71; YC) and 45 y (n = 3490; OC) of age were reviewed for sex, smoking history, tumor stage at diagnosis, histopathology, and genomic alterations. Fisher's exact test was used to compare significance levels between the groups ($\alpha = 0.05$). Significant p-values are marked with an asterisk.

Results: 71/3561 patients with lung cancer (1.99% of the entire cohort) were ≤ 45 years (YC; median 39 years, Q1: 35.5; Q3: 44) with comparable gender distribution (YC vs. OC; 47.89% vs. 45.11% females). YC were more frequently never smokers (23.94% vs. 6.93%, p < 0.05*), diagnosed with advanced disease stage (IVA and IVB: 53.52% vs. 23.48%, p < 0.05*), more advanced lymph node metastases (N+: 70.42% vs. 52.66%, p < 0.05; N3: 32.39 vs. 20.09%, p < 0.05*) and high prevalence of brain metastases (16.9% vs. 12.03%, p = 0.2). Adenocarcinomas (63.27% vs. 51.81%, p = 0.11) and undifferentiated tumors (18.37% vs. 4.98%, p < 0.05*) were the dominant histological subtypes in the YC with NSCLC (n = 49; 69.01% of YC vs. 80.56% of OC; p = 0.31), while there was only a single squamous cell carcinoma. Neuroendocrine differentiation was more frequent in the YC group (30.99% vs. 15.36%, p < 0.05*), particularly carcinoid tumors (n = 16; 68.18% vs. 21.83%), while SCLC was less common (31.82% of NET; 9.86% of YC) compared to OC (78.17% of NET; 12.01% of OC). Genomic alterations in patients with NSCLC in the respective cohorts are presented in the table below.

Conclusions: Lung cancer in young patients is characterized by distinct biologies with high prevalence of driver oncogenes, neuroendocrine differentiation, and non-smokers. The predominance of advanced disease at diagnosis suggests that increased awareness in the medical community is required.

Keywords: young lung cancer patients, NSCLC, neuroendocrine tumors

	YC	OC	p-value
ALK (n)	11	45	< 0.05*
% of NSCLC	22.45	1.52	
% female	63.64	59.18	
% never smokers	36.36	42.22	
EGFR (n)	4	156	0.33
% of NSCLC	7.84	5.11	
% female	50.00	55.13	
% never smokers	75.00	33.97	
MET (n)	5	139	0.083
% of NSCLC	10.20	4.71	
% female	20.00	38.13	
% never smokers	20.00	10.07	
KRAS (n)	8	400	0.529
% of NSCLC	16.33	13.54	
% female	50.00	53.00	
% never smokers	25.00	2.00	

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MA08.07 Transthoracic Versus Transbronchial Approaches for Diagnosis of Pulmonary Nodules Located in the Middle Lung Zone

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Introduction: Transthoracic biopsy (TT) and transbronchial biopsy (TB) are the two main modalities for diagnosis of pulmonary nodules (PN). Generally, TT has a higher diagnostic yield and complication rate. The approach for PN biopsy often depends on local expertise, resources, patient factors, and nodule characteristics. TT is used commonly for peripheral nodules, while TB is favored for central nodules. Limited data exist on the optimal diagnostic approach for middle lung zone nodules. The purpose of this study was to compare the diagnostic performance, complication rate, and attributable cost of a clinician-directed, TT- vs. TB-driven approach to the workup of middle lung zone PNs using real-world data.

Methods: This is a retrospective cohort study of prospectively collected data on consecutive patients referred to a tertiary thoracic oncology center from January 1, 2015 to June 30, 2016, including 5-year follow-up to confirm pathological accuracy. Patients requiring pathological diagnosis of PNs located in the middle third lung zone were included. Three independent clinicians with expertise in CT chest interpretation localized nodules in the middle lung zone using a concentric division method from the hilum as reported previously. The diagnostic approach was at the discretion of the managing clinician. Based on the first invasive diagnostic test performed, patients were classified into two groups: transthoracic biopsy first (TTF) or transbronchial biopsy first (TBF). We compared the diagnostic yield, complications, diagnostic workup length, and associated costs (in 2023 Canadian dollars [$CDN] {$1CDN=$0.741US}) between the two diagnostic approaches.

Results: The cohort included 207 patients; 99 were classified as TTF, and 108 as TBF. Compared to the TTF group, the TBF group had larger nodules (mean diameter ± SD, 43 ± 19 vs. 35 ± 24 mm, p = 0.0087), more nodules with a positive bronchus sign (94% vs. 68%, p <0.0001), and more patients with suspected clinical stage III lung cancer (38% vs. 19%). The diagnostic yield of the first diagnostic procedure was higher in the TTF group (90% vs. 78%, p = 0.0238). Throughout the diagnostic workup, pneumothorax rate was higher in the TTF group (28% vs. 3%, p <0.0001), including pneumothorax requiring chest tube placement (8% vs. 0%, p = 0.0023). There was no severe bleeding requiring advanced intervention in both groups. Diagnostic workup was longer in the TTF group (mean ± SD, 44 ± 29 vs. 31 ± 19 days, p = 0.0001). The overall TTF and the TBF workup costs were similar (median [IQR], $1,641 [951-2,897] vs. $1,809 [1,274-2,689], p = 0.5474). However, in patients requiring pathological mediastinal nodal staging, costs were higher in the TTF group (median [IQR], $3,061 [2,401-3,690] vs. $2,122 [1,724-2,875], p <0.0001).

Conclusions: Experienced clinician-driven diagnostic assessment of middle lung zone PNs results in comparable diagnostic workup costs for TTF and TBF approaches. Workup duration and cost for patients requiring invasive mediastinal nodal staging are lower with a TBF approach. This population-based study may guide clinicians and policymakers to improve the cost-effectiveness of PN diagnostic workup.

Keywords: Staging, transbronchial biopsy, transthoracic biopsy

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MA08.08 Association of FDG-PET/CT Findings with Sufficient Amount of Tissue Samples for Gene Panel Testing in TBB/TBNA

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Introduction: Application of gene panel testing has become the golden standard for deciding treatment of stage IV non-small cell lung cancer (NSCLC) patients and achieving adequate amount of tissue samples in biopsy is essential for its success. Fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) has high sensitivity for detecting viable tumor cells, and its efficacy has been shown in selecting biopsy sites of mediastinal lymph nodes for staging in preoperative settings. However, it remains to be seen whether FDG-PET/CT is also effective in acquiring sufficient amount of tissue for gene panel testing.

Methods: We retrospectively reviewed patients with stage IV NSCLC patients who underwent transbronchial lung biopsy (TBB) (including transbronchial lung cryobiopsy [TBLC]) or endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) for gene panel testing in Shizuoka Cancer Center from January 2022 to January 2024. For each patient multiple FDG-PET/CT parameters were obtained, including standardized uptake values (SUVs) and presence of necrosis (PET-necrosis) at the biopsy site, along with other clinical data of the patients. PET-necrosis was defined as areas of low/no FDG uptake surrounded by those with FDG uptake, whose CT level also indicated necrosis (between 10 and 30 Hounsfield units). The primary outcome was panel-biopsy failure, which was defined as cases that required re-biopsy, single-plex testing, or gene panel testing by cell blocks, due to inadequate or negative tissue samples in the initial biopsy. The association of FDG-PET/CT parameters with panel-biopsy failure was analyzed, using logistic regression analysis, adjusting for factors which have been shown to contribute to panel-biopsy failure in previous studies (TBB: tumor locations, EBUS-TBNA: number of biopsies).

Results: A total of 239 patients with stage IV NSCLC underwent bronchoscopy, including 176 patients with TBB and 63 with EBUS-TBNA. Panel-biopsy failure was observed in 33 patients (18.8%) with TBB and 15 (23.8%) with EBUS-TBNA. In patients who underwent TBB, univariate analysis of the risk of panel-biopsy failure revealed that the risk increased in the presence of PET-necrosis (OR 3.22; 95%CI 1.24-8.36, p=0.017), whereas the risk did not correlate with SUVs (OR 1.03; 95%CI 0.96-1.11, p=0.4). Likewise, in logistic regression analysis adjusting for tumor locations (right or left, upper/middle or lower lobe, central or peripheral) and tumor diameter, presence of PET-necrosis resulted in significantly higher risk of panel-biopsy failure (OR 5.60; 95%CI 1.62-19.30, p=0.0064), whereas no association was seen in terms of SUVs (OR 1.05; 95%CI 0.97-1.15, p=0.24). In patients who underwent TBNA, univariate analysis showed increased risk of panel-biopsy failure in the presence of PET-necrosis (OR 5.52; 95%CI 1.00-30.50, p=0.05), whereas the risk was not associated with SUVs (OR 0.98; 95%CI 0.87-1.11, p=0.75). In logistic regression analysis adjusting for number of biopsies, presence of PET-necrosis showed tendency of higher risk of panel-biopsy failure (OR 5.13; 95%CI 0.86-30.60, p=0.073), whereas the risk was not related to SUVs (OR 1.00; 95%CI 0.88-1.14, p=0.98).

Conclusions: PET-necrosis was associated with panel-biopsy failure in both TBB and TBNA. In choosing biopsy site for gene panel testing, FDG-PET/CT findings had better be considered, and lesions with PET-necrosis might not be optimal target of biopsy.

Keywords: FDG-PET/CT, PET-necrosis, gene panel testing

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MA08.09 Predictive CT Features of Visceral Pleural Invasion in Lung Cancer with Ground Glass Opacity

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Introduction: Visceral pleural invasion (VPI) is an independent prognostic indicator in patients with non-small cell lung cancer (NSCLC). However, radiological features of VPI in pure ground-glass opacity (GGO) and part-solid tumors (subsolid tumors) has not been sufficiently investigated. To determine the appropriate policy and timing of therapeutic intervention, it is important to diagnose VPI based on radiological findings. The objective of this study is to clarify the predictive CT features of VPI in patients with lung cancer presenting subsolid tumors.

Methods: We retrospectively reviewed the medical records of patients who underwent surgical resection for lung cancer between January 2012 and December 2017. The inclusion criteria were radiological subsolid tumors, and tumors in contact to the pleura. We evaluated the radiological features of the tumors from the preoperative thin-section CT scans, including the tumor diameter, distance from the solid component to the pleura, and CT numbers of the contact area with the pleura.

Results: A total of 193 tumors were eligible for this study. Of these, 192 tumors were adenocarcinoma, and the remaining one tumor was adenosquamous cell carcinoma. The median total tumor size was 19mm (range, 6 -53mm), and the median solid size was 9mm (range, 0 - 30mm). The median CT number of the contact area of the pleura was -336HU (range, -820 -247 HU). VPI (PL ≧ 1) was pathologically confirmed in 7 out of 193 tumors (3.62%). All tumors with VPI were part-solid tumors, and VPI was not confirmed in tumors without direct contact of solid component with the pleura. In 80 tumors with the solid component in direct contact with the pleura, the median CT number of the contact area with the pleura was -12 HU (range, -123 - 247HU). Univariate analysis for predictive radiological features of VPI revealed significant differences in contact between solid component and the pleura (p = 0.002), consolidation tumor ratio (CTR) (cutoff, 0.5, p = 0.050), solid component tumor size (cutoff, 10mm, p = 0.002), SUVmax on FDG-PET (cutoff, 2.5, p = 0.0001), and CT numbers of the contact area with the pleura (cutoff, -336, p =0.0067).

Conclusions: VPI was confirmed in part-solid tumors with direct contact of the solid component with the pleura. Early surgical resection is encouraged for these tumors.

Keywords: Non small cell carcinoma, Visceral pleural invasion, subsolid tumors

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MA08.11 Incidental Lung Nodule Program: A New Approach for Early Detection and Management of Lung Cancer

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Introduction: Outside of lung cancer screening, more than 1.5 million new incidental lung nodules (ILN) are detected yearly in the United States 1. More than 60% of ILNs may be lost to follow-up2. We implemented an ILN program as a safety net to prevent losses to follow up and improve early detection of lung cancer. Earlier versions of this abstract have been submitted to the 2024 ATS and CHEST meetings.

Methods: We searched for lung nodules in all chest-related radiological reports using natural language processing (NLP) from Mount Sinai Morningside and West hospitals. All reports included a radiologist recommendation. After applying exclusion criteria, imaging studies were classified according to the presence or absence of an established follow-up pathway. Patients in the latter category were contacted and offered a pathway including a nodule clinic. Studies with established pathways were only tracked and patients were contacted if the follow-up was incomplete. A completed follow-up was defined by any of the following occurring on or before the due date: a test to assess the nodule or an encounter indicating no further follow-up is necessary. We also searched for lung nodules before the implementation of the program to assess compliance with follow-up recommendations.

Results: Between 1/2023 - 4/2024, we identified 4,614 studies potentially containing lung nodules, of which 2973 (64.4%) were enrolled in the program. After reviewing the medical records, 1,968 (66.2%) had an established follow-up pathway, 808 (27.2%) did not, 2 were pending assessment, and 195 (6.6%) were closed for various reasons. As of 4/2024, 622 (58.6%) of the tracked studies were pending follow-up, 184 (17.3%) had been successfully followed-up, and 255 (24.0%) had not followed-up by due date. Upon further engagement, 71 (28%) of the initially unfollowed patients completed their follow-up, 138 (54%) were pending scheduled follow-up, and 46 (18%) were closed for various reasons. Of the 1,061 patients tracked after program engagement, 10 patients were diagnosed with lung cancer with 7 (70%) in stages I/II and 3 (30%) in stages III/IV. Of the 1,968 patients tracked without any engagement by the program due to the existence of an established follow-up pathway, 30 were diagnosed with lung cancer with 11 (36.7%) in stages I/II and 19 (63.3%) in stages III/IV. Because of the program, 188 follow-up CT scans, 23 positron emission tomography scans, 244 lung nodule clinic visits, 33 biopsies, and 2 surgeries were conducted. Between January-February 2022, we identified 809 scans with lung nodules, of which 374 (46.22%) were enrolled in this study. Of these, 209 (55%) did not complete the recommended follow-up. As compared to the outpatient setting, studies ordered for ED and hospitalized patients were less likely to have follow-ups (OR 0.230, [95% CI 0.119-0.443] and OR 0.137, [95% CI 0.054-0.347], respectively).

Conclusions: An ILN program mitigates the high risk of loss to follow-up of lung nodules. Navigating patients that do not have established pathways in the health system despite radiologist's recommendations, can lead to a high proportion of early-stage lung cancer diagnoses.

Keywords: Incidental lung nodule, early lung cancer, natural language processing

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MA08.12 Semi-Sold Lung Nodule Growth Rates, Need for Treatment, and Cancer-Specific Verses All-Cause Mortality in a Large North American Population

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Introduction: Semi-solid lung nodules (SSN) on chest CT pose a continued clinical dilemma as they often require no treatment but have the potential to be invasive lung adenocarcinoma. An improved understanding of the outcomes of patients, particularly non-Asian populations, with SSN is needed to improve treatment recommendations for patients at risk of invasive disease.

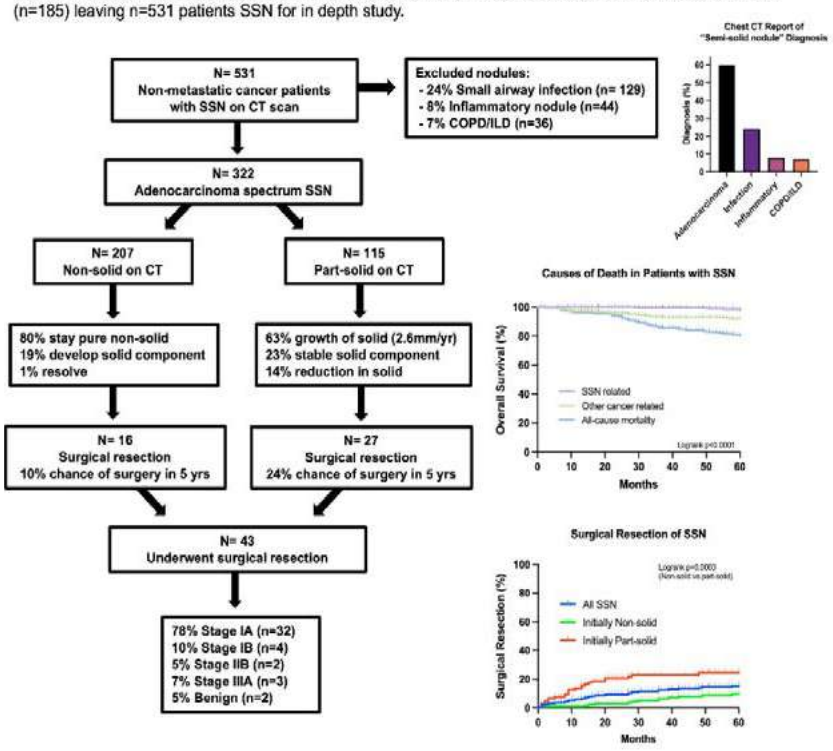
Methods: Patients with SSN reported on outpatient chest CT were identified retrospectively from all 2017 radiology reports in a large Northeast health system by natural language search. Manual chart review was performed for demographics, nodule size, growth on subsequent CT, suspected diagnosis, treatment, pathology, and survival.

Results: A total of 17,276 chest CT identified 952 patients with SSN (positive findings on 7% of all CT). Patients with metastatic cancer and limited documentation were excluded (n=421). Of patients with radiographic SSN, 25% of SSN were evaluated as small airway infection, 8% were inflammatory, and 7% were COPD/ILD related. The remaining 322 (34%) patients were thought to have nodules in the adenocarcinoma spectrum SSN. These SSN patients were predominately female n=242 (75%), median age 70.5 years, 87% white, 8% black, 3% Asian, 2% white-Hispanic, 81% ever-smokers, 19% never-smokers, and 12% had previously treated lung cancer. At diagnosis, n=115 (36%) SSN had a solid component in the SSN and n=207 (64%) were non-solid. In part-solid lesions over time, 23% had a stable solid component, 63% had growth of the solid component, and 14% had a reduction in size. Among non-solid SSN, 80% remained non-solid, 19% developed a solid component, and 1% resolved. Five-year all-cause mortality of those with SSN (n=322), was 80.1% overall survival, with 97.9% 5-year SSN-related survival, 91.9% 5-year other cancer-related survival (including n=2 who died of new second primary lung cancer). Within 5 years, n=43 (13%) underwent surgical resection, and patients with originally semi-solid SSN more likely to undergo resection than originally non-solid SSN (p=0.0003). On pathology 95% were lung adenocarcinoma, and positive lymph nodes were found in <5% of patients. Second primary lung cancers requiring treatment were identified in 34.9% within 5-years of surgery.

Conclusions: Patients found to have SSN should be reassured as to the slow growth and excellent survival associated with SSN. Most patients, particularly those with non-solid lesions, do not require surgical resection. Overly aggressive treatment of SSN should be tempered, particularly given high rates of developing multiple nodules and second primary lung cancer which may pose a greater mortality risk.

Keywords: ground glass opacity, semi-solid lung adenocarcinoma, lung nodules

Figure 1: Growth Patterns, Treatment and Survival of Semi-solid Lung Nodules (SSN). All 17,276 outpatient chest CT from 2017 were screened with natural language search yielding N=952 unique patients with SSN. Manual chart review removed patients with metastatic cancer (n=236) and those with limited documentation (n=185) leaving n=531 patients SSN for in depth study.



MA09.03 Plasma Proteomics-based Models for Predicting Immunotherapy-and Chemotherapy-Related Toxicity in NSCLC Patients

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Introduction: Patients with metastatic non-small cell lung cancer (NSCLC) are typically treated with PD-1/PD-L1-based immune checkpoint inhibitors (ICIs) depending on tumor characteristics and line of therapy. Toxicities resulting from such treatments can substantially affect quality of life and treatment trajectory. Currently, there are no reliable biomarkers for predicting the development of ICI-induced immune-related adverse events (irAEs) and chemotherapy-related adverse events (chemo-AEs). Here, we describe plasma proteomics-based models for the pretreatment prediction of severe irAEs, specific irAEs and chemo-AEs in patients with NSCLC.

Methods: Pretreatment plasma samples were collected from 426 NSCLC patients receiving PD-1/PD-L1 inhibitors with or without chemotherapy, and 138 NSCLC patients receiving chemotherapy alone. Proteomic profiling of plasma was performed using aptamer-based technology, covering ~7000 proteins per sample. Toxicity data were identified and graded using CTCAE v. 4.2. Toxicity data were collected and attributed to either immunotherapy or chemotherapy by the treating medical oncologist, and verified by two independent medical oncologists with irAE expertise. irAEs were defined as toxicities requiring treatment hold or immunosuppressive therapy, depending on the grade. In the ICI-treated cohort dataset, proteins associated with severe irAEs (defined as grade ≥3 irAEs or those resulting in ICI discontinuation within the first 100 days) were identified using a cross-validation approach and called Toxicity-Associated Proteins (TAPs). As a proof of concept for predicting specific irAE types, a similar approach was employed to identify proteins associated with ICI-induced skin rash (irAE-rash) termed rash-TAPs. Similarly, proteins associated with chemo-AEs in the chemotherapy cohort were classified as chemo-TAPs. TAP sets were integrated into three distinct machine learning-based models, where each model computes the probability of developing the respective toxicity type (i.e., severe irAE, irAE-rash or chemo-AE). Bioinformatic analyses were performed on all TAP sets.

Results: The models displayed significant predictive performance as demonstrated by area under the curve (AUC) of receiver operating characteristic (ROC) plots (severe irAE model: AUC=0.62, p-value=0.004; irAE-rash model: AUC=0.75, p-value<0.0001; chemo-AE model: AUC=0.67, p-value=0.002) as well as high correlations between predicted AE probability and observed AE rate (severe irAE model: R2=0.88, p-value=0.0016; irAE-rash model: R2=0.91; p-value=0.018; chemo-AE model: R2=0.80, p-value=0.01). The severe irAE, irAE-rash and chemo-AE models were based on 231, 108 and 114 proteins, respectively. Only two proteins were common to all three TAP sets, suggesting that these are independent models that reflect different biological mechanisms per toxicity type. The severe irAE TAP set displayed significant enrichment of inflammation and an abundance of neutrophil- and monocyte-related proteins. Multiple TAPs that were higher in patients who have experience ICI-related skin rash are significantly enriched with proteins related to gdT-cells, basophils, and inflammation. The chemo-TAP set displayed significant enrichment of angiogenesis pathways.

Conclusions: We describe three novel computational models for predicting severe irAEs, a specific irAE type and chemo-AEs based on pretreatment plasma proteomic profiles. Our findings also provide biological insights into treatment-related toxicity. Overall, the study demonstrates a viable framework for developing predictive models specific to different classes of treatment-related toxicity.

Keywords: Toxicity, Immunotherapy, Biomarkers

MA09 BEYOND THE MICROSCOPE: PREDICTING BENEFIT AND UNDERSTANDING BIOLOGY THROUGH BIOMARKERS
TUESDAY, SEPTEMBER 10, 2024 - 11:15 - 12:30

MA09.04 Differential CD8+FoxP3+ T Cell Infiltration Patterns Associate with Pathologic Response after Neoadjuvant Anti-PD-1 in NSCLC

M. Fotheringham[1], B. Green[2], J.S. Roskes[2], E. Cohen[1], B. Zhang[2], L.L. Engle[2], D. Wang[2], D. Jimenez-Sanchez[2], J.X. Caushi[2], J. Zhang[2], N. D'Amiano[2], J.C. Sunshine[2], J.S. Deutsch[2], S. Uttam[1], A. Fiorante[1], N.A. Espinosa[1], T. Popa[1], A. Ogurtsova[2], S. Soto-Diaz[2], M. Eminizer[2], D. Medvedev[2], J.E. Chaft[3], J.R. Brahmer[2], M. Conroy[2], J. Reuss[2], H. Ji[2], P.M. Forde[2], D.M. Pardoll[2], K.N. Smith[2], A.S. Szalay[2], J.M. Taube[2], T.R. Cottrell[1], [1]Queen's University, Kingston/ON/CA ,[2]Johns Hopkins University, Baltimore/MD/USA ,[3]Memorial Sloan Kettering Cancer Center, Middletown/NJ/USA

Introduction: Neoadjuvant immune checkpoint blockade (ICB) with anti-PD-1 based therapies is emerging as the new standard of care in resectable non-small cell lung carcinoma (NSCLC)1,2. Single-cell RNA sequencing performed by our group demonstrated CD8+FoxP3+ cells have a cytotoxic phenotype, suggesting a potential role in the anti-tumor immune response3. Building on this and our previous identification of CD8+FoxP3+ cell densities as a predictor of response to neoadjuvant ICB in NSCLC3, this study aims to evaluate the quantity and spatial dynamics of CD8+FoxP3+ cells in pre- and on-treatment tumor specimens from patients treated with neoadjuvant ICB as part of a phase 2 clinical trial.

Methods: All NSCLC tumor specimens were collected from patients enrolled in the first neoadjuvant clinical trial of anti-PD-1 (NCT02259621). Formalin-fixed, paraffin embedded sections of pre-treatment biopsies (n=25) and on-treatment resections (n=35), including n=23 pre/on-treatment pairs, were stained with a 6-marker multiplex immunofluorescence (mIF) panel (PD-1, PD-L1, CD8, CD163, FoxP3, and cytokeratin). Following whole-slide scanning, comprehensive cellular maps were generated using the AstroPath platform4. Wilcoxon signed-rank and Mann-Whitney U tests were used to compare immune cell densities between pre- and on-treatment specimens and across two thresholds of pathologic response5: ≤10% residual viable tumor (RVT) (i.e. major pathologic response (MPR)) and ≤50% RVT. Cell probabilities as a function of distance to the tumor-stroma boundary were plotted.

Results: The tumor microenvironment maps included a total of 18,515,905 cells. The densities of CD8+FoxP3+ cells significantly increased following neoadjuvant ICB (0.96 vs. 8.80 cells/mm2, for pre- vs. on-treatment specimens, respectively, p=<0.0001). Among on-treatment specimens, the densities of CD8+FoxP3+ cells were not significantly different in patients with and without MPR (median densities 10.94 vs. 7.59 cells/mm2, respectively, p=0.504). We next evaluated the spatial distribution of CD8+FoxP3+ cells to assess infiltration across the tumor-stroma boundary. Across all specimens, the probability distributions demonstrated a 5.8-fold increase in tumor infiltration by CD8+FoxP3+ cells in on-treatment vs. pre-treatment specimens (Figure 1). Moreover, tumor infiltration by CD8+FoxP3+ cells was increased (~2-fold) in on-treatment specimens with evidence of pathologic response to therapy (MPR and ≤50% RVT) relative to those without pathologic response (RVT>50%). These findings support a role for CD8+FoxP3+ cells in the anti-tumor immune response following ICB, including among partially responding tumors.

Conclusions: While CD8+FoxP3+ cells expand broadly in on-treatment tumors following neoadjuvant ICB, their infiltration across the tumor-stroma boundary coincides with pathologic response. Deeper spatial profiling of on-treatment specimens with additional mIF panels is ongoing.

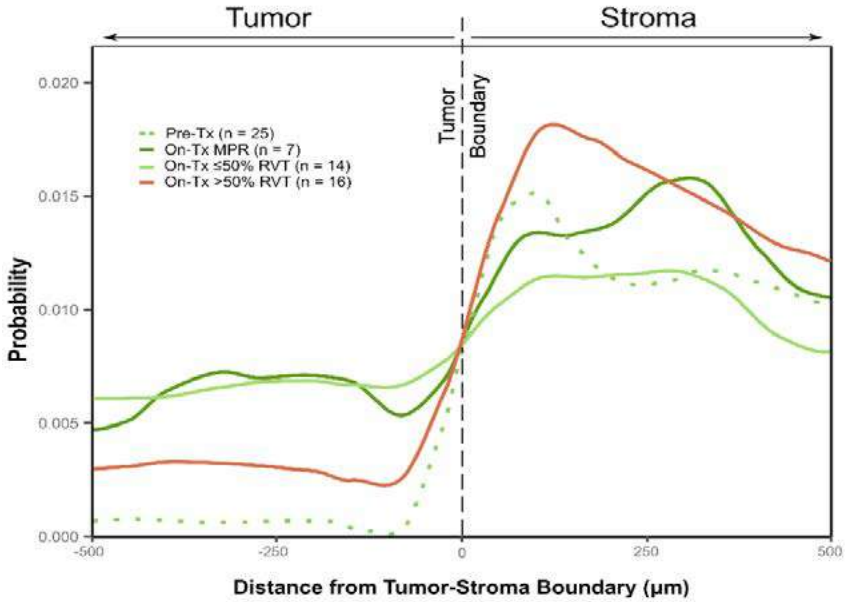

Figure 1. Probability distribution of CD8+FoxP3+ cells at tumor border. Probability distributions calculated from cell densities observed in pre-treatment biopsies (n=25; dotted light green line), and on-treatment resections achieving ≤10% (MPR; n=7; solid dark green line), ≤50% (n=14, including MPR; solid light green line), and >50% RVT (n=16; solid orange line) were plotted as a function of distance from the tumor-stroma boundary.

MA09.05 Circulating Protein Signatures and Immune Cells Are Predictive and Prognostic Markers for Patients with NSCLC in the SAKK 17/18 Trial

A. Rigutto[1], Y. Feng[2], P. Shichkova[2], L. Raess[2], S. Schaer[2], R. Bruderer[2], M. Tognetti[2], M. Joerger[3], S. Hayoz[3], V. Somasundaram[3], N. Nuñez[4,5], N. Fournier[6], J. Lourenço[6], R. Gottardo[6], B. Becher[5], A. Addeo[7], A. Gupta[1], A. Curioni-Fontecedro[1,8], [1]Faculty of Science and Medicine, University of Fribourg, Fribourg/CH ,[2]Biognosys AG, Schlieren/CH ,[3]Swiss Group for Clinical Cancer Research (SAKK), Bern/CH ,[4]Facultad de Ciencias Químicas, Universidad Nacional de Córdoba (UNC), Córdoba/AR ,[5]Institute of Experimental Immunology, University of Zürich, Zürich/CH ,[6]TDS, Swiss Institute of Bioinformatics, Lausanne/CH ,[7]Oncology Service University Hospital Geneva, Geneva/CH ,[8]Clinic of Oncology, Cantonal Hospital Fribourg, Fribourg/CH

Introduction: The multicentric phase II clinical trial (SAKK17/18) met its primary endpoint of ORR 31% in patients with non-small cell lung cancer (NSCLC) who progressed on immunotherapy. Advanced proteomics on plasma samples and high-dimensional analysis of circulating immune cells identified novel predictive markers of response in these patients.

Methods: Patients received atezolizumab and gemcitabine at day1 and gemcitabine alone at day 8 q3w until progression. Longitudinal blood samples were collected at baseline, at cycle1-day8 and at cycle 2-day1. High-dimensional spectral flow cytometry, analyzing 40 surface markers and transcription factors, was applied to characterize the circulating immune cell subsets over time. From plasma samples (1) extracellular vesicles (EVs) were analyzed by data-independent acquisition (DIA) mass spectrometry (MS) and (2) whole-plasma proteome profiling using Biognosys' enrichment workflow was performed.

Results: According to the Response Evaluation Criteria in Solid Tumors (RECIST 1.1.), patients were classified as partial response (PR, n=11; 31%), stable disease (SD, n=8; 22 %), progressive disease (PD, n=12; 33%), and no tumor assessment post baseline (NTA, n=5; 14%). Patients with NTA had a progression of disease before the scheduled first-restaging. Median overall survival (mOS) was 8.2 months (m) in these heavily pretreated patients. Based on the analysis of EVs, plasma of patients with NTA cluster together with PD, revealing their similar outcome. Strikingly, specific protein signatures were found in the plasma of patients with either PR, SD and PD. Low frequencies of CD8+ T cells and high frequencies of NK cells at baseline correlated with longer overall survival (CD8+ T cells high with mOS 6.7m, CD8+ T cells low with mOS 11m, p = 0.013. NK cells high with mOS 9.5m, NK cells low with mOS 7m, p = 0.021). Increase in CD4+ T cells at cycle1-day8 and cycle2-day1 also correlated with longer overall survival (at C1D8, CD4+ T cells high with mOS 10m, CD4+ T cells low with mOS 6.7m, p= 0.011. At C2D1, CD4+ T cells high with mOS 9.8m, CD4+ T cells low with mOS 6.6m, p=0.018). A broader characterization of T cell subsets revealed decreased frequencies of central memory CD8+ T cells at baseline in PR (p= 0.021).

Conclusions: Specific immune cell subtypes and protein signatures correlate with response to treatment and outcomes in patients with NSCLC included in the SAKK 17/18 ORIGIN trial. This data give new insights about treatment-related antitumor mechanisms in these patients.

Keywords: NSCLC, Proteomics, Immune cells

MA09.06 Use of Biosimulation to Predict Chemotherapy Benefit in Patients with Metastatic NSCLC Being Treated with Immunotherapy

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Introduction: Combination chemo-immunotherapy has emerged as a standard treatment option in patients with non-small cell lung cancer (NSCLC). Although PD-L1 is used as a biomarker to select patients for therapy, it is imperfect and the additive value of chemotherapy may not be the same in all patients. A mechanistic computational biology model was developed by Cellworks that integrates a patient's tumor-based genomic profile as determined via next-generation sequencing, revealing signaling pathway dysregulation and variable drug response. Model output was converted to a quantitative score called the Therapy Response Index (TRI) and then further dichotomized into Favorable and Unfavorable Risk Groups allowing identification of patients who may or may not respond to chemotherapy during immunotherapy treatment, independent of TMB and PD-L1 status.

Methods: The TRI algorithm was trained in a real-world retrospective cohort of 553 NSCLC patients from the U.S. Veteran's Health Administration (VHA) system who received tissue-based comprehensive genomic profiling. Of these patients, 223 received immunotherapy (IO) and 330 received immunotherapy plus chemotherapy (IO+C). The TRI, computational model and clinical thresholds were locked and then prospectively validated in 710 advanced NSCLC front-line patients receiving either IO (n = 251) or IO+C (n = 459), obtained from the nationwide (US-based) de-identified Flatiron Health-Foundation Medicine NSCLC clinico-genomic database (FH-FMI CGDB). The de-identified data originated from approximately 280 US cancer clinics (~800 sites of care).

Results: In the validation set, the TRI was significantly associated with OS after adjustment for clinical and genomic risk factors, including PD-L1 levels (LR p = 0.0355). Patients in the TRI Unfavorable Risk Group (TRI < 32) received an estimated incremental benefit in median OS of ~ 3 months with the addition of chemotherapy to immunotherapy. In contrast, patients in the TRI Favorable Risk Group (TRI ≥ 32) showed no improvement in median OS when receiving chemotherapy in addition to immunotherapy. A statistical test of interaction between TRI and chemotherapy treatment was marginally significant in the validation set (LR p = 0.1361) after adjustment for clinical and genomic risk factors, despite the study being inadequately sized for this type of analysis.

Conclusions: In this study, TRI was predictive of OS and incremental chemotherapy benefit in two real-world cohorts of patients with NSCLC receiving IO or IO+C. These results support the use of TRI to identify patients who may benefit from a combination of immunotherapy and chemotherapy and those unlikely to respond to immunotherapy alone, independent of PD-L1 levels. Future studies will be performed to confirm the hypothesis that TRI has utility in deciding whether patients should be offered chemotherapy.

Keywords: immunotherapy, biosimulation, chemotherapy

MA09.08 The Mechanical Change and Metastasis Promoting in Lung Adenocarcinoma Progression: From AIS, MIA to IAC

M. Li, J. Xi, M. Feng, Q. Wang, Zhongshan Hospital Fudan University, Shanghai/CN

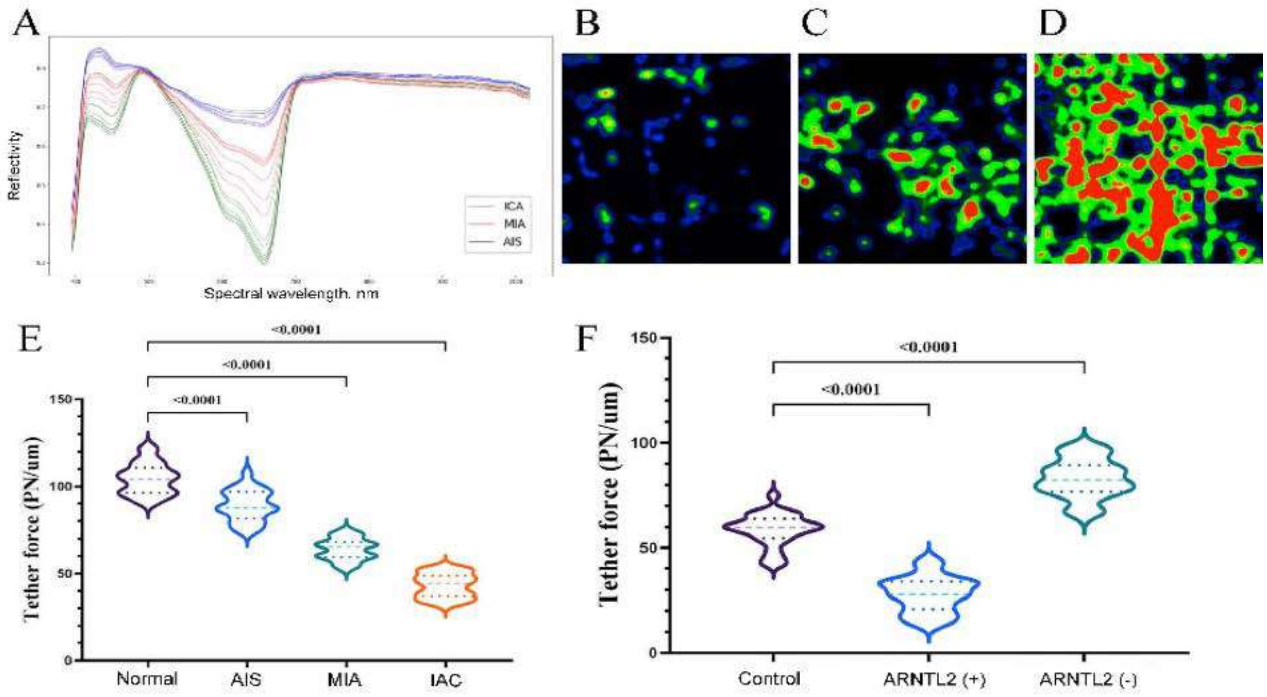
Introduction: The driving factors that promote invasive acquisition and change in tumor during the progression of lung adenocarcinoma still need to be explored. We explored the mechanical process and molecular mechanism of tumor invasion and metastasis from the intersection of mechanics and oncology.

Methods: The study qualitatively describes the mechanical rigidity of lung adenocarcinoma cells by analyzing the reflection spectrum characteristics of cell protein skeleton color rendering and simulating mechanical signals. Quantitative measurement of the mechanical rigidity of a single cell membrane is achieved through the capture and movement of microbeads attached to the cell membrane based on magnetic tweezers' micro rheology under the light field.

Results: The attributes of the cytoskeleton proteins can be displayed in spectral form. During the evolution of lung adenocarcinoma from AIS, MIA to IAC, it can be observed that there is a significant difference in spectral characteristics between the wavelength of 420 nm and 650 nm, indicating a significant change in the average cellular mechanical stiffness characteristics related to cytoskeletal protein characteristics per unit area of tumor tissue. Through computer mechanical signal simulation, we found that during the "AIS-MIA-IAC" progression of early lung adenocarcinoma, the mechanical rigidity heterogeneity of tumor cells gradually increased, indicating the presence of tumor cell heterogeneity during tumor progression, which may be closely related to the acquisition and enhancement of invasion and early metastasis ability of some tumor cells. Quantitative characterization of the mechanical stiffness of a single-cell membrane was achieved through the capture and movement of microspheres attached to the cell membrane based on magnetic tweezers under the light field. Bioinformatics analysis and in vitro experimental results indicate that changes in ARNTL2 expression can alter the mechanical rigidity of tumor cells through the ERK signaling pathway, thereby enhancing tumor cell migration, invasion, metastasis and promoting tumor progression.

Conclusions: Mechanical factors play an important role in lung adenocarcinoma progression from AIS, MIA to IAC. The change in mechanical rigidity of tumor cells may be a driving factor for the acquisition of invasion and metastasis ability of early lung adenocarcinoma cells. The expression of some key genes and activation of signaling pathways may be related to the change in mechanical rigidity of tumor cells.

Keywords: lung adenocarcinoma, progression, mechanical change



MA09 BEYOND THE MICROSCOPE: PREDICTING BENEFIT AND UNDERSTANDING BIOLOGY THROUGH BIOMARKERS
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MA09.09 Genomic Mapping of Evolutionary from Pre-Invasive to Advanced Stage in Lung Adenocarcinoma

Y-D. Lin[1,2], H-J. Li[1,2], H-Z. Hong[2], Y-F. Qi[2], Y-L. Wu[2], W-Z. Zhong[2], [1]School of Medicine South China University of Technology, Guangzhou/CN ,[2]Guangdong Lung Cancer Institute, Guangdong Provincial People's Hospital (Guangdong Academy of Medical Sciences), Southern Medical University, Guangzhou/CN

Introduction: Lung adenocarcinoma presents significant heterogeneity, with an extremely low survival rate in advanced stage, while the pre-invasive and early invasive lesions can be cured. Previous studies have focused on molecular events between pre-invasive and invasive adenocarcinoma (IAC), yet there remains a lack of continuous insight into identifying the genomic and evolutionary profiles from pre-invasive to advanced stage.

Methods: A total of 1525 next-generation sequencing (NGS) samples of adenocarcinoma, encompassing clinical stages 0-IV lung adenocarcinoma according to the Eighth Edition of the International Association for the Study of Lung Cancer TNM Classification, were retrospectively analyzed to identify key genomic profiling at different stages. The dataset of East Asian ancestry from OncoSG was used for prognostic assessment.

Results: Pre-invasive lesions and IAC of stage IA, stage IB-II, stage III, and stage IV accounted for 220, 884, 216, 118, and 87 samples, respectively. ERBB2, MAP2K1, BRAF, MED12, and TSC1 were significantly enriched in pre-invasive lesions. Meanwhile, EGFR, TP53, and LRP1B were notably enriched in IAC of stage IA, and APC, KEAP1, and POLE were exclusively observed in IAC. ERBB2 exhibited a continuous significant decrease from IAC of stage IA to stage IB-II, whereas TP53 showed a continuous significant increase. PTEN and BRCA2 were also enriched in stage IB-II. TP53 and RB1 were identified as key mutations in stage III compared to IB-II. No notable mutations were found between stage III and IV. Mutations including PTEN, STK11, APC, BRCA2, and LRP1B were associated with poor survival. In terms of oncogenic pathways, RTK-RAS was predominantly involved in pre-invasive lesions. TP53, Cell Cycle, WNT, and NRF2 were initially activated in IAC of stage IA, while PI3K and TGF-β were initially activated in stage IB.

Conclusions: This study provides a continuous depiction of the mutational features from pre-invasive to advanced lung adenocarcinoma. Elucidating this topic facilitates a systematic understanding of tumorigenesis and progression.

Keywords: Genomic mapping, Evolutionary profile, Adenocarcinoma

MA09.10 Spatial Transcriptomics and Next-Generation Sequencing Reveals the Gene Expression Andmolecular Immune Characteristics in LUAD

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Introduction: The individual prognosis of lung adenocarcinoma (LUAD) depend on their histologic growth pattern. The micropapillary component (MPC) is a poor prognostic indicator of LUAD. However, the transcriptome characteristics that lead to poor prognosis remain unclear, especially the spatial transcriptome (ST).

Methods: Spatial transcriptomic analysis of gene expression from 4 LUAD cases was performed with 10X Genomics. Targeted next-generation sequencing (NGS) was used to evaluate 72 LUAD samples. Tissue sections from 160 LUAD patients were stained with TCF12 and PD-L1 antibodies.

Results: We mapped the transcriptome of LUAD for the first time and revealed its broad heterogeneity, in which micropapillary (MP) pattern was associated with cAMP signaling and immune response. Moreover, the targeted next-generation sequencing results showed that MP-containing LUAD were mainly enriched in the cAMP signaling pathway, consistent with the ST results. Furthermore, the expression of the cAMP response element binding protein-TCF12 was elevated in the micropapillary region of LUAD. Next, the immunohistochemical results indicated that elevated TCF12 production was tightly connected to the poor survival and lymph node metastasis of MP patients. Finally, we detected a significant correlation between the PD-L1 heterogeneous expression and the presence of MP patterns. This is the first study to integrate spatial transcriptomics and targeted next-generation sequencing to illuminate the relationship between tissue structure and biological behavior in LUAD.

Conclusions: Our current results revealed the spatial heterogeneity of LUAD and identified molecules that can be used as a target for accurate LUAD diagnosis and treatment.

Keywords: Spatial transcriptome, Next-generation sequencing, Micropapillary component

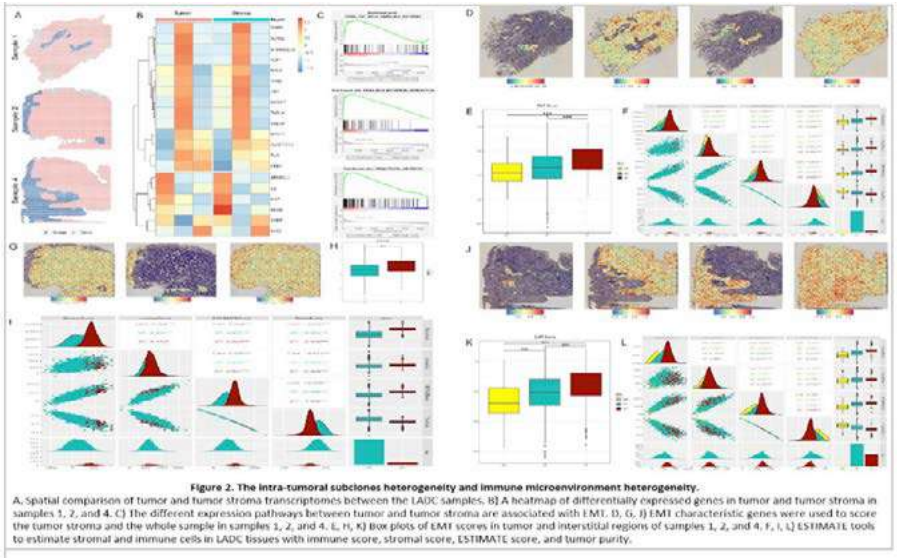


Figure 2. The intra-tumoral subclones heterogeneity and immune microenvironment heterogeneity.
A. Spatial comparison of tumor and tumor stroma transcriptomes between the LADC samples. B) A heatmap of differentially expressed genes in tumor and tumor stroma in samples 1, 2, and 4. C) The different expression pathways between tumor and tumor stroma are associated with EMT. D, G, J) EMT characteristic genes were used to score the tumor stroma and the whole sample in samples 1, 2, and 4. E, H, K) Box plots of EMT scores in tumor and interstitial regions of samples 1, 2, and 4. F, I, L) ESTIMATE tools to estimate stromal and immune cells in LADC tissues with immune score, stromal score, ESTIMATE score, and tumor purity.

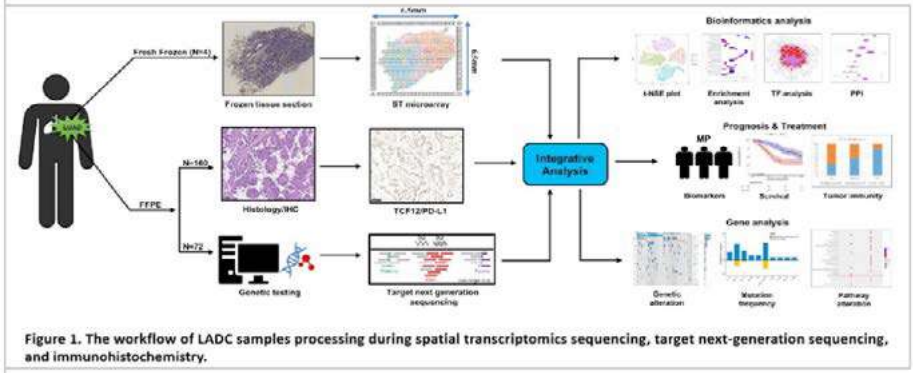


Figure 1. The workflow of LADC samples processing during spatial transcriptomics sequencing, target next-generation sequencing, and immunohistochemistry.

MA09.12 The Role of Different Lepidic Patterns for Determining Whether it is a Multiple Primary Pulmonary Adenocarcinoma

H. Xie[1], C. Wu[1], J. Guo[1], [1]Shanghai Pulmonary Hospital, Shanghai/CN

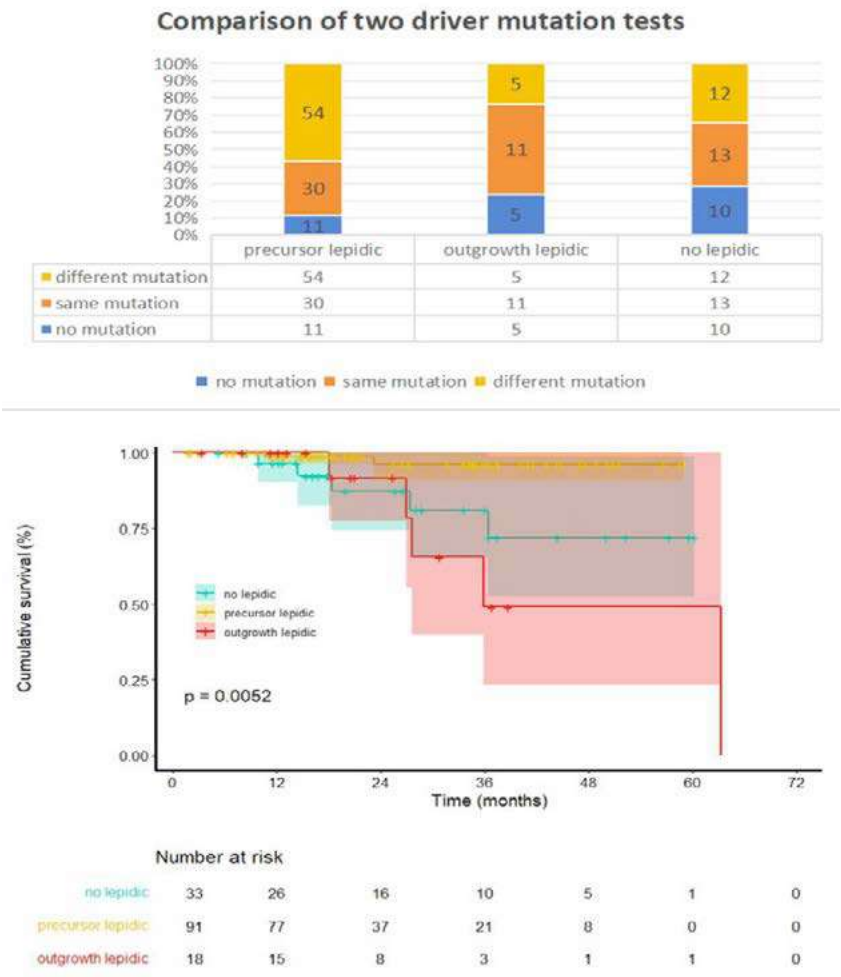
Introduction: Determining whether a second occurrence of lung adenocarcinoma is metastatic or a second primary is of great clinical significance, but sometimes it's difficult. The presence of carcinoma in situ (lepidic pattern) in the second tumor is one of the markers of double primary tumors, which can simplify the process of determining metastasis or double primary tumors. Outgrow lepdic was also judged to be a lepidic pattern according to the latest WHO classification and was considered not to need to be differentiated from precursor lepidic in clinical practice. We wanted to assess whether outgrow lepdic also had a role in determining whether the second lung adenocarcinoma was primary or metastatic by comparing the patient's prognosis and driver mutations between the two tumors.

Methods: We included 151 patients who underwent two times of surgery in Shanghai Pulmonary Hospital from September 2014 to January 2024, both of which were pathologically diagnosed as lung adenocarcinoma and had undergone at least 5 gene tests (EGFR, ALK, KRAS, BRAF, ROS1). We re-read all the slides and recorded the adenocarcinoma pattern they contained, especially the lepdic pattern in the second tumor, even if it was less than 5%. All patients were followed up for prognosis.

Results: There were 126 cases with at least one driver mutation in two tests, 116 cases with lepdic pattern in the second tumor (95 precursor lepidic cases, 21 outgrow lepdic cases). The mutation concordance rate was 31.57% and inconsistency rate was 56.8% in cases with precursor lepidic. The mutation concordance rate was 52.4% and inconsistency rate was 23.8% in cases with outgrow lepdic. Patients with precursor lepidic in the second tumor had a better prognosis than those with outgrow lepdic and those without lepidic pattern.

Conclusions: In multiple lung adenocarcinomas, patients with precursor lepidic in the second tumor have a lower probability of mutation coincidence and a better prognosis, which can be used as a basis for determining whether it is a multiple primary adenocarcinoma. Outgrow lepdic should not be used as a basis for determining whether it is a multiple primary adenocarcinoma. It should be distinguished from precursor lepidic in cases requiring confirmation of metastasis or a second primary.

Keywords: Outgrow lepdic, Driver mutation, multiple primary pulmonary adenocarcinomas



MA09.13 Clinical Outcome of Bilateral Invasive Mucinous Adenocarcinoma(IMA) without Mediastinal Nodal Involvement from SEER Database

J. Kim, Y.J. Heo, W. Woo, S. Kim, Y.K. Chae, Northwestern University Feinberg School of Medicine, Chicago/IL/USA

Introduction: Invasive mucinous adenocarcinoma (IMA) represents a distinct subset of lung adenocarcinomas, accounting for 5%-10% of cases, characterized by unique histopathological and molecular profiles. Despite its distinctive features, IMA's prognostic factors and clinical course remain underinvestigated. This study analyzes various prognostic factors of IMA, including bilateral lung involvement without mediastinal nodal involvement, and their impact on clinical outcomes.

Methods: We analyzed data from the SEER database for patients diagnosed with IMA from 2000 to 2020. Kaplan-Meier survival curves and log-rank tests were utilized to assess OS and lung cancer-specific survival (LCSS) across different cohorts. Additionally, Cox regression models were used to evaluate the hazard ratios (HRs) of risk factors impacting survival outcomes.

Results: Among stage IV IMA patients (n= 3211), those with bilateral parenchymal IMA (BP-IMA) without mediastinal lymph node involvement (n= 86, 2.68%) exhibited significantly better overall survival (OS: median 0.71 years vs. 0.42 years; p=0.047) and lung cancer-specific survival (LCSS: median 0.83 years vs. 0.50 years; p=0.024). Notably, survival rates for patients with BP-IMA were not significantly different from patients with stage III IMA (OS, p=0.097; LCSS, p=0.095). Furthermore, analysis identified bilateral tumors without mediastinal lymph node involvement(MLNI) (HR=0.71 [0.53-0.94], p=0.015), advanced T stages (HR=1.19 [1.09-1.30], p<0.001), age (≥70, HR=1.34 [1.23-1.45], p<0.001), and gender (male, HR=1.17 [1.07-1.27], p<0.001) as significant prognostic factors influencing survival in IMA patients.

Conclusions: Our study reveals that BP-IMA without mediastinal nodal involvement shows a more favorable prognosis than typically seen in other stage IV IMA. This finding underscores the need for a tailored approach for stage IV IMA patients lacking extensive lymph node involvement. Further prospective studies are warranted, given the complexity of IMA.

Keywords: Mucinous adenocarcinoma, SEER, histopathology

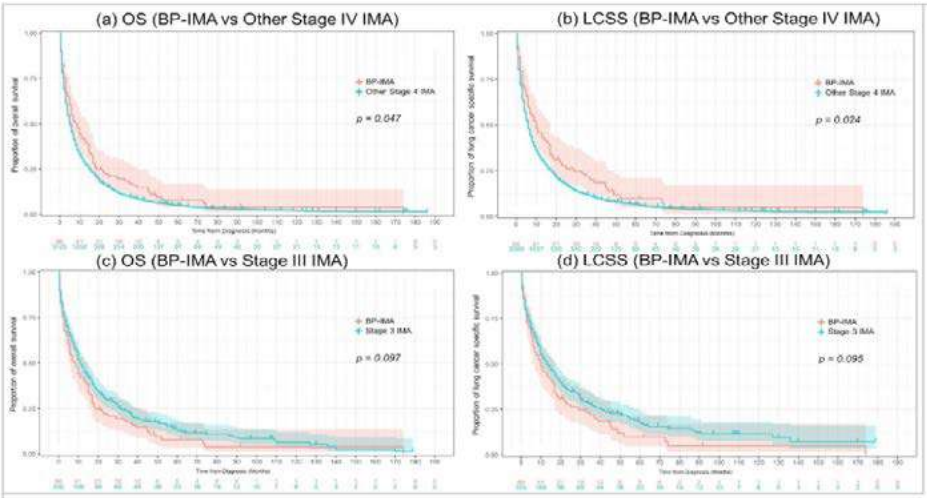


Table. Prognostic Factors of Stage IV Invasive Mucinous Adenocarcinoma

Factor	Hazard Ratio (95% CI)	P-value
Bilateral IMA without MLNI	0.71 (0.53-0.94)	0.015
T Stage (Ref. T1, T2)		
T3, T4	1.19 (1.09-1.30)	<0.001
Sex (Ref. Female)		
Male	1.17 (1.07-1.27)	<0.001
Age (Ref. age under 70)		
70 or older	1.34 (1.23-1.45)	<0.001

MLNI, Mediastinal Lymph Node Involvement

MA10 FINANCIAL TOXICITY, CLINICAL COMMUNICATION, AND THE NEEDS OF PATIENTS AND CAREGIVERS
TUESDAY, SEPTEMBER 10, 2024 - 11:15 - 12:30

MA10.03 Paying the Price: How Lung Cancer Care Impacts Wallets and Well-Being

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Introduction: While advances in lung cancer treatment have improved clinical outcomes, it is unclear the extent to which treatment initiation is accompanied by financial hardship that can negatively impact the quality of life of patients and their families. We investigated financial hardship and related sociodemographic inequities among patients with lung cancer.

Methods: This secondary analysis of standard-of-care treatment planning survey data included patients with lung cancer diagnosed from 2017 to 2023 at the University of Alabama at Birmingham. Surveys included two measures of financial hardship. The first was the validated Comprehensive Score for financial Toxicity (COST) tool (scored from 0 to 44, with lower scores indicating more financial distress). The second was a list of questions measuring 10 individual domains of financial difficulty, including: trouble paying for basic needs, utilities, transportation or lodging for treatment, medications, medical supplies, upfront medical payments, insurance or medical bills, child or eldercare, and employment or disability issues. The total number of patient-reported financial difficulties was measured, with values ranging from 0/10 to 10/10. Analysis was based on the first survey completed post-diagnosis, and subgroups were compared using independent-samples t-tests.

Results: Among 253 patients with financial toxicity survey data, median age was 67 years (range: 29 to 94). The cohort was majority male (53%) and White (65%; 21% minority groups, including those identifying as Black, Asian, and Hispanic; 12% missing race/ethnicity). Among the 204 patients (81%) which had COST data, median scores were 28.0 (IQR 17.3). Patients belonging to a minority group and those under the age of 65 reported more financial distress compared to White or older patients (>65y), with a mean difference in COST scores of -5.4 (95% CI -9.3 to -1.5) and -6.8 (95% CI -9.8 to -3.7), respectively. Minority and younger patients also reported greater financial difficulties compared to White or older (>65y) patients, with mean differences in reported financial difficulties of 1.5/10 (95% CI 0.5 to 2.6) and 1.3/10 (95% CI 0.5 to 2.1), respectively. When asked whether they had enough in savings to pay for their treatment, 47.8% of patients answered “Somewhat”, “Very much”, or “Quite a bit”. Additionally, patients reported an average of 2.5/10 financial difficulties (N=253). Among all patients, the most commonly endorsed domains of financial hardship were: upfront medical payments (n=91, 36.0%), insurance or medical bills (n=87, 34.4%), and medications (n=75, 29.6%).

Conclusions: In a sample of patients initiating treatment for lung cancer, financial hardship was greater among minoritized racial or ethnic groups and younger patients. Additional study of this cohort is ongoing, including construction of models to predict patients at higher risk of financial toxicity, and whether it impacts clinical trial participation. Finally, routinely delivered interventions to identify and address financial hardship before treatment onset, such as oncology financial counseling, warrant further investigation.

Keywords: Financial, Toxicity, Hardship

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MA10.04 The Financial Toxicity of Lung Cancer Impacts All Spheres of Life

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Introduction: Anecdotal evidence within the European lung cancer community has strongly suggested that a lung cancer diagnosis results in a significant economic burden. The aims of this study were to (i) assess if financial toxicity existed and the impact of it, and (ii) identify possible interventions.

Methods: This work was a descriptive research analysis that explored the economic burden of lung cancer, as reported by people diagnosed with the disease and those in a caregiving capacity. A survey was developed following an extensive literature review and discussion among the LuCE Report Working Group. The survey was translated into 16 languages and disseminated primarily via LuCE and its members through social media platforms. It was active for approximately 6 weeks and data was collected via an online platform.

Results: The survey was completed by 1,161 participants (834 people with lung cancer and 327 caregivers) across 28 European countries. Most participants experienced both medical (73.5%) and non-medical expenses (87%), with the primary cost most often relating to travel for medical reasons (84%). Approximately half of the participants (49.5%) experienced an income decrease of more than 30%. This was due to inability to work (1 in 4), being absent from work (28%) and the need to retire due to their diagnosis (27%). Nearly 40% found it difficult to live on their current household income. Almost 9 in 10 people (88%) felt that at least one sphere of their lives was negatively impacted due to the financial situation caused by lung cancer, predominately their mental health (67.5%). Additionally, they felt that these issues were a barrier to treatment, recovery, and care. Worryingly, more than a quarter (26.5%) had to make difficult decisions that affected their self-care or adherence to treatment. Overall, nearly half (47%) felt financially distressed after diagnosis (an increase of 19% from baseline), and 29% could not meet their monthly expenses, which was a doubling from baseline levels. Few participants sought help with their difficulties (approximately 21%), but even of that between 30-41% of participants did not receive the required support. Financial support in relation to medication and healthcare costs were identified as a high priority (53%).

Conclusions: Financial toxicity is common in Europe. People impacted by lung cancer need access to allied healthcare professionals who can screen for financial vulnerability and put assistance measures in place. Government policies must prioritise income replacement programmes to assist those struggling with the financial impact of a cancer diagnosis.

Keywords: Advocacy, Europe, Financial toxcity

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MA10.05 Characterization of the Basic Financial Needs of Those Living with Lung Cancer

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Introduction: Financial toxicity is a pervasive issue for patients, particularly in lung cancer, which is among the most expensive cancers to treat. As therapeutics and survival improve, survivors can struggle to balance personal financial goals with medical costs. Here, we sought to better understand the impact of these costs on personal finances.

Methods: GO2 for Lung Cancer has regular contact with survivors and caregivers through an email and phone call-based helpline, allowing those impacted by lung cancer to reach out for support. We analyzed contacts received between 11/28/17-12/31/23, looking at contact demographics and the nature of their financial request.

Results: There were 11375 total contact-points, with 1563 (11.7%) having Financial Assistance as the primary support need. 1730 reported needs were spread out across 34 deductive categories. The top 5 identified were Co-Pays (16.8%), Transportation (16.1%), Insurance (7.2%), Treatment-Chemotherapy (6.1%), and Treatment-Targeted Therapy (5.8%). We further categorized needs into those that were "Basic," or essential to maintain daily life for the caller and their dependents. These included housing, food, dependent care, prescriptions, and utilities. Almost 19% (18.8%) requested aid for at least one basic need. GO2 could only successfully refer to financial assistance 36.5% of the time due to funds being closed. The most common sources referred to were cancer-specific organizations (35.8%), other non-profits/charities (24.3%), and case managers/navigators (16.7%). There is a circuitous nature to financial aid referrals, as the leading referral sources to GO2 were also cancer-specific organizations, other non-profits/charities, and healthcare professionals. Callers were evenly represented between caregivers (40.6%) and patients (44%), primarily female (76%), had non-small cell lung cancer (57.2%), and late-stage disease (60.5%). The average age at diagnosis was 61.8 years. This mirrors current literature, showing those diagnosed <65 are more likely to face financial hardship. The most common treatments were chemotherapy (39.6%) and radiation (23.7%). Of those reporting insurance information, 45.8% had Medicare, 22% had private insurance, 17% received Medicaid, and 13.7% were uninsured. Starting in 2021, GO2 began recording patient reported barriers to care. Those most identified were Trouble Affording Co-Payments (16%), Housing Instability (11.6%), Under-insurance (11.6%), Lack of Income/Unemployment (10.5%), and Transportation (7.7%).

Conclusions: This analysis underscores the variety of financial resources needed for lung cancer patients. In addition to high treatment costs, nearly 1/5th of patients lack basic necessities. This can contribute to higher physical/mental stress, which may negatively impact their prognosis/adherence. Insurance status presents an issue, as the uninsured rate we found is higher than the 2022 data showing 8% of Americans are without health insurance. Care teams should utilize validated measures to identify how their patients are at risk to ensure they receive adequate support throughout their care. Policy makers must also consider the landscape of financial assistance, and how it can be transformed to aid cancer survivors and their families.

Keywords: Lung Cancer, Financial Toxicity, Financial Needs

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MA10.07 Understanding Symptom Burden in Young Adults with Lung Cancer Based on an Analysis from the E2C2 Pragmatic Clinical Trial

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Introduction: There is limited data on the symptom burden that young adults with lung cancer experience. In this large pragmatic trial, we evaluated patient-reported outcomes for patients with lung cancer based on age (<50 or >= 50 years old), gender, and history of smoking.

Methods: We conducted a subgroup analysis from the Enhanced, EHR-facilitated Cancer symptom Control (E2C2) study, which is a stepped-wedge, cluster-randomized pragmatic trial evaluating a collaborative care model for the assessment and management of six symptoms: Sleep disturbance, Pain, Physical function impairment, Anxiety, Depression, and Energy deficit/fatigue (SPPADE). Symptoms are rated on an 11-point numerical rating scale. Symptom severity is classified as mild (0-3), moderate (4-6), or severe (7-10). Our analysis included patients with any diagnosis of lung cancer who completed at least one survey regardless of the timepoint in their treatment course, then summarized SPPADE symptom data reported from their initial survey. We utilized a chi-square test with the binary outcome of symptom score >=7 or symptom score < 7.

Results: 5,039 patients with lung cancer completed a survey between March 2019 and January 2023. Of those patients, 2,651 identified as female (52.6%) and 2,388 identified as male (47.4%). 342 patients were <50 (6.8%) and 4697 were >=50 (93.2%). There was a history of smoking in 158 patients <50 (43.9%) and 3,519 patients >=50 years (74.9%). Patients <50 were more likely to report severe anxiety (16.22% vs 11.30%, p = 0.006). Women were more likely to report severe anxiety (13.82% vs. 9.2%, p < 0.001) and depression (10.14% vs. 7.98%, p = 0.008) compared to men. Women <50 were more likely to report severe pain (17.86% vs 7.69%, p = 0.007) and insomnia (20.92% vs 12.59%, p = 0.046) than men in this age group. Patients with a history of smoking were more likely to report severe anxiety (12.39% vs. 9.34%, p = 0.003), depression (9.74% vs. 7.33%, p = 0.01), fatigue (21.92% vs. 16.54%, p < 0.001), pain (14.31% vs. 8.19%, p < 0.001), impaired physical function (16.96% vs. 11.28%, p < 0.001), and insomnia (16.18% vs. 10.96%, p < 0.001) compared to patients who never smoked. Younger patients with a history of smoking reported more severe anxiety (22.29% vs. 10.67%, p = 0.004), depression (15.92% vs 7.3%, p = 0.013), fatigue (27.39% vs. 10.67%, p < 0.001), and impaired physical function (20.38% vs. 11.17%, p = 0.02).

Conclusions: Young patients with lung cancer experience more severe anxiety compared to older adults. Within the <50 cohort, women were more likely than men to report severe pain and insomnia, and younger patients with a smoking history had more severe anxiety, depression, fatigue, and physical dysfunction compared to patients who never smoked. A tailored approach to supportive care resources may be needed for these different patient populations. Further study will focus on understanding how patients utilize supportive care services, if symptom burden evolves over time, the incidence of co-occurring symptoms, and the ideal strategies to improve the quality of care for these patients.

Keywords: young adults, symptom burden, patient reported outcomes

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MA10.08 Unravelling the Impact: Understanding Caregivers in the Lung Cancer Community

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Introduction: Primary informal caregivers are with their person living with lung cancer the most and play a critical care role in the care pathway. Yet, these informal caregivers are too often an undervalued member of the healthcare team. In this study, we sought to understand how caregivers providing care for <1 year compared to those providing care for 1 or more years with respect to time spent on different care tasks, changes to employment, support networks, and well-being.

Methods: We analyzed data from LUNGevity Foundation's longitudinal study on the experiences of people living with lung cancer (Project PEER). In this analysis, we looked at respondents who identified as a caregiver (n=79). All caregivers completed an initial assessment survey online that includes questions on the diagnostic pathway of the person they care for and caregiver-specific questions and validated questionnaires (the CareGiver Oncology Quality of Life questionnaire (CarGOQoL) and ENRICHD Social Support Instrument (ESSI)). We focused on caregivers providing care for <1 year (n=37) and 1 year or more (n=42).

Results: Half of the caregivers were spouses/partners (40% wives/10% husbands) with a median age of 57 and a quarter were children (20% daughters/5% sons) with a median age of 41. The remainder were a mix of other family and non-relative caregivers. Time spent on medical decision-making and household tasks were similar between the groups. However, looking at time spent in the last month on caregiving activities, differences were observed between caregivers of <1 year and long-term caregivers on daily tasks involved with caregiving (median hours per month were 9 and 1.5, respectively) and emotional support (median hours per month were 20 and 30, respectively). Caregivers, regardless of length of time caregiving, spent an average of 70 hours a month on unpaid caregiving tasks. Regarding changes to employment, 22% of <1yr caregivers and 31% of long-term caregivers reported a change. More long-term caregivers reported retiring early or quitting their job. Both groups reported taking leaves of absence and decreasing hours of paid employment. For social networks, long-term caregivers reported less support for daily chores (Most/all the time: 34% vs. 55%), however a larger proportion of caregivers of <1yr did not have someone they could trust and regularly confide in (none/a little of the time 21% vs. 14%). Psychological well-being was similar between groups, median score of 37 for <1yr vs. 41 for long-term caregivers (higher scores (maximum 100) indicate better well-being).

Conclusions: Around a quarter of the sample reported changing their employment by taking early retirement, decreasing hours at work, or taking medical leave to accommodate extra tasks. The long-term financial implications of decreasing paid employment for caregivers have been documented. Psychological well-being was similar between the groups; however, was lower than what was reported in the initial validation papers for the CarGOQoL, which included lung cancer caregivers, but not exclusively. Our findings underscore the need to develop caregiver support services to address the evolving needs of caregivers based on the duration of caregiving.

Keywords: caregivers, well-being, support needs

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MA10.09 Mapping of Patient-Reported Outcome Items to Symptomatic Adverse Events of Tyrosine Kinase Inhibitors in Non-Small Cell Lung Cancer

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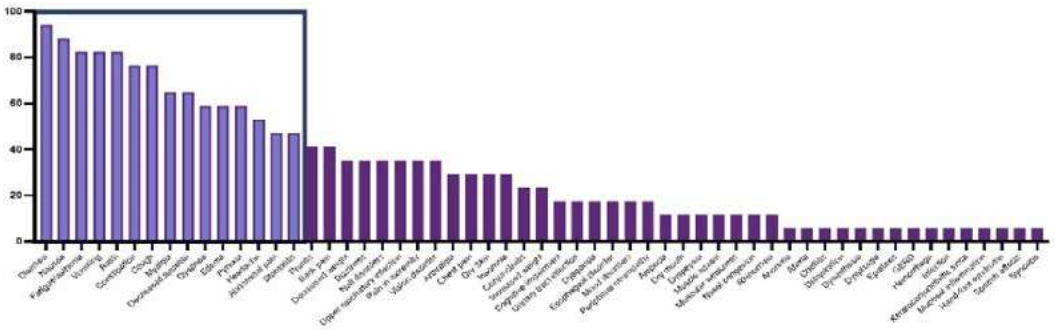
Introduction: Patient-reported outcomes (PROs) are critical for assessing symptomatic adverse events (AEs) in non-small cell lung cancer (NSCLC) clinical trials. However, PROs may not fully capture tyrosine kinase inhibitor (TKI)-specific AEs in metastatic NSCLC, impacting patient treatment expectations. This study evaluates the coverage of TKI-related symptomatic AEs by commonly used PRO item libraries.

Methods: A list of FDA-approved TKIs for NSCLC with alterations in EGFR, ALK, ROS1, RET, MET, and NTRK was compiled by physicians and patient advocates. Symptomatic AEs were extracted from drug labels using drugs@FDA. European Organisation for Research and Treatment of Cancer (EORTC), Patient-Reported Outcomes Measurement Information System (PROMIS), and Patient-Reported Outcomes Common Terminology Criteria for Adverse Events (PRO-CTCAE) item libraries were searched for items assessing the presence, frequency, and/or severity of symptoms corresponding to these AEs. Descriptive statistics were used to summarize AE coverage by items in each library. Items were classified based on whether they assessed an AE's physical, functional, or social/emotional impact.

Results: AE data from 29 clinical trials of 17 TKIs were analyzed. By TKI, EORTC included items that covered the highest average percentage of AEs (98%) followed by PRO-CTCAE (86%) and PROMIS (47%). Of the top 15 most common AEs across TKIs, 8 were covered by all 3 item libraries. EORTC and PRO-CTCAE covered all 15, while PROMIS covered 8 out of 15 (53%). Of these 8 AEs covered by all 3 item libraries, PROMIS included the greatest number of items assessing the functional impact of AEs compared to EORTC or PRO-CTCAE (12% vs 3% vs <1% respectively) as well as social/emotional impact (23% vs 10% vs 0%). For TKI-specific dermatologic AEs, EORTC and PRO-CTCAE covered all 5 identified reactions, while PROMIS covered 1 out of 5 (20%).

Conclusions: While EORTC and PRO-CTCAE covered most symptomatic AE occurrences, PROMIS showed potential in capturing the impact of AEs on patient wellbeing. No libraries addressed all TKI-specific adverse reactions, indicating a need to expand or combine PRO item libraries. These findings underscore the importance of tailoring PRO assessments to specific NSCLC treatments to enhance patient-centered care and shared decision-making between physicians and patients. Our study did not assess how PROs are administered during clinical trials. Future work should be done to address the timing of PRO administration (to capture symptoms at their peak severity) and the evolving drug tolerability over extended treatment durations that are common with targeted therapies.

Keywords: Patient-reported outcomes, Tyrosine kinase inhibitors, Non-small cell lung cancer



CTCAE	PRO-CTCAE	PROMIS	EORTC
Diarrhea	YES	YES	YES
Nausea	YES	YES	YES
Fatigue	YES	YES	YES
Vomiting	YES	YES	YES
Rash	YES	NO	YES
Constipation	YES	YES	YES
Cough	YES	NO	YES
Myalgia	YES	NO	YES
Decreased appetite	YES	YES	YES
Dyspnea	YES	YES	YES
Edema	YES	NO	YES
Pyrexia	YES	NO	YES
Headache	YES	NO	YES
Abdominal pain	YES	YES	YES
Stomatitis	YES	NO	YES

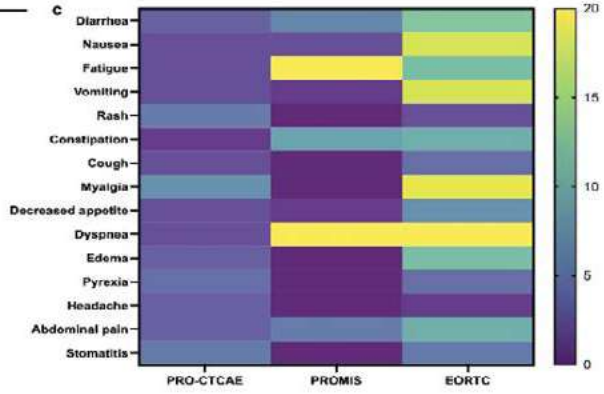


Figure 1. Item library coverage of most common symptomatic AEs across TKI clinical trials. (a) AEs in each study from most to least common, box highlights 15 most common AEs. (b) Item library coverage of 15 most common AEs. (c) Heat map representing number of items in each item library covering 15 most common AEs (NOTE: for scale, maximum number of items cutoff was set at 20).

MA10.11 Patient-Reported Doctor Communication and Preference on Treatment Decision Making: Oligometastatic vs Metastatic Lung Cancer

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Introduction: Oligometastatic NSCLC is a complex term, defining 1-5 metastatic sites in a controlled primary tumor with increased overall survival on treatment. Additional emerging terms (e.g., synchronous, oligo-progression) further complicate communication around the diagnosis, and shared decision-making (SDM) between patient and doctor. Our aim was to assess how a diagnosis of oligometastatic NSCLC impacts patient-reported preferences in SDM and provider-patient communication across patients with oligometastatic vs advanced NSCLC.

Methods: LUNGevity Foundation's Project PEER is an ongoing observational study aimed at understanding experiences of people living with lung cancer, currently with 410 patient participants. We focused on the subgroup with advanced (stage III and IV) NSCLC (n=237), comparing advanced disease (59%, n=139) and oligometastatic disease (41%, n=98).

Results: Participants reporting oligometastatic vs advanced disease were similar: Average age 57 vs 56 years, female gender 85% vs 80%, <2 years since diagnosis 49% vs 53%, adenocarcinoma prevalence 88% vs 81%, specific biomarkers 81% vs 82% and 1 line of treatment 35% vs 47% for participants with advanced vs oligometastatic disease respectively. Actual and preferred SDM were similar: 55% vs 54% and 78% vs 74% between participants with advanced vs oligometastatic disease respectively, though there were minute differences between actual and preferred for both groups (see table). Participants in the oligometastatic group were asked if their doctor explained the term, 66% reporting their doctor did not. In this group, fewer participants reported shared decision making (45%) than those whose doctors did explain (64%). Additional comparisons surrounding patient concerns, future treatment and provider communication between these groups showed a similar pattern. No patterns on access to multidisciplinary teams or prognostic awareness were observed between the groups.

Conclusions: We used the complex term of "oligometastatic disease" as a proxy to understand patient-provider communication and found that participants whose doctor explained oligometastatic disease were more likely to report SDM, and greater comfort talking to their doctor about their symptoms, care, and treatment trajectory than either those who reported advanced disease only or whose doctor did not explain oligometastatic NSCLC. Clinicians should be aware that in-depth discussions of complex terms, alternative treatments, and uncertainties are relevant to conversations that extend beyond the initial treatment plan and impact comfort in discussing other care issues (concerns, side effects).

Keywords: Oligometastatic disease, Shared decision making

	Advanced disease (n=139)	Oligometastatic Disease (n=98)	Doctor explained oligometastatic disease (n=33)	Doctor did not explain oligometastatic disease (n=58)
Role in shared decision making (SDM)				
Shared decision	76(55%)	53(54%)	21(64%)	26(45%)
Doctor led decision	41(29%)	27(28%)	8(24%)	18(31%)
Patient led decision	22(16%)	18(18%)	4(12%)	14(24%)
Future treatments/worries discussion with doctor				
Very well	78(56%)	49(50%)	20(61%)	20(34%)
Not very well	61(44%)	49(50%)	13(39%)	38(66%)
Comfort discussing worries/concerns with doctor				
Very comfortable	77(55%)	44(45%)	22(67%)	23(40%)
Not very comfortable	60(43%)	54(55%)	11(33%)	35(60%)
Comfortable talking to doctor about symptoms				
Very comfortable	103(74%)	68(69%)	28(85%)	35(60%)
Not very comfortable	36(26%)	30(31%)	5(15%)	23(40%)
Care team understands you				
Very well	60(43%)	35(36%)	19(58%)	13(22%)
Not very well	79(57%)	63(64%)	14(42%)	45(78%)

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MA10.12 Patient-Centered Communication and Knowledge and Preparedness in Treatment Decision-Making Among People with Lung Cancer

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Introduction: The management of lung cancer requires increasingly complex decision making by healthcare professionals and patients, particularly in the era of biomarker-driven therapeutic strategies. As a result, lung cancer healthcare professionals' ability to successfully provide patient-centered communication (PCC) is required for shared decision making that considers patient values and priorities. The aim of the present study was to examine the impact of PCC among people with lung cancer on knowledge and preparedness in treatment decision-making.

Methods: Participants in Cancer Support Community's Cancer Experience Registry self-reported sociodemographic information and clinical history, rated their level of knowledge about cancer treatment options and preparedness to make treatment decisions, and completed the Patient Centered Communication short form (6 items; α=0.88), which assesses PCC in six core domains: exchanging information, making decisions, fostering healing relationships, enabling patient self-management, managing uncertainty, and responding to emotions. We included select sociodemographic and clinical variables based on conceptual relevance to PCC and treatment decision-making. Due to a negatively skewed distribution, PCC was dichotomized using a median split (median=4). We fit three logistic regression models: (1) sociodemographic and clinical history variables predicting higher PCC (0=lower median, ≤4; 1=upper median, >4), (2) PCC predicting greater perceived knowledge about treatment options (0=Not at all-Somewhat; 1=Quite a bit-Very much), and (3) PCC predicting greater preparedness to make cancer treatment decisions (0=Not at all-Somewhat; 1=Quite a bit-Very much). The latter two models also included sociodemographic variables and clinical history.

Results: The sample consisted of 177 individuals with lung cancer (71% women; 84% non-Hispanic White; 52% college degree; 37% income ≥$40K; 31% metastatic). Mean age was 65 years (range: 30-92, SD=12); median time since diagnosis was 6 years (IQR: 3-9). 39% reported Quite a bit to Very much knowledge of treatment options, and 45% felt Quite a bit to Very much prepared to make treatment decisions. Bivariate analysis showed a significant relationship between PCC and gender (t=2.25, p=.03; PCC levels lower among women), knowledge about treatment options (r=.33, p<.001), and feeling prepared to make treatment decisions (r=.44, p<.001). In multivariable analysis, higher PCC was associated with greater knowledge about treatment options (OR=3.28; 95% CI=1.51, 7.12; n=151) and greater preparedness to make treatment decisions (OR=4.10; 95% CI=1.90, 8.84; n=151), after adjusting for sociodemographic and clinical history variables. In addition, higher income (≥$40K) was associated with greater knowledge (OR=3.14; 95% CI=1.25, 7.90) and older age (years) was associated with greater preparedness (OR=1.04; 95% CI=1.00, 1.07).

Conclusions: PCC was a significant predictor of greater knowledge and preparedness in treatment decision-making among people with lung cancer, even when including sociodemographic and clinical characteristics in the models. As supported by these findings, successful patient-provider communication influences treatment decisions among people with lung cancer. These findings suggest that providers can positively influence decision-making knowledge and preparedness of patients with lung cancer through improving communication. Continued research is needed to identify the elements of effective communication between clinicians and patients and families.

Keywords: patient centered communication, treatment decision-making, suvivorship

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MA10.13 TIME TOX Lung: Retrospectively Quantifying the Time Toxicity of Lung Cancer Clinical Trials

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Introduction: It is estimated that only 3-6% of US adults with cancer will participate in clinical trials, with study complexity and time burden ranking among fundamental barriers to enrollment. The increasing complexity of clinical trials has recently led to several NCI initiatives focused on decreasing operational burden. The concept of "time toxicity," (TT) a quantitative metric of patient-level time cost, has been proposed in the clinical setting, however, is not well defined in clinical trials. The purpose of this study is to develop and retrospectively apply a standardized time metric to lung cancer clinical trials, evaluate TT across study phases, and characterize evolution over time.

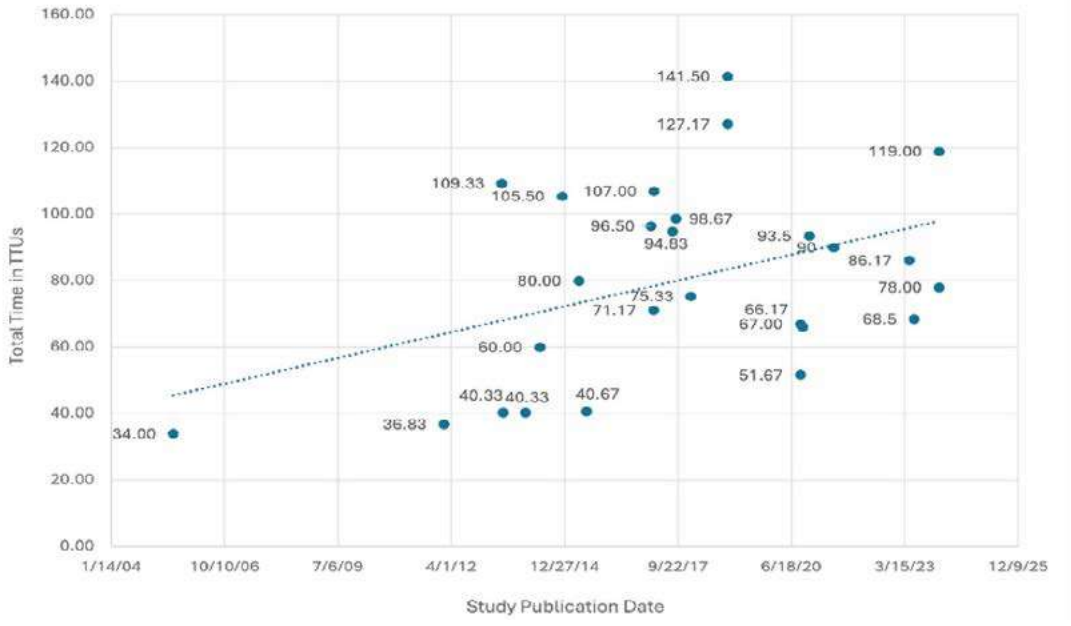
Methods: Protocols from 26 trials associated with FDA approvals of 14 oral targeted lung cancer therapies were obtained from public sources. Using each protocol's schedule of events, study-mandated procedures were assigned "Time Toxicity Units" (TTUs) based on standard time dedicated to those procedures in our institution (1TTU=30min). TTUs for each procedure were multiplied by their frequency and then summed for screening through cycle 5 to determine a trial's Total Time Toxicity (TTT). Descriptive statistics were used to summarize time burdens by publication year and study phase. Median TTT was compared for studies published 2005-2014 and 2015-2024 to assess change over time. Two sample Mann-Whitney U Tests were used for non-parametric comparisons.

Results: Publications spanned 2005-2024, including 5 Phase I, 9 Phase II, and 12 Phase III studies. There were 7 studies (1 Ph I, 0 Ph II, 6 Ph III) with associated publications between 2005-2014 and 19 (4 Ph I, 9 Ph II, 6 Ph III) with associated publications between 2015-2024. Median TTT was 80 (range 60-127.2), 86.2 (51.7-141.5), and 73.3 (34-109.3) TTUs for Ph I-III studies, respectively. Among studies published 2005-2014, median TTT was 40.3 (34-109.3) compared to 86.2 (40.7-141.5) for those published 2015-2024 (p=0.056). Exclusion of Phase I studies did not change the numerical median difference, however weakened the trend (p=0.173).

Conclusions: Clinical trials require considerable time investment from patients. In this study, TT was observed to increase over time, with a non-significant trend toward greater time burden in Phase I-III studies published 2015-2024 compared to 2005-2014. This study demonstrates the feasibility of applying a TT metric to trial protocols using the schedule of events. We now aim to prospectively validate this reportable metric, which can then be employed as a mechanism to both inform patients of TT and encourage streamlined protocol development.

Keywords: Time toxicity, Trial design, Targeted therapy

Figure 1: Evolution of TT over time for Phase I-III clinical trials evaluating oral targeted lung cancer therapies.



MA11 BUILDING ON THE FOUNDATIONS OF CURRENT IMMUNOTHERAPIES
TUESDAY, SEPTEMBER 10, 2024 - 13:30 - 14:45

MA11.03 First-Line Treatment of Locally Advanced or Metastatic Pulmonary Lymphoepithelioma-likecarcinoma: A Multicenter, Single-Arm, Phase II Trial

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Introduction: Pulmonary lymphoepithelioma-like carcinoma (PLELC) is a distinct subtype of non-small cell lung cancer, associated with Epstein-Barr virus (EBV) infection and a unique immune environment. Thus we aimed to investigate the efficacy and safety of sintilimab plus gemcitabine and carboplatin in untreated locally advanced/metastatic PLELC.

Methods: This multicenter, single-arm, phase II study enrolled PLELC patients from April 2020 and November 2021. Eligible patients had a histologic diagnosis of locally advanced/metastatic PLELC without any prior systemic treatment. Patients received four cycles of sintilimab plus gemcitabine and carboplatin, followed by maintenance treatment with sintilimab. Primary endpoints were objective response rate (ORR) and safety. Secondary endpoints included progression-free survival (PFS), overall survival (OS), and disease control rate (DCR). Association between biomarkers and PFS was exploratorily analyzed

Results: A total of 30 patients were enrolled. At a median follow-up of 31.2 months (95%CI,28.4-36.7), the ORR was 73.3% (95%CI, 54.1-87.7), and the DCR was 100% (95%CI, 88.4-100). The median PFS was 14.0 months (95% CI, 12.2-20.7). The median OS was not reached, but it was predicted to be 36.1 months (95% CI, 25.7-46.6) based on the Gaussian distribution model. Twenty-one (70%) patients experienced ≥ grade 3 treatment-related adverse events, of which neutropenia (n=12, 40%), anemia (n=4, 13.3%), thrombocytopenia (n=2, 6.7%), decreased white blood cell count (n=3, 10%) were the most common. Exploratory analysis revealed that a higher T-cell-inflamed gene-expression profile (GEP) score was independently associated with longer PFS (HR=0.22, 95%CI, 0.07-0.67, p=0.004). The dynamic analysis of plasma EBV DNA load showed a significant decline when the best response was achieved after treatment (p=0.006) and an increase along with PD (p=0.006) in all evaluable patients.

Conclusions: Sintilimab combined with gemcitabine and carboplatin demonstrates promising efficacy and acceptable safety in patients with advanced PLELC as first-line treatment.

Keywords: Pulmonary lymphoepithelioma-like carcinoma, PD-1 inhibitor, T-cell-inflamed gene-expression profile

MA11 BUILDING ON THE FOUNDATIONS OF CURRENT IMMUNOTHERAPIES
TUESDAY, SEPTEMBER 10, 2024 - 13:30 - 14:45

MA11.04 First-in-Class PD-1/IL-2 Bispecific Antibody IBI363 In Patients with Advanced Non-Small Cell Lung Cancer in a Phase I Study

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Introduction: IBI363 is a first-in-class PD-1/IL-2α-bias bispecific antibody fusion protein to block PD-1 checkpoint and rejuvenate exhausted tumor-specific T cells by cis-activating α-bias IL-2. It has great potential to address the unmet clinical need of patients (pts) with immunotherapy (IO)-resistant and cold tumors. Here, we report the initial safety and efficacy results from a phase I, multicenter, first-in-human study of IBI363 in pts with advanced non-small cell lung cancer (NSCLC).

Methods: Eligible pts with advanced NSCLC who failed or were intolerant of standard therapy were enrolled and received IBI363 intravenously at dose levels of 2/10/300/600 ug/kg every week (QW), 0.3/0.6/1 mg/kg every two weeks (Q2W) or 1.5/2/3 mg/kg every three weeks (Q3W). Endpoints included safety, objective response rate (ORR), disease control rate (DCR), duration of response (DoR) and progression-free survival (PFS) by investigator per RECIST v1.1. Data cut-off date for this analysis was Mar 21, 2024.

Results: A total of 89 pts were enrolled (median age: 60.0 years, males: 83.1%, ECOG PS 1: 74.2%, prior treatment lines ≥2: 79.8%), including 5 pts at 0.6 mg/kw Q2W cohort, 51 pts at 1 mg/kg Q2W, 11 pts at 1.5 mg/kg Q3W, 3 pts at 2 mg/kg Q3W, and 12 pts at 3 mg/kg Q3W. Median duration of IBI363 exposure was 8.4 weeks (range: 2.0-41.9); 25 pts (28.1 %) were still on treatment as of data cutoff date. Treatment-related adverse events (TRAEs) occurred in 78 pts (any grade: 87.6%, grade ≥3: 19.1%). Most common TRAEs (incidence ≥20%) were arthralgia (any grade: 37.1%, grade ≥3: 1.1%), anemia (any grade: 30.3%, grade ≥3: 2.2%), and rash (any grade: 21.3%, grade ≥3: 1.1%). TRAEs led to treatment discontinuation and death in 4 (4.5%) and 1 (1.1%) pts, respectively. As of data cutoff, 79 pts (EGFR-mutant: 8 pts) were treated at dose levels ≥0.3 mg/kg and had ≥1 post-baseline tumor assessment. For these pts, ORR was 24.1% (95% CI: 15.1-35.0) and DCR was 68.4% (95% CI: 56.9-78.4); of the 7 efficacy-evaluable pts at 3 mg/kg Q3W cohort, 6 achieved partial response (ORR: 85.7%). Among them, 74 pts were previously IO-treated and they had an ORR of 24.3% (95% CI: 15.1-35.7) and DCR of 68.9% (95% CI: 57.1-79.2). In pts with squamous NSCLC (n = 37, previously IO-treated: 36 pts, EGFR positive by immunohistochemistry: 1 pt), ORR and DCR were 35.1% (95%CI: 20.2-52.5) and 75.7% (95%CI: 58.8-88.2), respectively; median PFS was 5.5 months (95% CI: 4.0-NC) with 16 (43.2%) PFS events.

Conclusions: IBI363 was well tolerated with encouraging efficacy observed in pts with advanced NSCLC including those previously IO-treated pts.

Keywords: First-in-class PD-1/IL-2 bispecific antibody, Advanced non-small cell lung cancer, Phase I trial

MA11 BUILDING ON THE FOUNDATIONS OF CURRENT IMMUNOTHERAPIES
TUESDAY, SEPTEMBER 10, 2024 - 13:30 - 14:45

MA11.05 Nivolumab + Ipilimumab vs Chemotherapy in Patients with Stage IV/recurrent NSCLC and PD-L1 ≥ in China: Checkmate 227 CHESS

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Introduction: The phase 3 CheckMate 227 study demonstrated significant overall survival (OS) benefit with nivolumab (NIVO) + ipilimumab (IPI) vs chemotherapy in patients with advanced non-small cell lung cancer (NSCLC) and tumor programmed death ligand 1 (PD-L1) expression ≥1%.1 CheckMate 227 CHESS (China ExtenSion Study) was a China-specific extension of the CheckMate 227 Part 1A study comparing NIVO+IPI vs chemotherapy in treatment-naive Chinese patients with advanced NSCLC and PD-L1 ≥1%. The aim of this bridging study was to evaluate the consistency in OS benefit (defined as retaining ≥50% risk reduction) compared with CheckMate 227 Part 1A.

Methods: In this open-label study, adult treatment-naive patients with stage IV/recurrent NSCLC, PD-L1 ≥1%, ECOG performance status 0-1, and no known EGFR/ALK alterations were randomized 1:1 to NIVO 3 mg/kg Q2W + IPI 1 mg/kg Q6W ≤24 months or platinum-doublet chemotherapy Q3W ≤4 cycles. Patients were stratified by histology, sex, and PD-L1 expression (≥50% vs <50%). The primary endpoint was OS. Secondary endpoints were progression-free survival and objective response rate per blinded independent central review. Exploratory endpoints included safety and tolerability assessments and patient-reported outcomes. Analysis time was based on a minimum study duration of 30 months. Changes in the treatment landscape for NSCLC led to a reduction in sample size, and, as a bridging study, it was not statistically powered; however, the number of randomized patients was sufficient to provide ≥80% probability to show consistency of OS benefit with CheckMate 227 Part 1A (OS hazard ratio [HR] <0.895).

Results: Overall, 253 patients were randomized; 126 to receive NIVO+IPI and 127 to receive chemotherapy. Baseline characteristics were balanced between treatment arms. Most patients were male (85%); median age was 62.0 (range, 29-77) years. Median OS was 20.99 months with NIVO+IPI vs 15.11 months with chemotherapy (HR, 0.85, meeting the criterion for showing consistent OS benefit; Table). Median time to deterioration in symptoms per the Lung Cancer Symptom Score average symptom burden index was not reached (NR) with NIVO+IPI vs 22.6 months (95% CI, 11.5-NR) with chemotherapy (HR, 0.52 [95% CI, 0.30-0.90]). Similar rates of any-grade treatment-related adverse events (TRAEs) were observed in both treatment groups (NIVO+IPI, 88.9%; chemotherapy, 92.7%). Fewer grade 3/4 TRAEs occurred with NIVO+IPI vs chemotherapy (35.7% vs 48.8%).

Conclusions: Chinese patients with advanced NSCLC and tumor PD-L1 ≥1% receiving first-line NIVO+IPI vs chemotherapy had consistent OS outcomes compared with the CheckMate 227 global study, with no new safety signals.

Keywords: Advanced NSCLC, CheckMate 227, Immunotherapy

	NIVO+IPI (n = 126)	Chemotherapy (n = 127)[a]
	OS (all randomized)	
No. of events (%)	95 (75.4)	96 (75.6)
Median OS, months (95% CI)	20.99 (16.95–25.17)	15.11 (13.17–18.89)
HR (95% CI)	0.85 (0.64–1.14)	
OS rate, % (95% CI)		
12 months	68.3 (59.4–75.6)	65.1 (56.0–72.8)
24 months	42.8 (34.1–51.2)	36.8 (28.3–45.4)
30 months	37.1 (28.7–45.5)	31.6 (23.5–40.0)
	PFS per BICR (all randomized)	
No. of events (%)	98 (77.8)	94 (74.0)
Median PFS, months (95% CI)	5.78 (4.14–8.34)	5.49 (4.37–6.77)
HR (95% CI)	0.66 (0.49–0.89)	
	ORR per BICR	
Confirmed best overall response,[b] n (%)		
Complete response	8 (6.3)	0
Partial response	40 (31.7)	39 (30.7)
Stable disease	46 (36.5)	55 (43.3)
Progression	22 (17.5)	17 (13.4)
Unable to determine	10 (7.9)	12 (9.4)
Not reported	0	4 (3.1)
ORR, events/n (%); [95% CI][c]	48/126 (38.1); [29.6–47.2]	39/127 (30.7); [22.8–39.5]
	DOR (all responders)	
Median DOR, months (95% CI)	29.37 (15.47–44.35)	4.40 (3.91–8.41)

[a]Of 127 patients randomized to receive chemotherapy, 4 patients were not treated. [b]Per RECIST v1.1. [c]Complete response + partial response; CI based on the Clopper–Pearson method. BICR, blinded independent central review; CI, confidence interval; DOR, duration of response; HR, hazard ratio; IPI, ipilimumab; NIVO, nivolumab; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors.

Reference:

1. Hellmann MD, et al. *N Engl J Med*. 2018;378:2093–2104.

MA11 BUILDING ON THE FOUNDATIONS OF CURRENT IMMUNOTHERAPIES
TUESDAY, SEPTEMBER 10, 2024 - 13:30 - 14:45

MA11.07 Pembrolizumab Plus Maintenance Olaparib as First-Line Therapy for Metastatic Nonsquamous NSCLC: Phase 3 KEYLYNK-006 Study

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Introduction: Pembrolizumab plus pemetrexed and a platinum is a standard-of-care first-line treatment for metastatic NSCLC. Preclinical data show that PARP inhibitors such as olaparib upregulate PD-L1 expression. The randomized, open-label, phase 3 KEYLYNK-006 trial evaluated pembrolizumab plus maintenance olaparib versus pembrolizumab plus maintenance pemetrexed following induction with pembrolizumab plus pemetrexed and a platinum for nonsquamous NSCLC (NCT03976323).

Methods: Eligible adults with newly diagnosed, previously untreated stage IV nonsquamous NSCLC without targetable EGFR, ALK, or ROS1 aberrations with CR, PR, or SD following induction therapy with 4 Q3W cycles of pembrolizumab 200 mg, pemetrexed 500 mg/m2, and carboplatin AUC 5 mg/mL/min or cisplatin 75 mg/m2 were randomized 1:1 to olaparib 300 mg BID or pemetrexed 500 mg/m2 Q3W, both given with ≤31 cycles of pembrolizumab 200 mg Q3W. Randomization was stratified by ECOG PS (0 vs 1), PD-L1 TPS (<50% vs ≥50%), and response at randomization (CR/PR vs SD). Dual primary end points were PFS (RECIST v1.1 by blinded, independent central review) and OS. Per the prespecified analysis plan, testing was complete at interim analysis 2 (IA2) for PFS and final analysis for OS.

Results: Of the 1003 participants who received induction therapy with pembrolizumab, pemetrexed, and a platinum, 672 (67.0%) were randomized to pembrolizumab plus maintenance olaparib (olaparib arm; n=337) or pembrolizumab plus maintenance pemetrexed (pemetrexed arm; n=335). At randomization, 56.7% of participants had CR or PR and 43.3% had SD. Median time from randomization to the final analysis cutoff date of February 7, 2024, was 3.3 years (range, 2.3-4.3). At IA2 (data cutoff, May 18, 2022), median (95% CI) PFS was 7.1 months (5.6-8.7) in the olaparib arm versus 8.3 months (6.9-11.5) in pemetrexed arm (HR, 1.12; 95% CI, 0.92-1.36; P=0.87). At final analysis, median (95% CI) OS was 20.7 months (18.0-24.8) in the olaparib arm and 23.0 months (19.0-26.4) in the pemetrexed arm (HR, 1.04; 95% CI, 0.87-1.25; P=0.66). At final analysis, grade 3-5 treatment-related AEs occurred in 26.1% in the olaparib arm versus 30.1% in the pemetrexed arm; treatment-related AEs led to death in 0.3% versus 0.3% and discontinuation of ≥1 drug in 13.9% versus 22.6%.

Conclusions: Pembrolizumab plus maintenance olaparib did not improve PFS or OS compared with pembrolizumab plus maintenance pemetrexed in participants who had CR, PR, or SD following induction therapy with pembrolizumab, pemetrexed, and a platinum as first-line therapy for stage IV nonsquamous NSCLC without targetable genetic alterations. There were no new safety signals.

Keywords: non-small cell lung cancer, immune checkpoint inhibitor, PARP inhibitor

MA11 BUILDING ON THE FOUNDATIONS OF CURRENT IMMUNOTHERAPIES
TUESDAY, SEPTEMBER 10, 2024 - 13:30 - 14:45

MA11.08 Preliminary Efficacy and Safety of SHR-1701 Plus Fluzoparib as Maintenance Therapy for Patients with Advanced Lung Squamous Cell Carcinoma

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Introduction: Lung squamous cell carcinoma (LUSC) is associated with high mortality. Even with the treatment of PD-(L)1 inhibitors, the survival for advanced LUSC patients is relatively limited. SHR-1701 is a new bifunctional fusion protein composed of a monoclonal antibody against PD-L1 fused with the extracellular domain of TGF-β receptor II. Poly-ADP-ribose polymerase inhibitor (PARPi) has the potential to enhance the response to immunotherapy by promoting neoantigen release, increasing tumor mutational burden, and enhancing PD-L1 expression. Fluzoparib is a PARPi that has shown synergy with immunotherapy. This single-arm, phase 2 study aimed to evaluate the efficacy and safety of SHR-1701 plus fluzoparib as first line maintenance therapy for patients with advanced LUSC.

Methods: Previously untreated patients with stage IV LUSC were enrolled to receive SHR-1701 (30 mg/kg, administered intravenously q3w) and investigator's choice of platinum-based chemotherapy. Patients without disease progression after 4 cycles of treatment would receive SHR-1701 and fluzoparib (100 mg, administered orally bid) until progression or unacceptable toxicity. The primary endpoint was progression-free survival (PFS) per RECIST v1.1 by investigator. Secondary endpoints included objective response rate (ORR), PFS rate at 6 months, disease control rate (DCR), overall survival (OS), and safety.

Results: Between Feb 2023 and Feb 2024, a total of 23 patients were enrolled and received SHR-1701 and chemotherapy.11 patients had received fluzoparib. The median number of treatment cycles of fluzoparib was 5 (range: 1-13). The median age was 65 years and 91.3% were male. 21 (91.3%) patients had stage IV disease, 3 (13.0%) patients had brain metastasis, 4 (17.4%) patients had liver metastasis. 16 pts had at least one post-treatment tumor assessment. 15 pts achieved a partial response (10 pts confirmed), and 1 pt had stable disease as best response. The unconfirmed ORR was 93.75%. The confirmed ORR was 62.5% and DCR was 100%. The median PFS was 8.7 months. Treatment-related adverse events (TRAEs) occurred in 16 (69.6%) patients. 4 (17.4%) pts experienced grade≥3 TRAEs. The most common grade≥3 TRAEs included anaemia, alanine aminotransferase increased and neutrophil count decreased. No unexpected adverse events were reported.

Conclusions: SHR-1701 plus fluzoparib demonstrated encouraging clinical activity with manageable safety profile as first line maintenance therapy for patients with advanced LUSC. The results warranted further investigation.

Keywords: LUSC, Immunotherapy, PARP Inhibitors

MA11 BUILDING ON THE FOUNDATIONS OF CURRENT IMMUNOTHERAPIES
TUESDAY, SEPTEMBER 10, 2024 - 13:30 - 14:45

MA11.09 Phase II Trial of Atezolizumab Plus Cobimetinib in PD-(L)1 Inhibitor Resistant NSCLC: NCI ETCTN Study 10166

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Introduction: Immunotherapy with a PD-(L)1 inhibitor alone or in combination is the current first-line standard for patients with advanced NSCLC without an actionable genomic alteration. Novel treatment options are needed for patients resistant to these therapies, particularly those with primary resistance. MEK inhibition in preclinical models enhances tumoral T-cell infiltration and favorably alters the immune microenvironment. We report primary results from a two-cohort, single arm phase II study of atezolizumab (anti-PD-L1) plus cobimetinib (MEK inhibitor) in patients with PD-(L)1 inhibitor resistant or refractory NSCLC (ETCTN NCI# 10166, NCT03600701).

Methods: Eligible patients had advanced NSCLC with primary resistance to PD-(L)1 inhibition defined as lack of partial or complete response and progression within 6 months of starting anti-PD(L)1 therapy. There were no PD-L1 expression criteria. Given the potential for transient response from MEK inhibition in a KRAS mutant NSCLC, patients were assigned to either cohort 1 (KRAS mutant NSCLC) or cohort 2 (KRAS wild type NSCLC). Patients received atezolizumab 1680 mg intravenously on day 1 and cobimetinib 60 mg by mouth daily on days 1-21 in 28-day cycles until progression, loss of benefit, or unacceptable toxicity. Each cohort had a Simon two-stage design where one response would be needed to expand accrual from 9 patients to 24 patients. Paired research biopsies were required at baseline and during week 3 of cycle 1 for correlative studies including assessment of changes in T-cell infiltration in response to therapy.

Results: Overall, 48 patients enrolled from 10 sites received at least one dose of study therapy (24 in each cohort); median age was 65 years (range 27-88). In cohort 1 (KRAS mutant), the response rate (RR) was 10% (2/20 evaluable patients) with response durations of 5.7 and 23.6 months. In cohort 2 (KRAS wild type), the RR was 10% (2/20 evaluable patients) with response durations of 16.7 and 8.4+ months. Overall, the median PFS was 3.4 months; median PFS was 4.8 months in cohort 1 (KRAS mutant) and 2.0 months in cohort 2 (KRAS wild type). The median OS was 29.6 months with a median OS of 8.2 months in cohort 1 (KRAS mutant) and the median has not been reached in cohort 2 (KRAS wild type). Two patients remain on therapy in cohort 2 without progression. Grade 3-4 treatment related adverse events were seen in 45.8% of patients with no grade 5 related adverse events; 8 patients (16.7%) discontinued therapy due to adverse events. Analyses of paired biopsies is ongoing.

Conclusions: Though durable responses were noted in both KRAS mutant and wild type cohorts, the combination of atezolizumab plus cobimetinib displayed minimal clinical activity in PD-(L)1 resistant NSCLC.

Keywords: NSCLC, Atezolizumab, Cobimetinib

MA11 BUILDING ON THE FOUNDATIONS OF CURRENT IMMUNOTHERAPIES
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MA11.11 Benmelstobart, a PD-L1 Mab, Plus Anlotinib in EGFR+ Advanced NSCLC Patients Failed to Prior EGFR TKI Therapies:Phase II Results Update

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Introduction: Platinum-based chemotherapy is the standard therapy for the patients with EGFR+ advanced NSCLC failed to prior EGFR TKI therapies. However, the IMpower151 study analyses shows Atezolizumab (PD-L1) plus bevacizumab and chemotherapy did not show a significantly survival benefit (mOS 20.7 months in ABCP group) in EGFR TKI treated NSCLC. The effect of immunotherapy in EGFR-TKI resistant population is uncertain. Benmelstobart plus Anlotinib had demonstrated encouraging PFS and favorable safety profile in the same population in previously reported phase II Results (Meiqi Shi, et al, 2023 WCLC MA15.11). Here, we update the latest efficacy and safety data of the phase II study in 2024.

Methods: This ongoing phase I/II, open-lable trial(ChiCTR1900026273) enrolled patients aged 16-75 years old with pathologically confirmed metastatic or advanced EGFR+ NSCLC who failed to prior EGFR TKI therapies. Pts with previous received platinum-based chemotherapy were excluded. Participants in phase II study were given intravenous Benmelstobart (1200mg, q3w) and oral anlotinib (12mg/d, 2 weeks on/1 week off) until progression or unacceptable toxicity. The primary endpoint is progression free survival (PFS). Secondary endpoints were objective response rate (ORR), disease control rate (DCR), overall survival (OS), and safety.

Results: As of 10 March 2024 (data cut-off), a total of 55 patients (median age 64.0 years, female 69.1%), received at least one dose of anlotinib and Benmelstobart in phase II. The median follow-up time was 22.80 months. Among all, 14 achieved confirmed PR, 34 achieved SD, the ORR was 25.5%(14/55)and the DCR was 87.3% (49/55). The median PFS was 8.97 months(95% CI 6.28, 11.76), 6-month PFS rate was 69.7% and 9-month PFS rate was 49.0%. The median OS was 28.9 months(95% CI 19.12, NE), 24-month OS rate was 59.6%. Overall, Benmelstobart and anlotinib was well tolerated. Treatment-related adverse events (TRAEs) of grade 3-4 were observed in 15 (27.3%) of the 55 patients. The most common TRAEs were hypertension(47.3% , 26/55), hand-foot syndrome(38.2%, 21/55), proteinuria(27.3% , 15/55) and cough(27.3% ,15/55). 15pts had previous covid-19 infection.

Conclusions: The chemo-free combination of Benmelstobart plus anlotinib has shown incredible anti-tumor efficacy, mOS over 2 years (mOS 28.9 months), and well tolerance in this study, which will support further development in this field.

Keywords: EGFR-TKI resistant, NSCLC, chemo-free

MA11 BUILDING ON THE FOUNDATIONS OF CURRENT IMMUNOTHERAPIES
TUESDAY, SEPTEMBER 10, 2024 - 13:30 - 14:45

MA11.12 A Phase Ib Study of TQB2618 (Anti-TIM-3) in Combination with Penpulimab and Chemotherapy in Patients with Non-Small Cell Lung Cancer

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Introduction: T-cell immunoglobulin and mucin-domaincontaining molecule-3(TIM-3) can be co-expressed with PD-1 on exhausted T-cells and may be upregulated in tumors refractory to anti-PD-1 therapy.TIM-3 upregulation on PD-1 positive tumor infiltrating lymphocytes is associated with reduced proliferation and secretion of cytokines important for T cell-mediated anti-tumor activity.Concurrent TIM-3 and PD-1 blockade is more effective at reducing tumor growth than blocking anti-PD-1 only.TQB2618,a humanized IgG4 mAb targeting TIM-3,activates immune cell function and induces significant anti-tumor activity when combined with anti-PD-1 agents.It is unknown how effective TIM-3 combined with PD-1 and chemotherapy is in human.The main purpose of our study was to explore the feasibility of this combination.

Methods: This is an open-label, multicenter, phase Ib study.Inclusion criteria included: age between 18-75 years, pathologically confirmed diagnosis of advanced/metastatic NSCLC(squamous or non-squamous),absence of EGFR, ALK or ROS-1 mutations.Study was divided into two parts: dose-escalation and cohort expansion(cohort A-C).All patients(pts) in cohort A were PD-L1 TPS≥1% and received TQB2618 (1200/1500mg i.v.), Penpulimab (200mg i.v.) Q3W.Pts in cohort B were all squamous and were treated with TQB2618(1500mg i.v.),penpulimab(200mg i.v.), paclitaxel(175mg/m2 i.v.), carboplatin(AUC 5) Q3W. Pts in cohort C, also with squamous,were received TQB2618(1200mg i.v.),penpulimab(200mg i.v.),carboplatin(AUC5) Q3W and albumin abound paclitaxel(100 mg/m2 i.v.) Q1W.TQB2618 and penpulimab treatment will continue until disease progression,unacceptable toxicity,pts withdrawal,investigator's decision,or death. Paclitaxel and carboplatin treatment will continue for 4 cycles or until unacceptable toxicity or disease progression.The primary endpoint is investigator-assessed confirmed objective response rate(ORR) and 6-months progression-free survival(PFS) rate(RECIST v1.1).

Results: As of Feb 29, 2024, 93 pts had been treated in the cohort extension.36 pts were enrolled in cohort A (TQB2618 1200mg[n=20], 1500mg[n=16] with penpulimab) ,21 pts in cohort B and 36 pts in cohort C. 50% of the pts enrolled in Cohort A were squamous,and 44.44% had PD-L1≥50%. 35 pts were evaluated for efficacy,ORR was 39.4%, disease control rate(DCR) was 71.4%. ORR in pts with low PD-L1 expression was 31.6% (6/19) ,and 50.00% (7/14) for PD-L1≥50%. In cohort B and C,52.4% and 55.6% of pts PD-L1-negative,respectively. 17 pts in cohort B had efficacy evaluation,compared with 35 in cohort C. The ORR for two cohorts was 71.2% and DCR was 92.3%. Objective responses occurred in 19 pts in Cohort B and C with PD-L1<1%(ORR was 70.4%), when 18 pts with PD-L1≥1% received partial response(ORR was 75.0%). Moreover, we found that Cohort C had better overall efficacy relative to Cohort B. In cohort C, pts with PD-L1<1% had an ORR more than 73%. TEAEs occurred in 91.7%, 95.2%, 97.2% of pts in cohort A-C, respectively. TEAEs were common but primarily low-grade events in cohort A. Grade≥3 TEAEs(≥10%) were neutropenia(49.1%), leukopenia(29.8%) and anemia(21.1%) in cohort B and C.Serious adverse events(SAEs) related to study treatment(≥5%) was infectious pneumonia(5.6%) in cohort A,and neutropenia(10.5%), leukopenia(8.8%), infectious pneumonia(5.3%), anemia(5.3%) in cohort B and C.

Conclusions: TQB2618 plus Penpulimab was well tolerated and showed preliminary signs of antitumor activity,especially in pts with low PD-L1 expression. In combination with chemotherapy,the efficacy of albumin abound paclitaxel over paclitaxel,regardless of PD-L1 status.

Keywords: NSCLC, TIM-3, Penpulimab

MA11 BUILDING ON THE FOUNDATIONS OF CURRENT IMMUNOTHERAPIES
TUESDAY, SEPTEMBER 10, 2024 - 13:30 - 14:45

MA11.13 Peripheral T-Cell Receptor Repertoire Differentiates a Typical Progression in Non-Small Cell Lung Cancer Patients Treated with Immunotherapy

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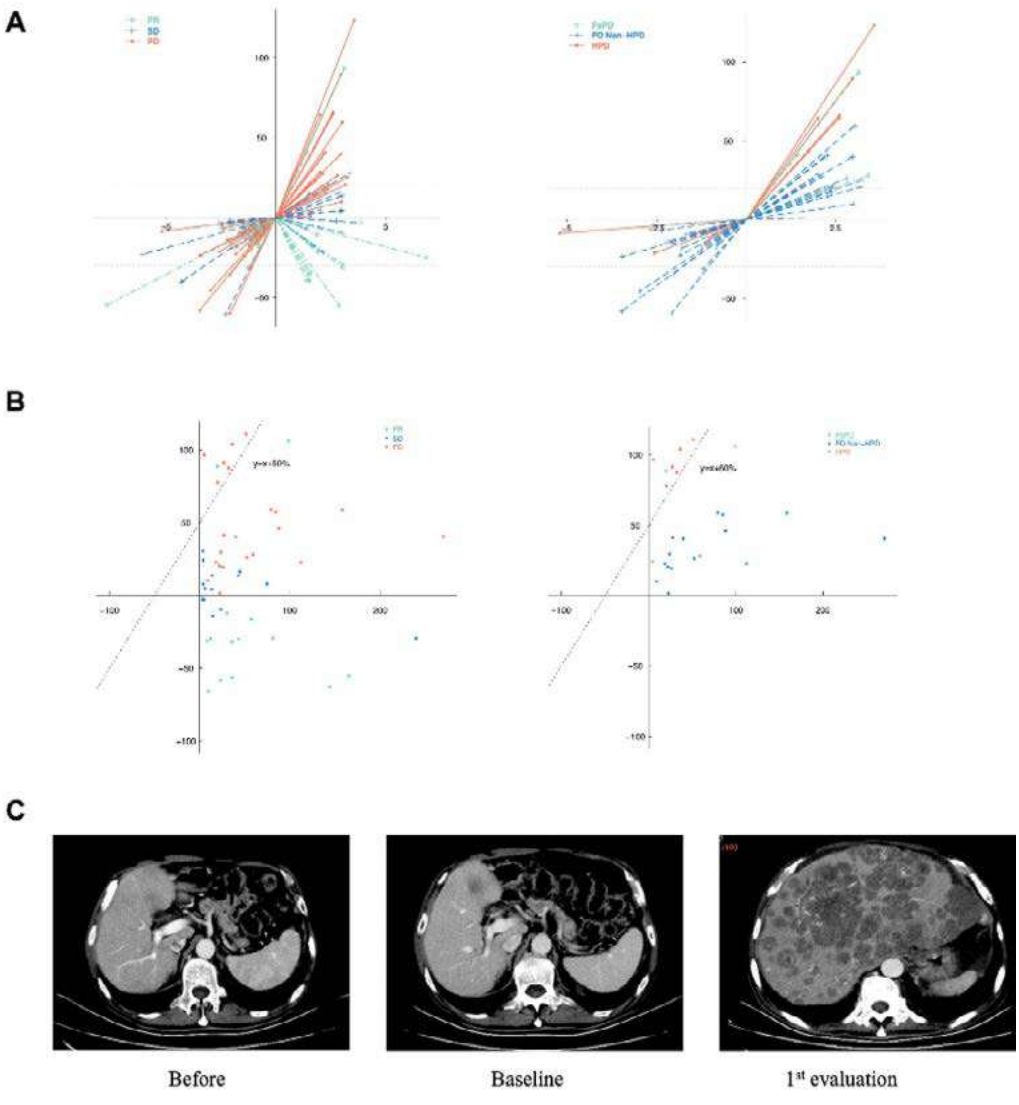
Introduction: Immune checkpoint inhibitors (ICIs) have revolutionized the treatment landscape for non-small cell lung cancer (NSCLC) patients. However, the response to immunotherapies can vary from that of standard chemotherapeutic drugs or therapeutic strategies, and accurately determining treatment response can be challenging. This study aimed to identify biomarkers capable of distinguishing between different response patterns in NSCLC patients treated with ICI.

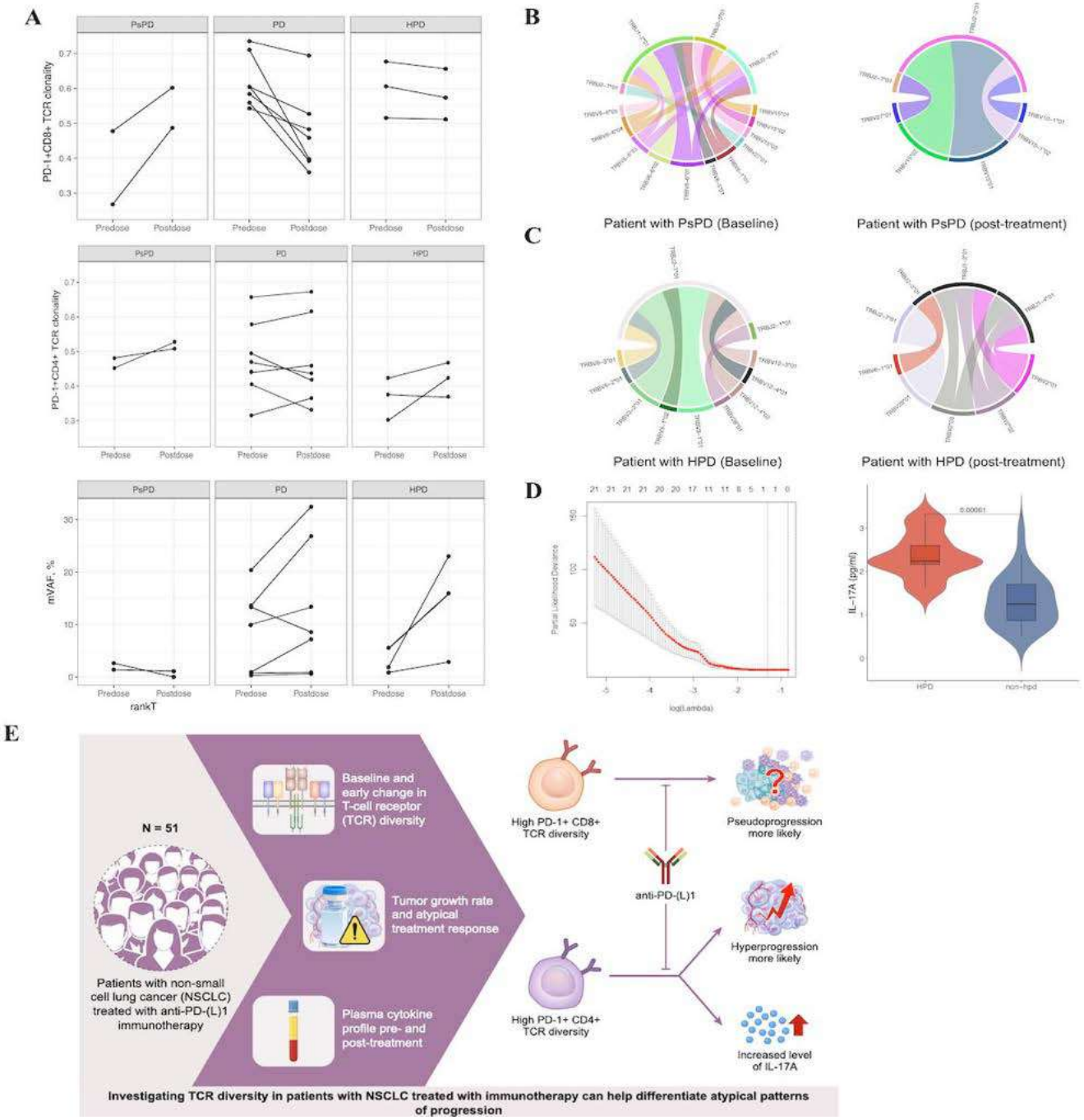
Methods: We performed radiological evaluations on NSCLC patients treated with ICI, with at least two computed tomography (CT) scans prior to treatment and one CT scan during treatment. Tumor growth rate (TGR) was calculated as per the RECIST version 1.1 guidelines, and hyperprogressive disease (HPD) was defined as a ΔTGR greater than 50%. Blood mononuclear cells were sorted using flow cytometry to isolate PD-1+CD8+ and PD-1+CD4+ T cells.

Results: Our study included 51 NSCLC patients, with 11 responders (21.6%), 13 stable disease (25.5%), and 25 progressors (49.0%) at the initial radiological evaluation. Six patients were diagnosed with HPD, and three of the 25 progressors showed pseudoprogression during subsequent treatment. T-cell receptor (TCR) clonality changes ranged from 2.17 to 0.64 in all patients. Among the three types of disease progression, pseudoprogression was associated with a higher diversity of PD-1+CD8+ T cells (P = 0.030), while HPD patients exhibited the highest PD-1+CD4+ TCR diversity (P=0.013).Additionally, an increase in IL-17A levels was observed in patients with HPD.

Conclusions: Our findings suggest that the TCR repertoire of peripheral PD-1+CD8+ and PD-1+CD4+ T cells has the potential to differentiate atypical progression patterns in NSCLC patients treated with ICI. Regular monitoring of TCR changes during ICI therapy could serve as a valuable biomarker for predicting long-term treatment response.

Keywords: T cell receptor repertoire, atypical progression, immunotherapy




A
PsPD
PD
HPD
PD-1+CD8+ TCR clonality
PD-1+CD4+ TCR clonality
mVAF, %
Predose
Postdose
rankT
B
Patient with PsPD (Baseline)
Patient with PsPD (post-treatment)
C
Patient with HPD (Baseline)
Patient with HPD (post-treatment)
D
Partial Likelihood Deviance
log(Lambda)
IL-17A (pg/ml)
HPD
non-hpd
E
N = 51
Patients with non-small cell lung cancer (NSCLC) treated with anti-PD-(L)1 immunotherapy
Baseline and early change in T-cell receptor (TCR) diversity
Tumor growth rate and atypical treatment response
Plasma cytokine profile pre- and post-treatment
High PD-1+ CD8+ TCR diversity
High PD-1+ CD4+ TCR diversity
anti-PD-(L)1
Pseudoprogression more likely
Hyperprogression more likely
Increased level of IL-17A
Investigating TCR diversity in patients with NSCLC treated with immunotherapy can help differentiate atypical patterns of progression

MA12 PAVING THE PATH TO PRECISION ONCOLOGY: TARGETING EGFR AND HER2
TUESDAY, SEPTEMBER 10, 2024 - 13:30 - 14:45

MA12.03 FLAURA2: Resistance, and Impact of Baseline TP53 Alterations in Patients Treated With 1L Osimertinib ± Platinum-Pemetrexed

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Introduction: Osimertinib, a third-generation, CNS-active EGFR-TKI, is the preferred first-line treatment for EGFR-mutated (EGFRm) advanced NSCLC; however, most patients will develop progressive disease (PD) due to treatment resistance. The Phase III, open-label, randomized FLAURA2 study (NCT04035486) demonstrated a significant PFS benefit with first-line osimertinib + platinum-pemetrexed chemotherapy (osi+CTx) versus osimertinib monotherapy (osi) in patients with EGFRm advanced NSCLC. Preliminary results from a prespecified, exploratory analysis of acquired resistance mechanisms to osimertinib ± chemotherapy were presented previously. We report updated analyses further investigating resistance mechanisms in FLAURA2.

Methods: Patients ≥18 years with untreated EGFRm (Ex19del/L858R) advanced NSCLC were randomized 1:1 to receive osi+CTx or osi. Paired plasma ctDNA samples were collected at baseline and PD and/or treatment discontinuation up to 06Sep2023; samples were analyzed using NGS (Guardant Health, GuardantOMNITM). Tumor tissue was collected at screening for central EGFRm testing and exploratory NGS (Foundation Medicine, FoundationOne®CDx). Clinical outcomes were investigator-assessed (RECIST v1.1).

Results: Of 557 patients randomized to treatment (osi+CTx, n=279; osi, n=278), 181 matched baseline and PD plasma samples were evaluable for analysis, (osi+CTx, n=76; osi, n=105). Of these, 167 had EGFRm ctDNA detected at baseline (osi+CTx, n=68; osi, n=99). Resistance mechanisms were similar across arms, with no novel mechanisms detected. The most common acquired resistance mutations were C797S mutation in the osi arm and MET amplification in both arms (Table). There was no substantial change in tumor mutational burden between baseline and PD for either arm. At time of analysis, 141 baseline tissue samples were available for NGS (osi+CTx, n=72; osi, n=69); 41/72 and 38/69 had TP53 alterations detected, and 31/72 and 31/69 were TP53 wild-type, in the osi+CTx and osi arms, respectively. PFS Kaplan-Meier curves showed a separation in favor of patients with wild-type TP53 versus those with TP53 alterations at baseline, regardless of treatment: osi+CTx, HR not calculated (NC; as <20 events across arms); osi, HR 0.48 (95% CI 0.23, 1.0). Across treatment arms, PFS Kaplan-Meier curves showed a separation in favor of osi+CTx versus osi, irrespective of baseline TP53 status: wild-type TP53, HR NC; TP53 altered, HR 0.57 (95% CI 0.29, 1.12).

Conclusions: Although the plasma analysis set remains enriched for patients with early progression, these more mature data show acquired resistance mechanisms remain similar across treatment arms. Preliminary baseline tissue analyses suggest TP53 alterations to be a prognostic factor; the benefit of osi+CTx versus osi was similar in patients with or without TP53 alterations.

Keywords: Resistance, Osimertinib, NGS

Acquired gene alterations, n (%)	Osi+CTx (n=68)	Osi monotherapy (n=99)
EGFR C797S mutation	2 (3)	12 (12)
Other uncommon *EGFR* mutations	1 (1)	4 (4)
MET amp	8 (12)	11 (11)
ERBB2 amp	3 (4)	1 (1)
BRAF V600E	1 (1)	5 (5)
KRAS mutations	2 (3)	8 (8)
PIK3CA mutations	5 (7)	6 (6)
ERBB2 mutations	Not detected	1 (1)
Cyclin D/E amp	6 (9)	5 (5)
CDK4/6 amp	3 (4)	5 (5)
RET fusion	1 (1)	3 (3)
BRAF fusion	2 (3)	3 (3)
ALK fusion	Not detected	3 (3)
Other fusions	3 (4)	6 (6)
RB1 loss (with TP53 alteration)	2 (3)	4 (4)
No known acquired resistance alterations detected	46 (68)	54 (54)

MA12.04 FLAURA2: Impact of Tumor Burden on Outcomes of 1L Osimertinib ± Chemotherapy in Patients with EGFR-mutated Advanced NSCLC

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Introduction: Osimertinib is a third-generation, central nervous system (CNS)-active, EGFR-tyrosine kinase inhibitor with demonstrated efficacy in EGFR-mutated NSCLC and is the preferred first-line treatment for EGFR-mutated advanced NSCLC. In the Phase III FLAURA2 study (NCT04035486), osimertinib plus platinum-pemetrexed chemotherapy significantly improved progression-free survival (PFS) versus osimertinib monotherapy as first-line treatment of EGFR-mutated advanced NSCLC (investigator-assessed median PFS [mPFS] 25.5 vs 16.7 months, respectively; HR 0.62, 95% CI 0.49, 0.79; p<0.0001) and is now a recommended treatment option in this setting. To understand the impact of baseline tumor burden (characterized by the number of metastatic anatomical locations and extent of distant metastases at study entry) on outcomes, we assessed PFS in these patient subgroups from FLAURA2.

Methods: Patients were randomized 1:1 to receive osimertinib plus platinum-based chemotherapy, or osimertinib monotherapy until progression or a discontinuation criterion was met. Primary endpoint was investigator-assessed PFS per RECIST v1.1. Post-hoc analyses of PFS (by investigator assessment) were performed in baseline tumor burden subgroups characterized by the number of metastatic anatomical locations (<3 [defined as low] vs ≥3 [high]; patients with ≥1 metastatic lesion in an anatomical location were counted once within the specified metastatic anatomical location) and extent of distant metastases (intra-thoracic [M1a, low] vs extra-thoracic [M1b/M1c, high]; classified according to Version 8 of the IASLC Staging Manual in Thoracic Oncology). Data cut-off: 03 April 2023.

Results: 557 patients were randomized to osimertinib plus chemotherapy (n=279) or osimertinib monotherapy (n=278). The proportion of patients in the baseline tumor burden subgroups was similar across treatment arms (osimertinib plus chemotherapy/osimertinib monotherapy): <3 metastatic anatomical locations, 46/39%; ≥3 metastatic anatomical locations, 54/61%; M1a, 24/25%; M1b and M1c, 71/72%. Among patients with <3 metastatic anatomical locations, mPFS (95% CI) was 27.9 months (24.7, not calculable [NC]) with osimertinib + chemotherapy versus 30.5 months (16.6, NC) with osimertinib; PFS HR 0.75 (95% CI 0.51, 1.11). In those patients with ≥3 metastatic anatomical locations, mPFS (95% CI) was 24.9 months (21.9, 27.6) with osimertinib + chemotherapy versus 16.4 months (13.6, 19.2) with osimertinib; PFS HR 0.57 (95% CI 0.43, 0.77). For patients with intra-thoracic metastases, mPFS (95% CI) was 26.0 months (21.9, NC) versus NC (16.7, NC; PFS HR 0.97 [95% CI 0.59, 1.60]), and for those with extra-thoracic metastases, mPFS (95% CI) was 25.1 months (22.2, NC) versus 16.4 months (13.6, 19.4; PFS HR 0.54 [95% CI 0.41, 0.71]) in the osimertinib + chemotherapy versus osimertinib arms, respectively. Additional data on factors associated with a poor prognosis, including presence of liver and/or CNS metastases, will be presented.

Conclusions: Patients with characteristics associated with high tumor burden at baseline had a clinically meaningful PFS benefit with osimertinib plus chemotherapy compared with osimertinib monotherapy, further supporting the clinical utility of this combination and helping clinical decision making in patients with EGFR-mutated advanced NSCLC.

Keywords: Osimertinib, NSCLC, High tumor burden

MA12 PAVING THE PATH TO PRECISION ONCOLOGY: TARGETING EGFR AND HER2
TUESDAY, SEPTEMBER 10, 2024 - 13:30 - 14:45

MA12.06 PAPILLON: TP53 Co-mutations, Sites of Insertion, and ctDNA Clearance Among Patients with EGFR Ex20ins-Mutated Advanced NSCLC

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Introduction: Amivantamab is an EGFR-MET bispecific antibody with immune cell-directing activity. In PAPILLON (NCT04538664), amivantamab plus carboplatin-pemetrexed (amivantamab-chemotherapy) demonstrated significantly longer progression-free survival (PFS) versus chemotherapy (hazard ratio [HR], 0.395 [95% confidence interval [CI], 0.30-0.53]; P<0.0001). Amivantamab-chemotherapy is approved for first-line treatment of advanced non-small cell lung cancer (NSCLC) with EGFR Exon 20 insertions (Ex20ins). TP53 co-mutations and detectable circulating tumor DNA (ctDNA) are linked to poor prognoses. We evaluated treatment outcomes among patients from PAPILLON by biomarker subgroups.

Methods: 308 patients were randomized to receive amivantamab-chemotherapy (n=153) or chemotherapy (n=155). Blood samples, collected at screening and Cycle 3 Day 1 (C3D1), were analyzed for ctDNA using Guardant360 CDx (global/ex-China sites). Clearance of Ex20ins ctDNA was assessed at C3D1. Site of insertion was analyzed using Guardant360 CDx (plasma; global/ex-China sites) or AmoyDx LC10 next-generation sequencing panel (tissue; China sites). PFS, objective response rate (ORR), and duration of response (DoR) were assessed.

Results: Of 206 patients with analyzable ctDNA data at baseline, pathogenic alterations were detected in 178 (86%) patients; 154 had matched samples at C3D1. TP53 co-mutations were detected in 104/178 (58%) patients.

PFS was significantly longer for amivantamab-chemotherapy versus chemotherapy among patients with detectable baseline ctDNA (median, 11.1 vs 5.8 months; HR, 0.38 [95% CI, 0.26-0.55]; P<0.0001). At C3D1, 69% of patients in the amivantamab-chemotherapy arm cleared Ex20ins ctDNA versus 45% in the chemotherapy arm. PFS was approximately twice as long for amivantamab-chemotherapy versus chemotherapy with clearance (median, 12.2 vs 6.8 months; HR, 0.26 [95% CI, 0.13-0.50]; P<0.0001) and without clearance (median, 9.8 vs 4.8 months; HR, 0.55 [95% CI, 0.27-1.13]).

Amivantamab-chemotherapy significantly prolonged PFS versus chemotherapy in patients with TP53 co-mutations (median, 11.1 vs 5.6 months; HR, 0.29 [95% CI, 0.17-0.47]; P<0.0001) and wild-type TP53 (median, 11.3 vs 8.5 months; HR, 0.45 [95% CI, 0.25-0.82]; P=0.008). Significant improvements in ORR were seen with amivantamab-chemotherapy versus chemotherapy in patients with TP53 co-mutations (80% vs 53%; P=0.006) and wild-type TP53 (74% vs 49%; P=0.029). Amivantamab-chemotherapy prolonged DoR versus chemotherapy in patients with TP53 co-mutations (median, 9.8 vs 4.3 months) and wild-type TP53 (median, 8.2 vs 4.6 months).

Of 238 patients with site of insertion data, 197 (83%) insertions were in the near loop, 30 (13%) in the far loop, and 11 (5%) in the helical region. Amivantamab-chemotherapy prolonged PFS versus chemotherapy in the near loop (median, 11.3 vs 5.8 months; HR, 0.40 [95 % CI, 0.28-0.58]; P<0.0001) and far loop regions (median, 9.4 vs 4.1 months; HR, 0.19 [95% CI, 0.06-0.69]; P=0.005). Despite few patients with insertions in the helical region, amivantamab-chemotherapy demonstrated numerically longer PFS versus chemotherapy (median, 11.1 vs 9.1 months; HR, 0.55 [95% CI, 0.1-3.1]). ORR and DoR across Ex20ins sites favored amivantamab-chemotherapy.

Conclusions: Amivantamab-chemotherapy demonstrated superior outcomes versus chemotherapy in patients with and without biomarkers of high-risk disease. Consistent benefit favoring amivantamab-chemotherapy was seen across all Ex20ins sites. Amivantamab-chemotherapy is the first-line, standard of care for Ex20ins advanced NSCLC.

Keywords: NSCLC, TP53 co-mutations, Ex20ins

MA12 PAVING THE PATH TO PRECISION ONCOLOGY: TARGETING EGFR AND HER2
TUESDAY, SEPTEMBER 10, 2024 - 13:30 - 14:45

MA12.07 Amivantamab Plus Lazertinib vs Osimertinib in First-Line, EGFR-Mutant Advanced NSCLC: Patient-relevant Outcomes from MARIPOSA

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Introduction: Amivantamab is an epidermal growth factor receptor (EGFR)-MET bispecific antibody with immune cell-directing activity. Lazertinib is a highly selective, CNS-penetrant, EGFR tyrosine kinase inhibitor (EGFR-TKI). In MARIPOSA (NCT04487080), amivantamab plus lazertinib (amivantamab-lazertinib) significantly prolonged progression-free survival (PFS) vs osimertinib (hazard ratio [HR], 0.70; P<0.001) in patients with treatment-naïve, EGFR-mutant advanced non-small cell lung cancer (NSCLC; Cho Ann Oncol 2023;34:S1306;LBA14). We evaluated time to symptomatic progression (TTSP) and patient-reported outcomes (PROs) from MARIPOSA.

Methods: Analyses included the 429 patients randomized to receive amivantamab-lazertinib and the 429 to osimertinib. TTSP was defined as time from randomization to onset of new/worsening lung cancer symptoms requiring change in anticancer therapy, another clinical intervention, or death, whichever occurred first. PROs were measured using EORTC-QLQ-C30 and NSCLC-SAQ; all P-values are nominal. The threshold for a meaningful improvement was a 10-point increase on EORTC-QLQ-C30 functioning scales.

Results: At a median follow-up of 22.0 months, amivantamab-lazertinib demonstrated a significant improvement in TTSP versus osimertinib (HR, 0.72; 95% confidence interval, 0.57-0.91; P=0.005).

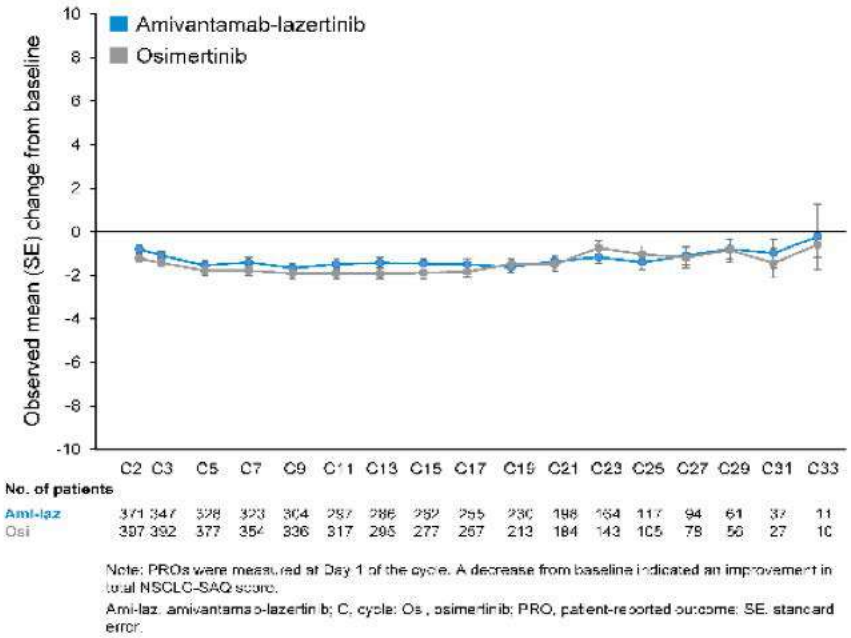
As median treatment duration was 18.5 months for amivantamab-lazertinib versus 18 months for osimertinib, PROs at 18 months are reported to evaluate the long term impact of treatment on quality of life. Based on the EORTC-QLQ-C30 functioning scales at 18 months, the percentage of randomized patients on treatment with improved or stable functioning relative to baseline in the amivantamab-lazertinib versus osimertinib arms was significantly higher for emotional functioning (38% versus 31%; P<0.05) and cognitive functioning (38% versus 31%; P<0.05). For other functioning scales, no statistically significant differences between amivantamab-lazertinib and osimertinib were observed. Functioning was maintained over time in both treatment arms as most changes over time were less than the defined threshold for clinically meaningful differences.

At 18 months, no statistical differences were observed between the amivantamab-lazertinib and osimertinib arms for the absence of key symptoms from the EORTC-QLQ-C30 including dyspnea (34% versus 31%), pain (27% versus 26%), and fatigue (15% versus 16%). There were no significant differences in symptoms between arms based on the NSCLC-SAQ (Figure).

Conclusions: For patients with treatment-naïve, EGFR-mutant advanced NSCLC, amivantamab-lazertinib significantly delayed symptomatic progression versus osimertinib indicating greater control of disease and related symptoms, while maintaining functioning as observed by PRO scales. PROs were comparable across treatment arms at the 18-month landmark, and treatment did not lead to meaningful decrements in patient quality of life.

Keywords: Amivantamab, EGFR TKI, NSCLC

Figure – Total NSCLC-SAQ Score Change from Baseline



Note: PROs were measured at Day 1 of the cycle. A decrease from baseline indicated an improvement in total NSCLC-SAQ score.

Ami-laz, amivantamab-lazertinib; C, cycle; Osi, osimertinib; PRO, patient-reported outcome; SE, standard error.

MA12 PAVING THE PATH TO PRECISION ONCOLOGY: TARGETING EGFR AND HER2
TUESDAY, SEPTEMBER 10, 2024 - 13:30 - 14:45

MA12.08 Preventing Infusion-Related Reactions with Intravenous Amivantamab: Primary Results from SKIPPirr, a Phase 2 Study

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Introduction: Amivantamab is an EGFR-MET bispecific antibody with immune cell-directing activity. Lazertinib is a CNS-penetrant, thirdgeneration EGFR tyrosine kinase inhibitor. Amivantamab-lazertinib demonstrated efficacy in treatment-naïve and refractory EGFR-mutated advanced non-small cell lung cancer (NSCLC). Intravenous amivantamab has an infusion-related reaction (IRR) incidence of ~67%, typically at first infusion (Park Ann Oncol 2021;32[suppl_5]:S981). This prospective study evaluated prophylactic strategies to reduce the incidence of IRRs.

Methods: The global SKIPPirr study (NCT05663866) enrolled patients with EGFR-mutated (Ex19del or L858R) advanced NSCLC after disease progression on sequential osimertinib and platinum-based chemotherapy. All patients received oral lazertinib and intravenous amivantamab. A Simon's 2-stage design was used to evaluate prophylactic approaches in 4 cohorts (Figure 1): 4-mg oral dexamethasone twice daily (BID) on C1D-1, 8-mg oral dexamethasone BID on C1D-2, C1D-1, and 1 hour prior to infusion on C1D1, 10-mg oral montelukast once daily from C1D-4 to C1D1, and 25-mg subcutaneous methotrexate as a single dose at some point between C1D-7 and C1D-3.

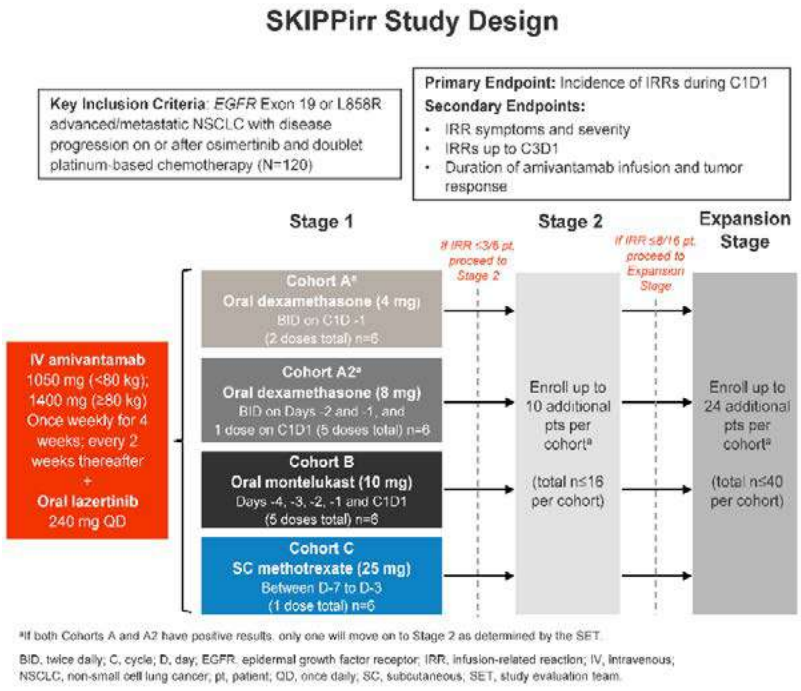
Results: As of February 7, 2024, 48 patients were enrolled. Median age was 64.5 years, 69% were female, and 60% were Asian, with a median of 3 prior therapy lines. The 4-mg dexamethasone and methotrexate cohorts did not pass stage 1 (5/6 patients each with IRR). The montelukast cohort passed stage 1 (3/6 patients with IRR) but not stage 2 (10/15 patients with IRR). The 8-mg dexamethasone cohort proceeded to expansion stage after stages 1 and 2 (2/6 and 6/16 patients with IRR, respectively). At the time of data cutoff (7-Feb-2024), 4 additional patients were enrolled in the expansion stage. Of 20 patients with available efficacy data, 7 experienced IRRs on C1D1.

Among 21 patients with available safety data, most common IRR-related symptoms were hypotension and nausea (both 29%). No patient discontinued amivantamab-lazertinib due to IRRs. Efficacy and safety profiles of amivantamab-lazertinib were consistent with prior reports and will be shared at the meeting.

As of April 1, 2024, an additional 20 patients have been enrolled in the expansion stage. Preliminary estimates from the fully enrolled cohort (n=40) showed 10 IRRs for an incidence rate of 25% on C1D1; further details will be reported at the meeting.

Conclusions: Prophylaxis with 8-mg oral dexamethasone resulted in a meaningful reduction in IRR incidence from historical data and is an effective strategy to reduce IRRs.

Keywords: SKIPPirr, infusion-related reaction, amivantamab



MA12 PAVING THE PATH TO PRECISION ONCOLOGY: TARGETING EGFR AND HER2
TUESDAY, SEPTEMBER 10, 2024 - 13:30 - 14:45

MA12.10 Zongertinib (BI 1810631) For HER2-Positive Solid Tumors with Brain Metastases: Subanalysis of the Beamion LUNG-1 Trial

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Introduction: Brain metastases are present in up to 30% of patients with human epidermal growth factor receptor 2 (HER2) mutation-positive (m+) non-small cell lung cancer (NSCLC) at diagnosis and are particularly common in patients with the HER2 ex20ins YVMA mutation. Zongertinib, a novel HER2-specific tyrosine kinase inhibitor, binds selectively and covalently to the HER2 tyrosine kinase domain while sparing wild-type epidermal growth factor receptor. Beamion LUNG-1 (NCT04886804), a Phase Ia/Ib, first-in-human, open-label trial, is evaluating the safety and efficacy of zongertinib in patients with HER2 aberration-positive solid tumors (Phase Ia) and HER2m+ NSCLC (Phase Ib). Here, we present data from Phase Ia, including patients with brain metastases at baseline.

Methods: Phase Ia enrolled patients with confirmed HER2 aberration-positive (gene mutations, rearrangements, amplification, or overexpression) advanced/unresectable/metastatic solid tumors, refractory to/unsuitable for standard treatment. Patients with asymptomatic brain metastases were eligible. Patients received escalating doses of oral zongertinib twice-daily (BID; ≥15 mg) or once-daily (QD; ≥60 mg), guided by a Bayesian model with overdose control. Brain lesion objective response (according to RANO-BM) and objective response in other lesions (according to RECIST v1.1) was assessed.

Results: At data cut-off (January 29, 2024), 83 patients in Phase Ia have received zongertinib, including 19 patients with brain metastases at baseline. In all treated patients, the median duration of treatment was 4.2 months (range 0-24); treatment was ongoing in 38 patients (46%) at data cut-off. Treatment-related adverse events (TRAEs) were reported in 63 patients (76%), including grade ≥3 TRAEs in 7 patients (8%). The most common TRAEs (any/grade ≥3) included diarrhea (42%/1%), rash (12%/0%), and decreased appetite (10%/0%). Thirty-four patients (41%) had serious adverse events (SAEs), including 2 patients (2%) with treatment-related SAEs. In 74 evaluable patients, the confirmed objective response rate (ORR) across all dose levels was 35%, with a disease control rate (DCR) of 85%. The median duration of response was 12.7 months. Median progression-free survival (PFS) was 8.0 months and 8.3 months with zongertinib BID and QD, respectively. In 41 evaluable patients with NSCLC, the ORR and DCR were 44% and 93%, respectively. The median duration of response was 15.8 months. Median PFS was 13.8 months and 12.3 months with zongertinib BID and QD, respectively. All 19 patients with brain metastases at baseline had lung cancer (NSCLC: 16 patients; unspecified cancer of the lung: 3 patients). Of these patients, 15 (79%) had TRAEs, including 5 (26%) with grade ≥3. The most common TRAEs (any/grade ≥3) included diarrhea (42%/0%), increased alanine aminotransferase (ALT; 26%/16%), and increased aspartate aminotransferase (AST; 21%/5%). SAEs were reported in 13 patients (68%), including 1 patient (5%) with treatment-related SAEs (grade 3 increased ALT and AST). Of the 17 evaluable patients with brain metastases, the ORR per RECIST v1.1 (without confirmation) and DCR was 53% and 94%, respectively.

Conclusions: Zongertinib demonstrated manageable safety and promising efficacy in patients with HER2 aberration-positive solid tumors, including in those with brain metastases at baseline. Updated data will be presented, including Phase Ia RANO-BM data and Phase Ib data.

Keywords: HER2, zongertinib, non-small cell lung cancer

MA12 PAVING THE PATH TO PRECISION ONCOLOGY: TARGETING EGFR AND HER2
TUESDAY, SEPTEMBER 10, 2024 - 13:30 - 14:45

MA12.11 Vebreltinib Plus PLB1004 In EGFR-Mutated, NSCLC with MET Amplification or MET Overexpression Following EGFR-TKI

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Introduction: The unmet therapeutic need exists in EGFR-mutated non-small-cell lung cancer (NSCLC) with MET-driven acquired resistance. We evaluated the efficacy and safety of Vebreltinib, a potent and highly selective c-MET inhibitor, plus PLB1004, an oral, potent, irreversible, and selective EGFR tyrosine kinase inhibitor (TKI), in NSCLC patients with EGFR mutation-positive, MET amplified or MET overexpression.

Methods: We conducted a multicenter, open-label, phase Ib/II study, phase Ib study included dose escalation and expansion phases. we enrolled Chinese patients with EGFRm locally advanced or metastatic NSCLC with MET amplification or MET overexpression, whose disease progressed following prior EGFR-TKI treatment. In the dose-escalation phase, patients received oral Vebreltinib(100mg/150mg/200 mg) BID plus PLB1004 (80/160 mg) once daily. In the expansion phase, patients were treated at three escalating dose levels of Vebreltinib and PLB1004 to identify a recommended phase II dose (RP2D). The primary objective of the dose escalation phase was to determine the maximum tolerated dose (MTD) for Vebreltinib plus PLB1004 and safety. In the dose expansion phase, the primary objective was objective response rate (ORR), and its secondary objectives included disease control rate (DCR), duration of response (DoR), progression-free survival (PFS) and overall survival (OS). Here, we present preliminary data of the study with a data cutoff date of February 29, 2024. This study is registered with ClinicalTrials.gov, NCT06343064.

Results: Between June 5, 2023, and Feb 19, 2024, in phase Ib, 44 patients received Vebreltinib 100mg plus PLB1004 160mg (n=15), Vebreltinib 150mg plus PLB1004 160mg (n=13), Vebreltinib 200mg plus PLB1004 80mg (n=3), or Vebreltinib 150mg plus PLB1004 80mg (n=13) and were included in the safety analysis. Among 44 patients, 36.4% of patients had brain metastases, and 86.4% of patients received third-generation EGFR-TKI, respectively. No patients experienced dose-limiting toxicities, and the maximum tolerated dose of Vebreltinib with PLB1004 was not reached. Objective responses occurred across all Vebreltinib and PLB1004 dose levels tested, with partial response (PR) observed in 19/32 (59.4%) response-evaluable patients. PRs were seen in 7/12(58.3%), 6/13(46.2%), 2/3(66.7%), 4/4(100%) response-evaluable patients at the dose of Vebreltinib 100mg plus PLB1004 160mg, Vebreltinib 150mg plus PLB1004 160mg, Vebreltinib 200mg plus PLB1004 80mg and Vebreltinib 150mg plus PLB1004 80mg, respectively. Among patients with brain metastases, ORR was observed in 75.0% (9/12) (95% confidence interval [CI], 42.8 to 94.5). The ORR was 58.6% (17/29) (95% CI, 38.9 to 76.5) in patients who received prior third-generation EGFR-TKI. Treatment-related adverse events occurred in 41 patients (93.2%) with 18.2% of grade ≥3. The most common TRAEs were rash in 19 (43.2%; Grade ≥3, 1 [2.3%]) and paronychia in 18 (40.9%; Grade ≥3, 0[0.0%]) patients. Vebreltinib dose was reduced in 2 (4.5%) and PLB1004 in eight (18.2%) patients. No patients discontinued treatment due to TRAEs.

Conclusions: Vebreltinib plus PLB1004 showed promising antitumor activity and a manageable safety profile in patients with EGFRm NSCLC with MET amplification or MET overexpression who have experienced disease progression after prior EGFR-TKI therapy, especially in those bearing brain metastases and treated with third-generation EGFR-TKI.

Keywords: Vebreltinib plus PLB1004, EGFR mutation-positive, MET amplified or MET overexpression

MA13 ADVANCING LUNG CANCER PREVENTION THROUGH UNDERSTANDING RISK FACTORS
TUESDAY, SEPTEMBER 10, 2024 - 13:30 - 14:45

MA13.03 Impact of a Tobacco Endgame Intervention on Lung Cancer Mortality in 185 Countries: A Population Birth Cohort Simulation Study

J. Rey Brandariz[1], H. Rumgay[2], O. Ayo-Yusuf[3], R. Edwards[4], F. Islami[5], S. Liu[6], M. Pérez-Ríos[1], P.C. Rodrigues Pinto Corrêa[7], A. Ruano-Ravina[1], I. Soerjomataram[2], [1]University of Santiago de Compostela, Santiago de Compostela/ES ,[2]International Agency for Research on Cancer, Lyon/FR ,[3]University of Pretoria, Petroria/ZA ,[4]University of Otago, Wellington/NZ ,[5]American Cancer Society, Atlanta/GA/USA ,[6]Chinese Center for Disease Control and Prevention, Beijing/CN ,[7]Universidade Federal de Ouro Petro, Ouro Preto/BR

Introduction: In 2019, tobacco use accounted for almost 70% of lung cancer deaths globally. To reduce mortality rates, it is crucial to implement tobacco control interventions aimed at decreasing tobacco use in the population such as the tobacco-free generation. The aim of this study was to estimate the impact of eliminating tobacco consumption (i.e tobacco-free generation) on lung cancer mortality among people born between January 1, 2006 and December 31, 2010 in 185 countries.

Methods: To assess the impact of eliminating tobacco use on lung cancer mortality, the following steps were taken: 1-Lung cancer mortality or incidence data was used to calculate predicted lung cancer rates by age and sex up to 2040-2044. 2-Based on the predicted rates, lung cancer mortality rates were calculated for the birth cohort of 2006-2010 in 185 countries. 3-The number of avoidable lung cancer deaths and the population impact fraction (i.e. proportion of lung cancer deaths that would be avoided) in the birth cohort up to 2095 were calculated. The results are presented in absolute numbers, proportions and age-standardized rates (ASR) by region and the four World Bank income groups (Figure-1).

Results: Eliminating tobacco consumption would prevent 1.2 million deaths (40.2%) from lung cancer in 185 countries. In men, 844,200 deaths (45.8%) and in women 342,400 deaths (30.9%) would be avoided. The highest number of deaths in men that could be prevented would be in Central and Eastern Europe, specifically 48,900 deaths (74.3%). Among women, the region with the highest potential for preventing deaths is Western Europe, where 56,200 deaths (77.7%) could be avoided. In terms of ASRs, the regions with the highest ASRs for prevented lung cancer deaths in men are Eastern Asia and Eastern Europe, with 18.6 and 18.4 prevented deaths per 100,000 population, respectively. In women, the highest ASRs are observed in Western Europe and Southern Europe, with 13.8 and 10.8 prevented deaths per 100,000 population, respectively. In both men and women, high-income countries would prevent the highest number of lung cancer deaths. Specifically, in men, 201,900 deaths (56.7%) would be prevented, and in women, 212,300 deaths (66.0%) would be prevented.

Conclusions: The implementation of the tobacco-free generation alongside other tobacco control measures could substantially reduce lung cancer mortality worldwide. The greatest impact of this intervention would be in more developed regions, such as Europe, North America, Australia, and New Zealand, which have experienced an earlier onset of the tobacco epidemic.

Keywords: tobacco, lung cancer, tobacco-free generation

Figure 1. Number, population impact fraction (PIF) and age-standardised rate (ASR per 100,000) of expected and prevented lung cancer deaths in men, women and both sexes combined by world region and income group

	MEN					WOMEN				
World region	Expected deaths	Prevented deaths	PIF	ASR expected deaths	ASR prevented deaths	Expected deaths	Prevented deaths	PIF	ASR expected deaths	ASR prevented deaths
Africa										
Eastern Africa	32600	1800	5.4	3.5	0.2	32400	1300	4.0	2.6	0.1
Middle Africa	8600	180	2.1	2.8	0.1	6400	60	0.9	1.6	0.0
Northern Africa	90400	45000	49.8	17.0	8.6	26500	3300	12.6	4.1	0.2
Southern Africa	14300	6500	45.8	17.7	8.6	10900	4600	42.1	8.1	2.9
Western Africa	17200	1100	6.3	2.7	0.2	10000	320	3.2	1.5	0.1
America										
Latin America and Caribbean	115100	17000	14.7	8.3	1.4	120800	49800	41.2	7.4	2.8
North America	91200	45000	49.3	10.3	6.1	94900	59700	63.0	9.1	5.7
Asia										
Eastern Asia	702800	422000	60.0	28.2	18.6	369600	45300	12.2	13.3	0.5
China	628300	379500	60.4	29.4	19.7	329900	30400	9.2	14.0	0.4
South Central Asia	251700	15000	5.9	7.1	0.6	122300	9600	7.8	3.5	0.2
India	153600	3100	2.0	6.5	0.4	81500	1100	1.3	3.6	0.1
South East Asia	161400	49300	30.6	16.2	6.9	78800	11600	14.7	6.6	1.5
Western Asia	134337	86375	64.3	21.4	14.0	42702	18372	43.0	7.3	3.3
Europe										
Central and Eastern Europe	65800	48900	74.3	22.6	18.4	34000	19900	58.4	7.9	4.7
Northern Europe	30700	18500	60.3	13.1	9.0	35600	26400	74.2	11.8	8.5
Southern Europe	51200	37000	72.3	18.7	14.5	40700	29400	72.2	13.7	10.3
Western Europe	64200	44200	68.9	19.6	15.4	72300	56200	77.7	17.2	13.8
Oceania										
Australia and New Zealand	9900	5600	56.2	13.0	8.8	9500	6100	63.8	10.5	7.1
Melanesia, Micronesia, Polynesia	1700	940	56.7	10.1	6.2	1200	500	42.6	5.7	2.6
Country income group										
High-income	356000	201900	56.7	13.4	8.4	321600	212300	66.0	10.5	6.9
Upper middle-income	959500	541100	56.4	22.5	14.1	522700	109000	20.9	10.5	1.7
Lower middle-income	457600	89900	19.6	8.7	2.2	205200	15000	7.3	3.8	0.4
Low-income	69800	11300	16.3	4.8	0.9	59100	6100	10.3	3.0	0.3
World	**1842900**	**844200**	**45.8**	**13.2**	**6.6**	**1108500**	**342400**	**30.9**	**6.7**	**1.8**

MA13 ADVANCING LUNG CANCER PREVENTION THROUGH UNDERSTANDING RISK FACTORS
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MA13.04 A Comparison of Ever vs Never Smoking Surgically Treated Lung Cancer Patients

S.J. Tuminello, A. Kaufman, A. Wolf, D-S. Lee, A. Hakami-kermani, D. Nicastri, E. Taioli, R. Flores, Icahn School of Medicine at Mount Sinai, New York City/NY/USA

Introduction: Lung cancer is the leading cause of cancer-related mortality. While smoking substantially increases the risk of lung cancer, cancer in non-smokers is commonly seen and the proportion has increased over time. There are likely substantial clinical and molecular differences in smoking vs non-smoking related lung cancers, however, early-stage non-smoking cancers have been underrepresented in prior studies, as screening is mostly limited to those with smoking histories. We report here demographic, clinical and molecular factors associated with non-smoking lung cancers treated surgically at a diverse New York City health system, as well as differences in surgical outcomes based on smoking status.

Methods: The Department of Thoracic Surgery Prospectively Maintained Database (DTS) contains data on all surgical cases at the Icahn School of Medicine at Mount Sinai between 2012 and 2022. Demographics, pre-operative assessment, details of the surgical procedure, tumor features, and surgical outcomes are recorded. Factors associated with ever vs never smoking were assessed using Pearson test for normal and categorical variables and the Spearman test continuous non-normal variables. Investigated outcomes of surgery were adverse post-operative events, additional surgery for recurrence or secondary primary cancers, and long-term survival, assessed using logistic regression.

Results: Of the 1,832 surgically-treated patients, smoking history was reported for 1,767 patients, among which were 420 (24%) never smokers vs 1,347 (76%) ever smokers. Compared with the ever smokers, never smoking patients were younger ($p<0.001$), female ($p<0.001$), Hispanic ($p<0.001$), privately insured ($p<0.001$), and were more likely to have had their surgery after 2015 ($p=0.022$). Never smokers appeared to be healthier at the time of surgery, with never-smoking patients having a better average % predicted FEV1 (90.7% vs 84.7%, $p<0.001$) and fewer comorbidities (hypertension: 44% vs 58%, $p<0.001$; coronary artery disease: 8% vs 18%, $p<0.001$; no difference in diabetes). Tumors of never smokers were of similar size to ever smokers ($p=0.803$), but were more likely to be located in the upper lobe ($p<0.0001$) and to have had nodal metastasis ($p=0.020$), indicative of more advanced clinical stage. Of the 929 patients with a molecular test, never smokers had more EGFR mutations (57% vs 15%, $p<0.001$), and fewer KRAS and P53 mutations (16% vs 43%, $p<0.001$ & 25% vs 38%, $p=0.004$, respectively). There was not a statically significant difference observed in ALK mutations ($p=0.787$). Never and ever smoker had similar likelihoods of surgery type (pneumonectomy, lobectomy, or wedge resection, $p=0.110$) and pre-surgical treatments (chemotherapy or immunotherapy, radiation, $p=0.200$). While odds of post-operative events and additional surgery for recurrence or second primary cancer were comparable between never vs ever smoking lung cancer patients, of the 1,377 patients for whom long-term survival was known, odds of death was lower for never smokers, even after adjustment for confounding (ORadj [odds ratio]: 0.65; 95% CI [confidence interval]: 0.40-1.02).

Conclusions: Never vs ever smokers with surgically resectable lung cancers differ in clinically meaningful ways. Nevertheless, surgery for never-smokers is effective, and if screening can be implemented for high-risk never smokers, this could help to reduce the burden of lung cancer mortality.

Keywords: Smoking, Never Smokers, Surgery

MA13 ADVANCING LUNG CANCER PREVENTION THROUGH UNDERSTANDING RISK FACTORS
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MA13.05 The Impact of Tobacco Control on Lung Cancer Mortality Across 48 Countries

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Introduction: Lung cancer is the leading cause of cancer-related mortality globally. The widespread success of tobacco control policy and smoking cessation campaigns have led to drastic reductions in tobacco consumption and lung cancer mortality rates that peaked decades ago in many countries. However, it is currently not known how many more lung cancer deaths would have occurred if not for the substantial progress made in lung cancer control.

Methods: We obtained age-specific population counts and lung cancer mortality rates by sex and country from 1950 to 2019 (from 48 countries) from the World Health Organization's Global Cancer Observatory. To identify peak lung cancer mortality for each country, we estimated age-standardized mortality rates (ASMR), standardized to the World Health Organization (WHO 2000-2025) Standard Population. Peak mortality was defined as the maximum ASMR (based on a five-year rolling average), separately for each country and sex. For every year in the period following peak mortality, the expected number of lung cancer deaths was estimated using the peak-year age-specific mortality rates and age-specific population counts for the index year. The total number of avoided deaths was estimated as the difference between the expected and observed number of lung cancer deaths in that period (Figure 2).

Results: Lung cancer mortality rates have peaked for males in all countries but have yet to reach their peak for 11 out of 37 (30%) countries for females. In total, there have been 3.10 million avoided lung cancer deaths since mortality rates peaked for many countries (2.95 million for males, 0.15 million for females). Across all countries, 21.5% and 4.3% of expected lung cancer mortality has been avoided since mortality rates peaked for males and females, respectively. Sixteen countries have reduced lung cancer mortality by more than 25% for males, while only two countries have achieved this feat for females. There has been a statistically significant reduction in lung cancer deaths for 46 out of 48 (96%) countries for males, but only 17 out of 37 (46%) countries for females.

Conclusions: This study highlights the considerable progress made in reducing premature lung cancer mortality due to cancer control initiatives. There has been a substantial number of lung cancer deaths avoided since mortality rates peaked for many countries, though the reduction in mortality has not been observed in all countries or equally for males and females.

Keywords: Avoided deaths, Tobacco control, Lung cancer mortality

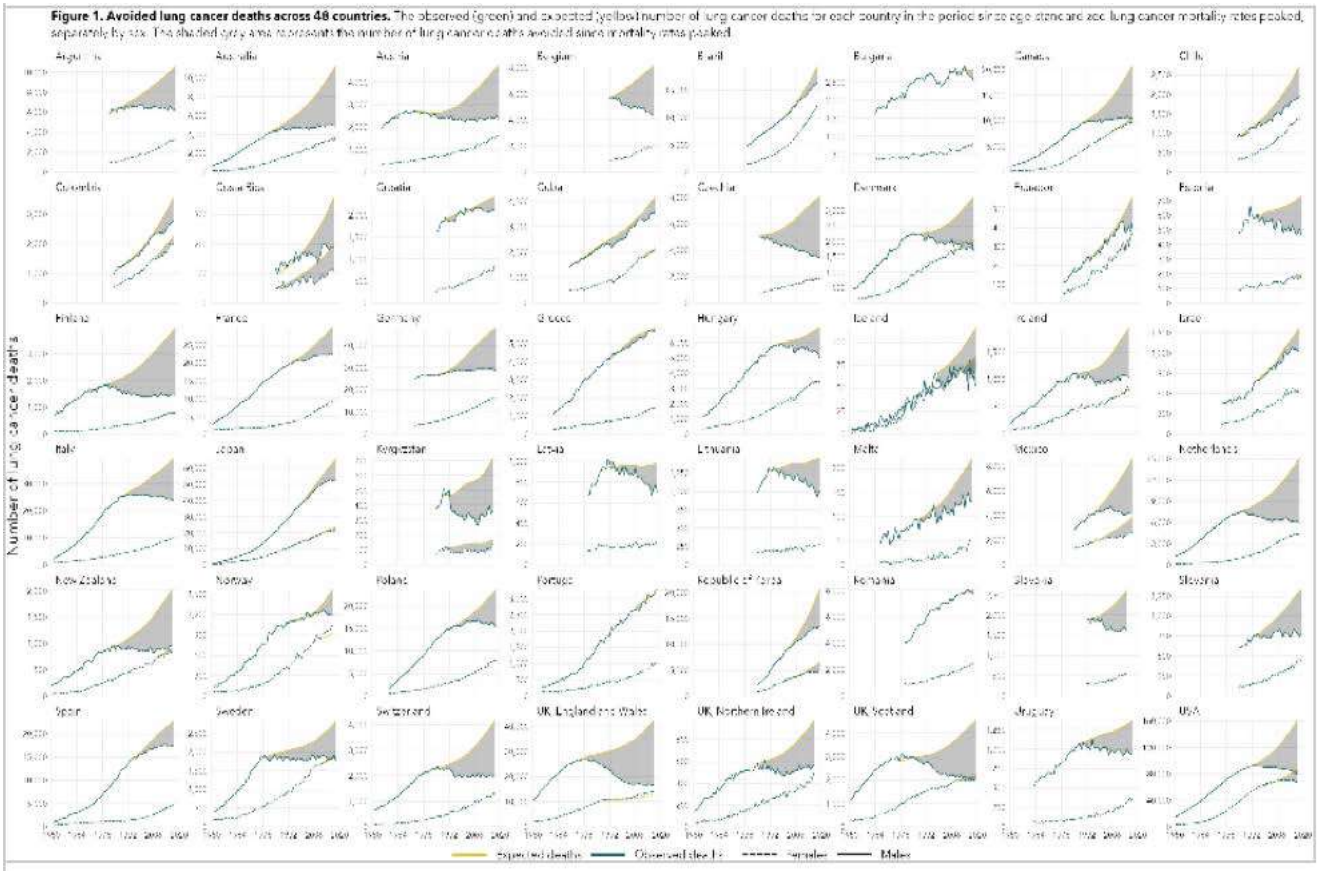

Figure 1. Avoided lung cancer deaths across 48 countries. The observed (green) and expected (yellow) number of lung cancer deaths for each country in the period since age-standardized lung cancer mortality rates peaked, separately by sex. The shaded grey area represents the number of lung cancer deaths avoided since mortality rates peaked.

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MA13.07 Practical Implementation of Outdoor Air Pollution Exposure Measurement for Lung Cancer Risk Assessment

C. Durney[1], Y. Chen[1], K. White[2], M. Brauer[2], S. Atkar-Khattra[1], R. Myers[1,2], R. Meza[1,2], S. Lam[1,2], [1]British Columbia Cancer Research Institute, Vancouver/BC/CA ,[2]The University of British Columbia, Vancouver/BC/CA

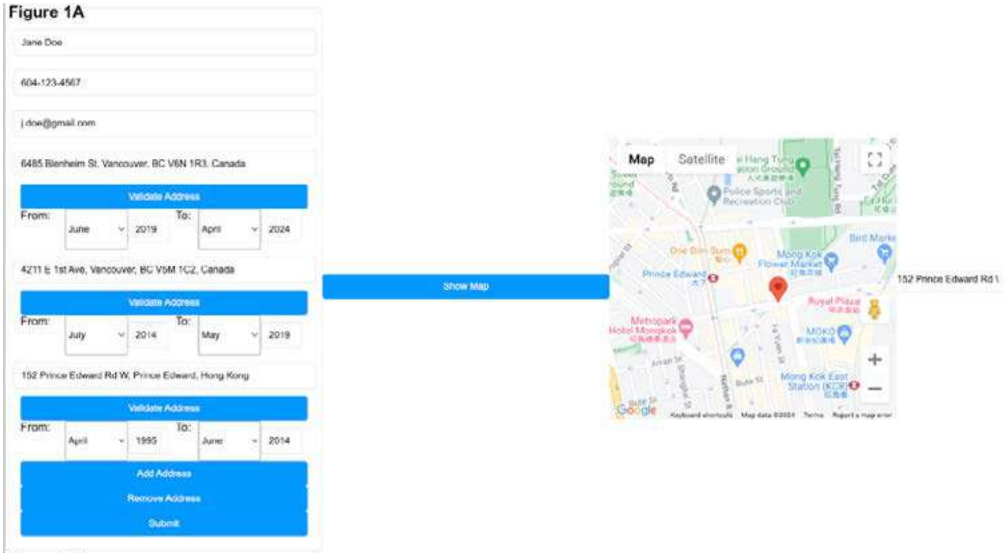
Introduction: In 2013, the International Agency for Research on Cancer (IARC) classified outdoor air pollution and one of its major components, particulate matter PM2.5, as carcinogenic to humans (Group 1) and causes of lung cancer. Air pollution is the major cause of lung cancer in people who have never smoked tobacco. Previous lung cancer risk prediction models using clinical-demographic risk factors have modest performance. None have incorporated air pollution as a lung cancer risk factor because quantifying long-term exposure to PM2.5 has proven time consuming and difficult to be completed at a point-of-care visit. The purpose of our study is to develop an interactive, real time, PM2.5 assessment tool to measure long-term PM2.5 exposures over several decades that can be readily integrated into a lung cancer risk prediction tool.

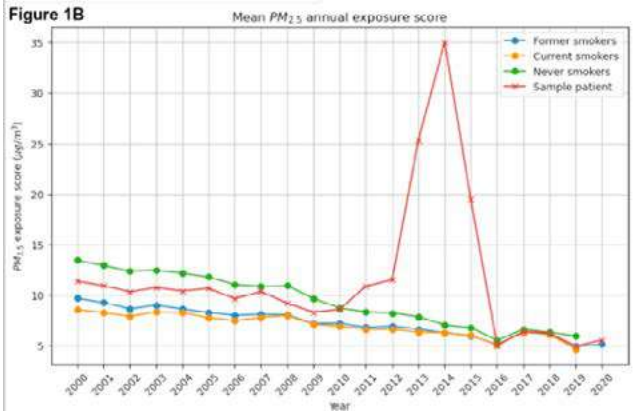
Methods: We introduce a novel web-based tool designed to efficiently collect detailed residential histories and covariate information from participants to estimate outdoor exposure to PM2.5. This tool integrates the use of an interactive map to pinpoint, as close as possible, the residential location. To assess PM2.5 exposure, we geocode each residential address and analyze high-resolution concentration estimates from satellite data, chemical transport models, and ground measurements within roughly ~10 x 10 km areas corresponding to the time the individual lives at a given address. From the annual PM2.5 exposure data since 1990 when accurate information became available, cumulative or timed exposure to PM2.5 is estimated in real-time.

Results: The interactive tool is shown in Figure 1A. This tool was implemented in a cohort of lung cancer cases (N=899) to measure PM2.5 exposure during a 20-year window. A sample patient (never smoker) with a varied residential history in North America and Asia (Figure 1B) was analyzed against this cohort for comparison. It takes approximately 30 seconds to enter a known address and 45 seconds to use a map assisted address. An average patient can be completed in under 5 minutes.

Conclusions: Our interactive, web-based air pollution exposure tool can be efficiently applied to generate estimates of long-term PM2.5 exposure information for lung cancer risk assessment. The tool will be very useful for development of an accurate lung cancer risk prediction tool for people who have never smoked that incorporates the carcinogenic effects of air pollution exposure.

Keywords: Lung Cancer Risk Assessment, Air Pollution, Particulate Matter





MA13 ADVANCING LUNG CANCER PREVENTION THROUGH UNDERSTANDING RISK FACTORS
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MA13.08 PM2.5 Exposure Impact on Never-Smoking Lung Cancer Patients

Y.C. Chen[1], C.H. Durney[1], K.R. White[2], M. Brauer[2], S. Atkar-Khattra[1], R. Myers[1,2], R. Meza[1,2], S. Lam[1,2], [1]British Columbia Cancer Research Institute, Vancouver/BC/CA ,[2]The University of British Columbia, Vancouver/BC/CA

This abstract is under embargo until September 10 at 11:35.

MA13 ADVANCING LUNG CANCER PREVENTION THROUGH UNDERSTANDING RISK FACTORS
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MA13.09 A World Map of Air Pollution and EGFR Prevalence

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Introduction: Contamination of air by fine particulate matter (PM2.5), represents an unresolved global environmental health problem. It is responsible for 6.7 million premature deaths worldwide in 2019. Currently, lung cancer (LC) in non-smokers ranks among the 10th most common causes of cancer death. Substantial epidemiological evidence supports a causal link between air pollution (AP) and LC incidence and mortality. Long-term exposure to fine particulate AP has genotoxic and mutagenic effects, which may increase LC risk through inflammatory injury, reactive oxygen species production, and oxidative DNA damage. This risk increases with increasing exposure to PM2.5. A recent study hypothesized that increasing PM2.5 levels exposure was linearly associated with increased risk of EGFR-mutant LC. Considering this background, we analyzed the association between the mean PM2.5 levels from 2000-2020 and the EGFR-mutant prevalence reported worldwide

Methods: To estimate the strength of the association between both variables, we fitted linear regression models weighted by the total number of non-small cell lung cancers (NSCLC). Adjusted R2 values were calculated (the closer the adjusted R2 to 1, the stronger the association). A total of sixty-nine countries had data available for both variables

Results: Overall, the association between PM2.5 levels and EGFR-mutant prevalence was moderate-weak (R2= 0.34). Indeed, when we stratified the analysis according to the different areas worldwide (European, Asia, and Latin-American countries), the association became weaker (R2 < 0.15 in all comparisons). Although there were countries with high air pollution and high EGFR-mutant lung cancer prevalence (China: PM2.5 level of 46.9 and 45.7% EGFR-mutant prevalence), this association was not always observed

Conclusions: Discrepancies between PM2.5 level and EGFR-mutant lung cancer prevalence worldwide could be explained by different access to LC genomic profiling, potential over or underestimation of EGFR-mutant prevalence in some countries as population tested was over-selected, patients tested in some countries are not those more exposed to the AP (PM2.5 level may not be homogenous in all areas of one specific country), this prevalence includes all patients with LC, regardless of the smoking pattern, and alternative contributory factors to pathogenesis of never smoker lung cancer (genomic background and ancestry). All these factors should be considered as potential limitations to directly relate AP PM2.5 to the development of EGFR-mutated LC.

Keywords: Air pollution, EGFR mutation

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MA13.11 Glucagon-Like Peptide 1 Receptor Agonists Associated with Reduced Risk of Lung Cancer in Type 2 Diabetes Mellitus

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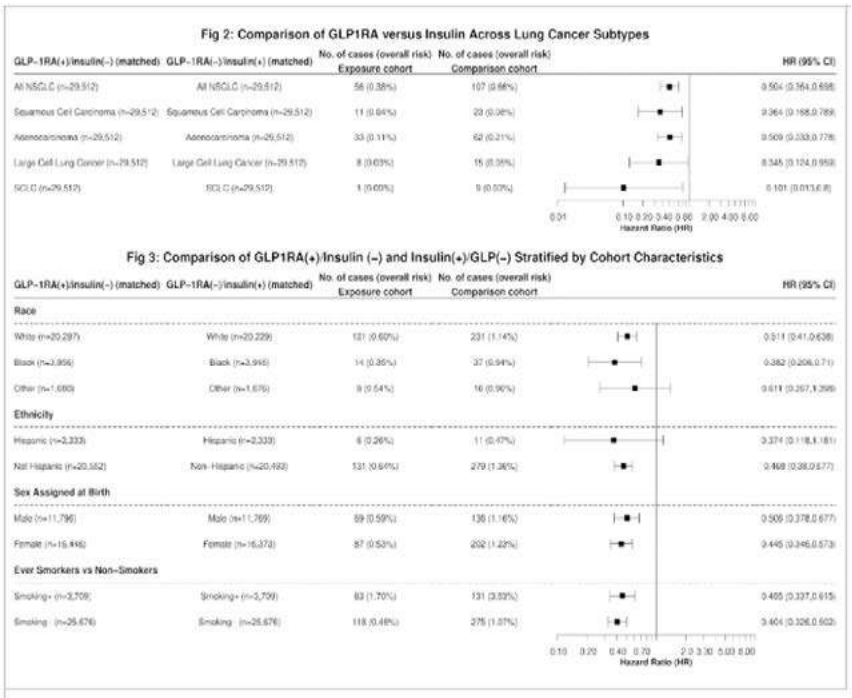
Introduction: Lung cancer (LC) is the second most common cancer in the US and the foremost cause of cancer mortality in the U.S. Insulin therapy, a mainstay strategy for glycemic control in Type 2 Diabetes Mellitus (T2DM), has been implicated in elevating LC risk. The impact of non-insulin antidiabetic agents on LC risk, particularly GLP-1 receptor agonists (GLP-1RAs) is incompletely understood and has not been compared to insulin therapy. We conducted a nationwide retrospective cohort study to evaluate LC risk among T2DM patients treated with seven non-insulin antidiabetic agents in comparison to insulin therapy.

Methods: Utilizing the TriNetX platform, we accessed deidentified electronic health records from 105.9 million patients, across diverse U.S. demographics. The study population comprised 1,040,341 patients with T2DM prescribed antidiabetics between 2005-2019, excluding those with prior antidiabetic use or LC diagnoses. Hazard ratios and 95% confidence intervals for LC risk were calculated comparing users of 7 non-insulin antidiabetics against insulin. Propensity score matching on key LC risk factors was performed to address known confounding factors.

Results: All non-insulin antidiabetics except alpha-glucosidase inhibitors were associated with significantly decreased LC risk versus insulin, with GLP-1RAs offering the most significant decrease (HR: 0.489, 95% CI: 0.408, 0.586). Sub-group analyses revealed GLP-1RAs significantly lowered LC risk across all LC histological types. Risk reduction was significant among Black and White patients, with consistent findings across genders and smoking status.

Conclusions: Our findings suggest that non-insulin antidiabetics, especially GLP-1RAs, are associated with significantly reduced risk of lung cancer after accounting for key confounders. The findings highlight an important consideration for the management of T2D, especially for those patients at an elevated risk of developing lung cancer.

Keywords: GLP-1, Diabetes Mellitus, Risk



MA13 ADVANCING LUNG CANCER PREVENTION THROUGH UNDERSTANDING RISK FACTORS
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MA13.12 Prevalence of Pathogenic or Likely Pathogenic Germline Variants in Cancer Predisposition Genes in Selected Lung Adenocarcinoma Patients

O. Arrieta[1], E. Caballé-Pérez[1], N. Hernández-Pedro[1], E. Romero-Nuñez[1], J. Lucio-Lozada[1], C. Castillo-Ruiz[1], K. Acevedo-Castillo[2], R.M. Álvarez-Gómez[1], C. Molina-Garay[2], M. Jiménez-Olivares[2], K. Carrillo-Sánchez[2], E.C. Mendoza-Caamal[2], A.F. Cardona[3], J. Remon[4], C. Alaez-Verson[2], [1]Instituto Nacional de Cancerología, Mexico City/MX ,[2]Instituto Nacional de Medicina Genómica, Mexico city/MX ,[3]Cancer Treatment and Research Center, Bogotá/CO ,[4]Gustave Roussy Cancer Campus, Villejuif/FR

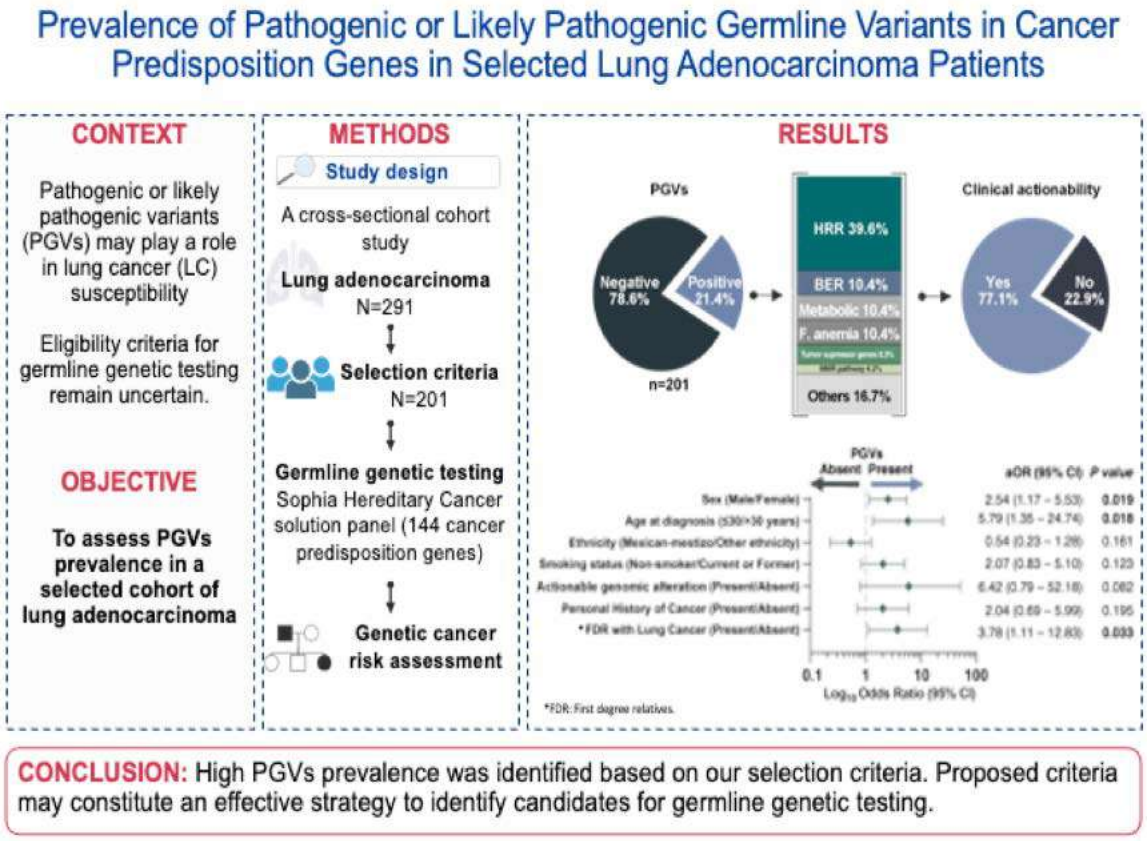
Introduction: Pathogenic or likely pathogenic germline variants (PGVs) in cancer predisposition genes may play a role in lung cancer (LC) susceptibility. However, determining an eligible population for genetic testing remains uncertain. This study aimed to assess the prevalence of PGVs in a selected cohort of individuals with lung adenocarcinoma.

Methods: A cross-sectional cohort study was conducted to assess the PGVs rate in lung adenocarcinoma patients with a family history of LC, young-onset presentation, history of never/light smoking, or actionable genomic alterations (AGAs). Sequencing was performed using Sophia Hereditary Cancer Solution panel F, including 144 cancer predisposition genes. Variants classified as pathogenic or likely pathogenic were included for further analysis.

Results: Of 201 patients, 43 (21.4%) exhibited PGVs, among which 64.5% were DNA damage repair genes, and 86.1% were clinically actionable. The main PGVs were in ATM (9.3%), TP53 (6.9%), BRCA2 (6.9%), and CHEK2 (6.9%) genes. PGVs were associated with male sex (adjusted odds ratio [aOR] 2.46, 95% CI 1.15-5.32, p=0.021), along with a trend toward association with AGAs (aOR 6.04, 95% CI 0.77-49.74, p=0.094).

Conclusions: In this study, a high PGVs prevalence was identified based on our selection criteria, which represents an effective strategy to identify candidates for germline genomic testing, potential screening strategies in close relatives, and personalized therapeutic modalities. Our results warrant further exploration in other populations to confirm them.

Keywords: Germline Pathogenic/Likely pathogenic variant, Hereditary Cancer, Actionable genomic alterations



MA14 GLOBAL PERSPECTIVES OF LUNG CANCER ACROSS THE CARE CONTINUUM
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MA14.03 Breathing Dangers: Unraveling Particulate Matter and Asbestos-Associated Lung Cancer Trends in the Top Ten Most Populous Countries.

C.T. Jani[1], D. Morgenstern-Kaplan[2], S. Kareff[3], G. Hanbury[4], A.S. Salazar[2], H. Singh[5], E. Rodriguez[3], G. Lopes[3], [1]University of Miami, Sylvester Comprehensive Cancer Center, Doral/FL/USA ,[2]University of Miami, Miami/FL/USA ,[3]University of Miami, Sylvester Comprehensive Cancer Center, MIAMI/FL/USA ,[4]Imperial College of london, London/GB ,[5]Medical College of Wisconsin, Milwaukee/WI/USA

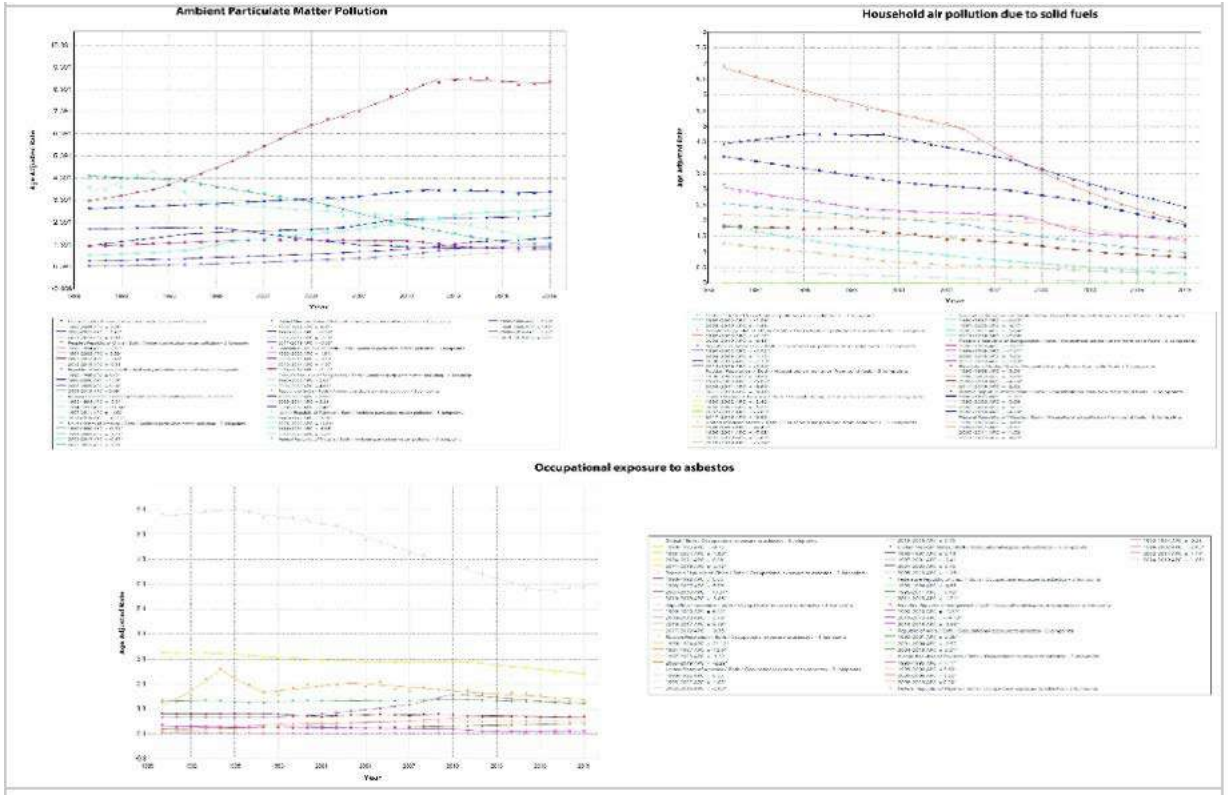
Introduction: Amid evolving tobacco policies and escalating air pollution levels, the landscape of lung cancer etiology has experienced significant shifts. This study aims to examine the dynamic trends in air pollution and asbestos-associated Tracheal, Bronchial, and Lung Cancer (TBLC) mortality across top ten most populous countries globally.

Methods: We utilized Global Burden of Disease database to extract overall and risk factor-associated Age Standardized Mortality Rate (ASMR) for TBLC from 1990-2019 for top ten most populous countries (2023 census). For risk factors, we included Asbestos and Particulate matter air pollution, including ambient air matter pollution (PM) and household air pollution from solid fuels (household). Data was reported per 100,0000 population. Estimated Annual Percentage Change (EAPC) were calculated using JoinPoint Trend analysis for overall and gender-based trends.

Results: The global TBLC mortality decreased by 8%, with reductions in asbestos-associated (25%) and particulate matter pollution (15%) associated TBLC ASMR. However, there was a 25% increase in PM and a 62% decrease in the household-associated TBLC ASMR. In recent years, there has been an increase in PM-associated TBLC ASMR observed in 7/10 countries for males and 6/10 countries for females, with Bangladesh experiencing the highest rise for both genders (EAPC males: 8.2, females: 4.2). Pakistan showed the highest overall increase (226%), while China had the highest ASMR in 2019 (8.8), contrasting with a significant decline in the USA (-68%) despite its highest ASMR in 1990 (4.5). However, the USA has shown a modest recent increase since 2017 (EAPC 0.1). In household air pollution, all countries demonstrated a decline. Analysis of asbestos trends showed the highest increase in Indonesia (262%). Despite a decline in the USA's ASMR from 8.91 (1990) to 6.0 (2019), it remained 2x higher than the global average, recording the highest amongst all ten countries. While males consistently exhibited higher ASMR, females experienced a slower decline across most risk factors, accompanied by a concerning increase in recent years.

Conclusions: Our analysis highlights alarming increases in ambient particulate matter pollution globally and in several countries, including a recent uptick in the USA. Recognizing the association of different particulate matter with lung cancer, there's an urgent need for effective policies addressing air pollution and associated health risks. Additionally, trends in asbestos-related mortality, particularly in the USA, underscore the critical necessity for stricter asbestos bans to mitigate its detrimental health impacts. Urgent gender-specific interventions are needed to curb the recent increase in female mortality.

Keywords: Lung Cancer, Air Pollution, Asbestos



MA14 GLOBAL PERSPECTIVES OF LUNG CANCER ACROSS THE CARE CONTINUUM
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MA14.04 Global Burden and Trends of Asbestos-Related Thoracic Cancers & Their Associations with National Asbestos Ban Status: A Cross-Sectional Study

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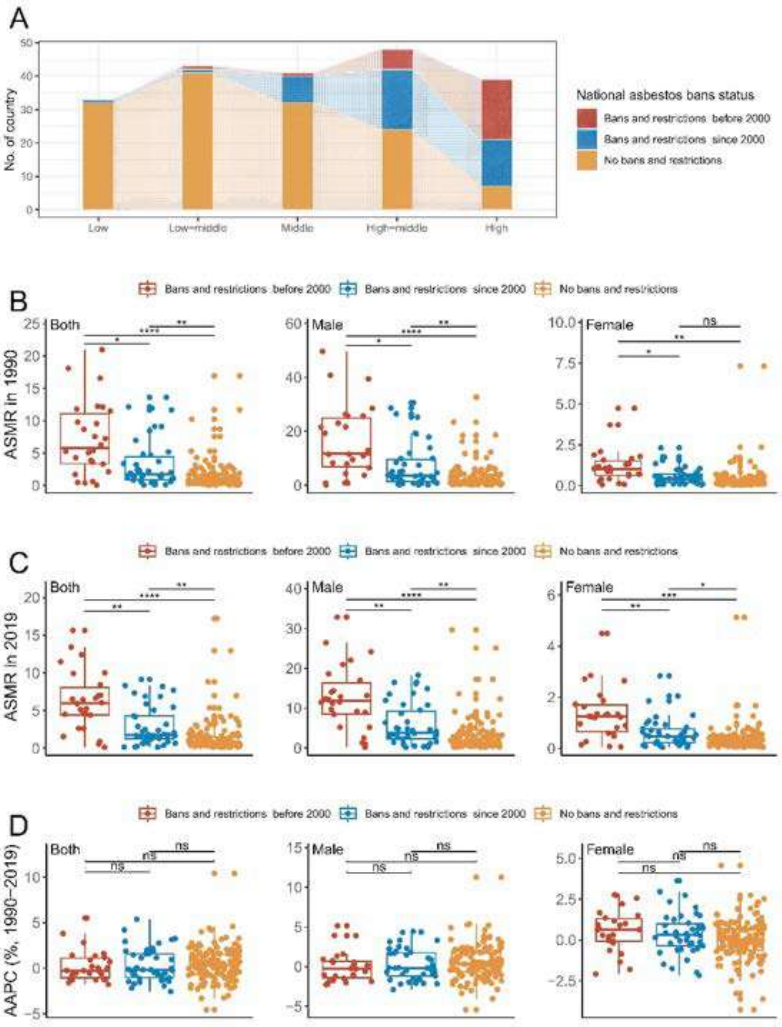
Introduction: Asbestos-related thoracic cancers (ARTCs), comprising asbestos-related lung cancer (ARLC) and mesothelioma, constitute the majority of asbestos exposure fatalities. This study evaluates the global burden and trends of ARTCs and investigates their association with national asbestos ban status.

Methods: Utilizing data from the Global Burden of Diseases Study 2019, we estimated the age-standardized mortality rates (ASMRs) for ARTCs and analyzed their temporal trends from 1990 to 2019, stratified by sex, location, and socio-demographic index (SDI) quintile. We investigated the association between the burden or trends of ARTCs and the national asbestos ban status. The evolving trends of the past three decades and the projections for the next two decades were scrutinized using Decomposition analysis and the Bayesian age-period-cohort model, respectively.

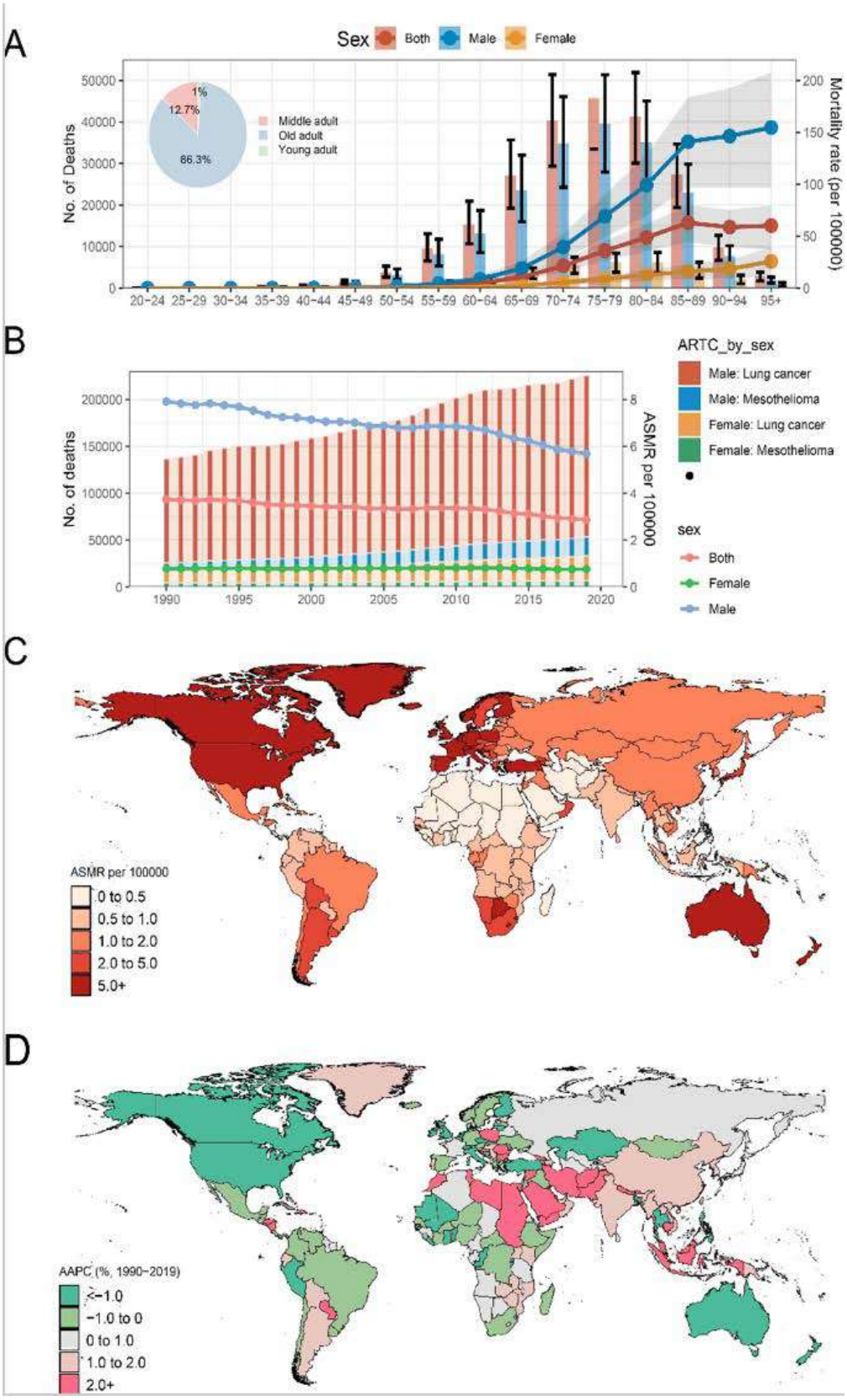
Results: In 2019, ARTCs resulted in an estimated 225,523 deaths and an ASMR of 2.9 per 100,000, with higher burden among males, older adults, and high SDI countries (Figure 1A-C). From 1990 to 2019, there was a global decrease in the ASMR for ARTCs (AAPC: -1.0 [95% CI -1.1 to -0.8], P<0.001), notably in ARLC cases, males, and higher SDI quintiles, whereas increases were noted in lower SDI quintiles (Figure 1D).



Despite a steady decline in ASMR over three decades and expectations of this trend continuing, the total number of ARTCs deaths is rising, probably driven by population growth and aging.

Conclusions: Our findings highlight notable geodemographic disparities in ARTCs burden and trends. Although national asbestos bans are associated with a historically and presently higher ARTCs burden, this correlation does not extend to trends over the study period.

Keywords: Asbestos, Lung cancer, Mesothelioma



The portion of asbestos bans showed a significantly increasing trend from the low- to high-SDI quantiles (P<0.001; Figure 2A). National asbestos bans correlate with higher ARTC burdens historically and currently, yet they don't influence the ASMR trend over the period (Figure 2B-D).

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MA14.06 Cost-effectiveness Analysis of Entrectinib in the First-Line Treatment of ROS1+ Locally Advanced or Metastatic NSCLC in China

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Introduction: Lung cancer, predominantly non-small cell lung cancer (NSCLC), causes a heavy global disease burden, with high incidence and mortality rates. ROS1+ NSCLC accounted for approximately 1%-2% of cases. Compared to crizotinib, entrectinib has demonstrated favorable intracranial efficacy in the ROS1 NSCLC and has been approved in China. The study aimed to examine the cost-effectiveness of entrectinib versus crizotinib in the Chinese setting.

Methods: This study included Asian patients with ROS1+ NSCLC from three clinical trials of entrectinib (STARTRK-1/NCT02097810, STARTRK-2/NCT02568267, and ALKA-372-001/EudraCT 2012-000148-88; data cutoff: 02 August 2021) and one clinical trial of crizotinib (OxOnc/NCT01945021). The entrectinib group comprised 52 patients as a study subgroup, while crizotinib as a control group comprised 127 patients. A partitioned survival model was adapted to China clinical practice. Proportion of patients within each health state were based on the progression-free survival (PFS) and overall survival (OS) curves, estimated by parametric extrapolation of observed data from the pooled entrectinib trials. Due to the lack of head-to-head studies, a matching-adjusted indirect comparison (MAIC) was conducted previously, with the crizotinib group as the control and the entrectinib group matched for demographic characteristics to ensure that baseline characteristics were as similar as possible between the two groups. The matched baseline characteristics included gender, age, race, smoking history, ECOG scores, histologic classifications, extent of disease, CNS metastases, and prior therapeutic regimens. The utility values of different health states were retrieved from the clinical trial results and adjusted according to age. The drug cost was calculated according to the local prices in China, dose per week and medication intensity in clinical trials. The drug management cost and the cost to treat brain metastases and side effects was estimated from clinician survey. Finally, the health outcomes and total medical costs of two treatment regimens based on the above partitioned survival model were measured to evaluate the cost-effectiveness of entrectinib versus crizotinib with the discount rate of 5%.

Results: Compared to crizotinib, entrectinib first-line treatment of ROS1+ locally advanced or metastatic NSCLC yielded an additional 1.02 quality-adjusted life years (QALYs) at an increased total treatment cost of CNY48,482 (USD6,735). The incremental cost-effectiveness ratio (ICER) was CNY47,408 (USD6,586) per QALY obtained, equivalent to 0.55 times of GDP per capita in 2022. The probability sensitivity analysis indicated that at a willingness-to-pay threshold of 3 times GDP per capita, most data points fall below the threshold line, suggesting that entrectinib is more cost-effective than crizotinib. The cost-effectiveness acceptability curve showed that at the three times GDP threshold, there is an 80% probability that entrectinib treatment is cost-effective compared to the crizotinib.

Conclusions: Entrectinib can improve patient health outcomes and is more cost-effective than crizotinib in the Chinese ROS1+ NSCLC population.

Keywords: Entrectinib, Crizotinib, Cost-effectiveness analysis

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MA14.07 Access Disparities to Lung Cancer Radiotherapy Across Brazil: An Observational Analysis

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Introduction: In Brazil, the equitable distribution of healthcare resources remains a challenge, particularly for high-complexity treatments like lung cancer radiotherapy. This observational study aims to evaluate the disparities in access to lung cancer radiotherapy across Brazil, specifically focusing on the distances patients must travel for treatment. Analyzing official data from 2019 to 2022, it seeks to quantify the geographical barriers impacting individuals needing radiotherapy.

Methods: Official data from 2019 to 2022 were collected from Brazil's national Outpatient Procedure Authorization (APAC) system in .dbc format and processed using Python. The dataset encompassed variables such as procedure type and year, patient demographics (including gender and race), residential city, treatment location (by state and region), and instances where treatment was received in a city different from the patient's residence. Distances to treatment centers were calculated using the Haversine formula, expressed in kilometers. This dataset was then integrated into a Power BI database for enhanced analysis. The official annual lung cancer case estimates were juxtaposed with the volume of radiotherapy procedures over the same timeframe to ascertain the utilization rate of radiotherapy. Statistical analysis employed the two-sided Student's t-test and 1-way ANOVA, setting significance at $p < 0.05$.

Results: Among the 13,184 lung radiotherapy procedures, we examined the distance information from 7,904 treatments that required traveling beyond the patient's city of residence. We did not consider the 5,280 treatments within the resident's town in the distance analysis. The national average distance traveled for radiotherapy access was 111.45 kilometers, with non-significant yearly variation ($p=0.719$). Notable regional disparities emerged, with average travel distances reaching 469.76 kilometers in the North, 239.60 kilometers in the Midwest, 152.90 kilometers in the Northeast, 78.24 kilometers in the Southeast, and 63.66 kilometers in the South ($p < 0.001$). At the state level, the disparity widened, ranging from 48.76 kilometers in Santa Catarina (South) to 1,354.54 kilometers in Roraima (extreme North) ($p < 0.001$). Racial disparities in travel distance were also evident; white patients traveled an average of 98.49 kilometers, whereas non-white patients traveled 120.67 kilometers ($p = 0.007$). Gender did not significantly impact travel distance, with females traveling an average of 109.54 kilometers compared to 112.86 kilometers for males ($p = 0.373$). Radiotherapy utilization rates for lung cancer varied regionally: North (12.00%), Northeast (13.49%), Midwest (14.56%), Southeast (14.47%), and South (18.14%), with $p=0.0007$. A higher average travel distance was significantly correlated with a lower radiotherapy utilization rate ($p < 0.05$).

Conclusions: The study uncovers significant geographical and racial disparities in access to lung radiotherapy in Brazil, especially affecting residents of less developed areas and non-white patients. The overall low rates of radiotherapy utilization for lung cancer across regions underscore the urgent need for strategic enhancements in healthcare infrastructure and the accessibility of lung cancer treatment services. The findings can contribute to policy discussions and healthcare planning to mitigate these barriers and enhance cancer care delivery across the nation.

Keywords: radiotherapy access, lung cancer, Brazil

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MA14.08 Revolutionizing Survival: The Real-World Impact of High-Cost Therapies on Advanced NSCLC

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Introduction: The advent of targeted therapy and immunotherapy has radically improved outcomes for advanced NSCLC, yet access hurdles persist due to medication costs. Propensity score analysis (PS) aids in assessing treatment effects in real-world settings. This study evaluates the impact of high-cost drugs on the overall survival (OS) among patients in a public Peruvian institution.

Methods: Retrospective observational study conducted at INEN from 2014 to 2022, including NSCLC patients who underwent systemic treatment for advanced disease at some point in their evolution. Patients were divided into 3 cohorts according to their access to high-cost drugs; A) patients who did not have access to targeted therapy or immunotherapy at all; B) patients who had access only to erlotinib and, C) patients who had access to osimertinib, alectinib or immunotherapy. Patients from cohort B and C may have received chemotherapy in other line of treatment and patients who received erlotinib followed by osimertinib were allocated to cohort C. OS was calculated from the start of systemic therapy for advanced disease until death, with living subjects censored at their last follow-up. To further assess the impact of these drugs vs chemotherapy we conducted a PS analysis using the nearest-neighbor matching method considering covariates likely to influence OS, including sex and smoking status; as well as age, ECOG, brain metastases (BM) and burden of disease at the initiation of systemic therapy for advanced disease.

Results: FIve-hundred patients were included: cohort A, 294; B, 118 and; C, 88. For the whole population, median age was 59, with 58.2% females, 4% had family history of lung cancer, 19.8% were former/current smokers, 22% were exposed to indoor wood smoke, 34% presented with ECOG PS≥2, and 86.4% had adenocarcinoma histology. At diagnosis 90.4% were at stage IV, 18% had oligometastases and, 25.3% had BM. Erlotinib, alectinib and pembrolizumab were used as 1L in 70.34%, 75% and 92% of patients, respectively. Osimertinib was only used after erlotinib in T790M+ cases, mostly in 2L (63.64%). Median OS (mOS) since the initiation of systemic treatment was 7.36m (6.38-8.71) for cohort A; 21.76m (18.74 - 27.12) for cohort B and 27.16m (19.00 - 50.66) for cohort C ($p < 0.001$). Within the latter, mOS was 46.52m for osimertinib, NR for alectinib and 16.08m for pembrolizumab. PS-adjusted Kaplan-Meier curves showed that the mOS for patients treated with any high-cost drug versus those who only received chemotherapy was 21.04 (16.90 - 31.0) vs 9.17m (6.77- 12.3). For EGFR-driven disease, the mOS for patients who received EGFR-TKI vs those who only received chemotherapy was 25.78 vs 6.67m ($p<0.001$). Due to the limited number of matches, analyzing ALK-driven disease was unfeasible. For driver-negative disease, mOS for patients treated with immunotherapy vs those who only received chemotherapy was 15.9 vs 10.7mp<0.001).

Conclusions: Access to standard-of-care drugs remains a challenge for Latin American NSCLC patients, affecting the choice of initial treatment. Our real-world data affirms that incorporating these high-cost medications significantly improves survival rates, thus, it is imperative to strive for expanding access to these treatments.

Keywords: high-cost drugs, survival, real-world

MA14.09 Disparities in Outcomes of Hospitalized Unhoused Patients with Lung Cancer

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Introduction: Lung cancer is a leading cause of cancer-related mortality worldwide, with outcomes significantly influenced by socioeconomic status, access to healthcare, and comorbid conditions. Unhoused individuals represent one of the most vulnerable populations affected by lung cancer, facing unique challenges that may worsen their health outcomes. This study aims to explore the disparities in clinical outcomes among hospitalized unhoused patients diagnosed with lung cancer. Understanding these disparities is crucial for highlighting the need for targeted interventions to improve care and outcomes for this marginalized population.

Methods: This study identified all hospitalized adults aged ≥18 with a lung cancer diagnosis in the 2017-2020 National Inpatient Sample. The primary endpoint was inpatient mortality, with secondary endpoints including cardiac arrest, intubation, length of stay, and total hospital charges. Multivariable logistic regression analysis was utilized to estimate clinical outcomes, with a significance threshold of $P<0.05$.

Results: The analysis included 1,615,135 hospitalizations for lung cancer, with 6,634 (0.4%) involving unhoused patients. A significantly higher proportion of unhoused patients were male (78.5%) and younger (mean age 61) compared to their housed counterparts (50.9% male, mean age 69). The racial composition also differed, with higher percentages of Black (23.8% vs. 12.2%) and Hispanic (6% vs. 4.5%) individuals among unhoused patients. Notably, unhoused patients exhibited higher rates of nicotine and alcohol use. Significant disparities in the prevalence of comorbidities such as anemia, diabetes mellitus, hypertension, systolic heart failure, and chronic obstructive pulmonary disease were observed, indicating poorer health status among the unhoused. Unhoused patients experienced longer hospital stays and incurred higher total charges compared to housed patients. Despite these challenges, the rates of cardiac arrest and intubation were comparable between the two groups. Interestingly, a higher rate of in-hospital mortality was observed in the housed population compared to homeless patients.

Conclusions: Unhoused individuals face not only higher rates of comorbidities and substance use but also longer hospital stays and increased healthcare costs. Despite these challenges, the comparable rates of intubations suggest that unhoused patients do receive critical care when hospitalized. However, the overall higher mortality rate among housed patients may reflect differences in access to palliative care services and end-of-life care. These findings call for a concerted effort to address the specific needs of unhoused individuals with lung cancer, aiming to improve their access to comprehensive care and ultimately, their clinical outcomes.

Keywords: Homeless patients, Lung Cancer, Health Disparity

Outcome	Lung Cancer, housed	Lung Cancer, unhoused	OR [95% CI]	IRR [95% CI]	p-value
Primary					
Death during hospitalization	138815 (8.6%)	415 (6.2%)	0.6 [0.51-0.85]	NA	P < 0.01
Secondary					
Cardiac arrest	19960 (1.2%)	70 (1.0%)	0.5 [0.25-1.01]	NA	P = 0.05
Intubation	74804 (4.6%)	309 (4.6%)	0.7 [0.5-0.96]	NA	P = 0.02
LOS, days (SD)	5.9 (0.01)	10.2 (0.3)	NA	1.56 [1.4-1.7]	P < 0.01
Total charge (SD)	17465 (91)	22976 (783)	NA	1.19 [1.1-1.29]	P < 0.01

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MA14.11 Duration of Intervals in the Care-Seeking Pathway of Lung Cancer in Nepal - Unraveling the Delays from Symptom Onset to Treatment Initiation

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Introduction: Nepal is a Lower Middle Income Country in South Asia. According to Global Cancer Statistics (2022), lung cancer is the commonest malignancy in Nepal and is the leading cause of cancer mortality. Over two-thirds of Nepal's lung cancer patients present at an advanced stage. Delays in the timely diagnosis and treatment of lung cancer limits opportunities for curative treatment and can cause adverse outcomes.

OBJECTIVES: The objective of this study was to determine the expected interval (in days) from first symptom onset to first healthcare visit (access interval), first health care visit to diagnosis (diagnostic interval) and diagnosis to treatment (treatment interval) as per the World Health Organization Guide to Cancer Early Diagnosis 2017 and to identify the reasons for delay.

Methods: A cross-sectional study was conducted at Bir Hospital, Nepal. Fifty-eight patients diagnosed as primary lung malignancy between July 2022 to December 2022 were enrolled and interviewed with a standardized questionnaire. The access, diagnostic and treatment intervals were calculated in days (Figure 1). The patients were inquired about the possible reasons for delay. Frequencies/percentages and mean/median were calculated for categorical and quantitative variables respectively.

Results: The mean age was 64.0 ± 11.1 years (Range 27-80 years). Male to female ratio was 1.6:1. Cough (44.0%) and chest pain (15.5%) were the most common initial symptoms, while hemoptysis (31.0%) and dyspnea (22.4%) were the commonest symptoms for seeking healthcare attention. The majority of patients had stage IV disease (60.3%) followed by stage III (37.8%). Squamous cell carcinoma was the commonest histology (46.5%), followed by adenocarcinoma (36.2%). None of the patients visited an oncologist as their first point of healthcare contact, 74.1% visited a trained medical professional, whereas the remaining 25.9% visited an informal healthcare provider. The common reasons for access delay was misinterpretation of initial symptoms (41.3%) and financial difficulties. Reasons for diagnostic delay include being treated for other diseases (36.2%), long waiting time for investigation and lack of timely referral. Reasons for treatment delay include treatment with alternative medicines and fear of adverse effects of cancer treatment.

Conclusions: Our study shows that there is significant delays in the access and diagnostic interval of patients with lung cancer. In order to reduce delays in the care-seeking pathway of lung cancer, we need to focus on developing awareness programs for the general population and encourage medical professionals to rule out lung cancer in patients with high index of clinical suspicion.

Keywords: lung cancer, diagnosis, treatment delay

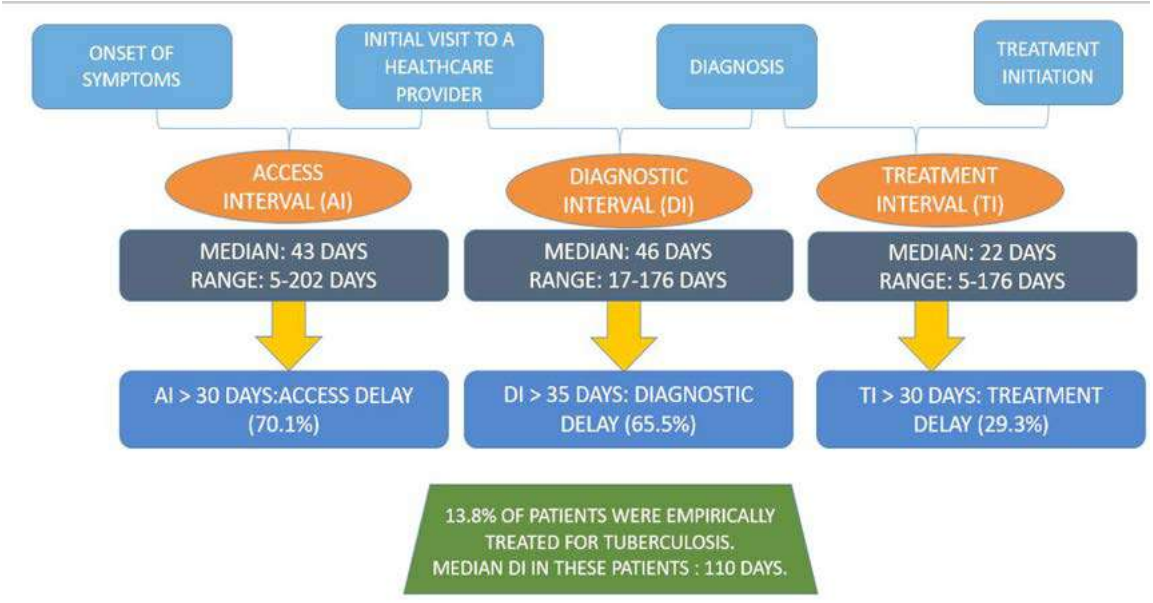

Figure 1: Duration of intervals in the care-seeking pathway of lung cancer.

MA14.12 Characterization of Sexual Dysfunction in Patients with Lung Cancer Undergoing Oncological Management: Results from the LUDICAS Study.

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Introduction: Advances in therapeutic options have increased the number of survivors patients with lung cancer. They may suffer from cancer treatment-related effects, including exacerbation of sexual dysfunction (SD), a condition that affects their quality of life and is under-recognized. Our aim was to describe the frequency, severity, and factors associated with SD in a cohort of Ibero-American patients.

Methods: Prospective, analytical, observational, multicenter study. Clinical and demographic variables were collected between July 2023 and February 2024. Sexual function was assessed with a validated questionnaire for each gender. Descriptive analysis, measures of differences in categorical variables by chi2 ($\chi 2$) and logistic regression analysis were performed.

Results: 448 patients from 24 hospitals were included. Of these, 277(61.83%) were male and 365(81.48%) had metastatic disease. 284(63.39%) reported occurrence of SD after starting anticancer treatment and 396(88.39%) considered it important to be evaluated for this condition.398(88.84%) were on active treatment, 47(10.93%) reported improvement of SD after discontinuation of therapy, but 275(63.95%) had never discontinued treatment. Population characteristics in Table 1. Statistically significant associations for global SD were female gender OR 3.53 (95% IC 1.88-6.6) p 0.001, smoking history OR 1.77 (95% IC 1.01-4.01) p 0.04 and obesity OR 1.7 (95% IC 1.01-3.16) p 0.05. Differences by gender and risk factors for SD are shown in Table 2.

Keywords: Sexual Dysfunction, Lung Cancer, Oncological treatment

Table 1. Characteristics of population

Variable	% (N 448)
Mean Age	60.44 years SD 7.29(range 28-70)
Residence country	
Spain	91.07% (408)
Colombia	4.02% (18)
Argentina	3.12% (14)
Portugal	1.79 % (8)
Education level	
Basic	37.28% (167)
Bachelor"s degree	32.59% (146)
University studies	23.44% (105)
Marital status	
Married/couple relationship	72.77% (326)
Divorced	12.28% (55)
Single	10.27% (46)
Smoking status	
Ex-smoker	57.14% (256)
Former smoker	25.45% (114)
Never smoker	16.74% (75)
Comorbidities	
No comorbidities	29.24% (131)
Hypertension	25.44% (114)
COPD	14.95% (67)
Type 2 Diabetes mellitus	10.26% (46)
Obesity	6.69% (30)
Tumoral response	
Partial	56.47% (253)
Stable disease	30.80% (138)
Follow up after curative treatment	7.81% (35)

Table 2. Differences by gender and risks factors for SD

Women% (n 171)	**Men% (n 277)**
Mean Age 60.07 years (range 28-70)	60.72 years (range 34-70)
Molecular Biomarkers	χ^2= 41.94 P 0.001
EGFR 26.31% (45) ***ALK*** 9.94% (17) ***KRAS*** 9.35% (16) ***BRAF*** 4.09% (7) ***ROS1*** 3.50% (6) **Negative** 36.25% (62)	***EGFR*** 9.38% (26) ***ALK***6.49% (18) ***KRAS***12.63% (35) ***BRAF***1.44% (4) ***ROS1***0.72% (2) **Negative**47.29% (131)
Type of treatment	χ^2= 18.9464 P 0.125
IO 22.22%(38) **Ch IO** 18.13%(31) **TKi** 29.24%(50) **Ch** 9.94%(17)	**IO** 27.44%(76) **Ch IO** 25.63%(71) **TKi** 15.52%(43) **Ch** 10.11%(28)
Severe Disturbances in sexual response phases	
Desire 41.52% (71) **Arousal** 45.78% (76) **Orgasm** 48.27%(70)	**Desire**17.45% (275) χ^2 = 31.2158 P 0.001 **Arousal**18.68% (51) χ^2= 36.8785 P 0.001 **Orgasm**27.20% (71) χ^2= 10.2500 P 0.001
Dissatisfaction with sexual function	
37.69% (49)	20.33% (54) χ^2= 41.8679 P 0.001
Absence of sexual activity during last 4 weeks	χ^2 = 6.0504 P 0.014
56,75% (97)	44.77% (124)
Risks factors for severe disturbances of sexual response phases	
Desire : Female gender OR 3.35 (95% IC 2.17 - 5.18) p 0.001	
Arousal : Female gender OR 3.67 (95% IC 2.38 - 5.65) p 0.001	
Orgasm : Female gender OR 3.72 (95% IC 2.48 - 5.60) p 0.001	
Risks factors for decreased sexual activity	
Female gender OR 1.98 (95% IC 1.17 - 3.19) p 0.01 Age > 65y OR 3.86 (95% IC 1.01 - 15.25) p 0.04	

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MA14.13 Analysis of Lung Cancer-Specific Patient-Reported Outcome Measures (PROMs): Results from the PRO4All Project

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Introduction: Assessment of Quality of Life (QoL) should be included among endpoints in oncology clinical trials. However, a plethora of distinct patient-reported outcome measures (PROMs) eligible for adoption in clinical trials exists. Therefore, we aimed to establish a lung cancer-specific comprehensive list of PROMs developed for clinical trials, investigating their unique properties and characteristics.

Methods: As part of the PRO4All project, we explored the following resources to identify lung cancer-specific PROMs: facit.org; eortc.org; eprovide.mapi-trust.org; ema.europa.eu (European Public Assessment Reports); published reviews. For each identified PROM, we collected information about name, type of questionnaire (self-reported, observer-reported or caregiver's report), recall period, number of items and presence of minimum clinically important difference (MCID) reference in literature. Finally, each item of various questionnaires was assigned to a specific list of predefined 38 outcome domains.

Results: We identified 386 PROMs in oncology clinical trials. Among them, 17/386 (4.4%) were lung cancer-specific. The sources were eprovide, facit.org, eortc.org or published reviews in 8 (47.1%), 6 (35.5%), 2 (11.8%) and 1 (5.8%) cases, respectively. Five (n=5/17, 29.4%) were variants of other questionnaires. The recall period was "last week", "today" or "treatment related" in 10 (58.8%), 2 (11.8%) and 2 (11.8%) cases, respectively. In 3 PROMs (17.6%), the recall period was not specified. All questionnaires were self-reported, none of them was observer-reported (e.g., by family members or caregivers). The median number of items for each PROM was 9 (range 4-38). We identified a total of 231 items. The most represented domains were: i) Respiratory, thoracic and mediastinal outcomes (n= 53 items); ii) General outcomes (n=39); iii) Emotional functioning/wellbeing (n=30); iv) Social functioning (n=28). Of note, only 4 (n=4/231, 0.2%) items, reported in 4 different questionnaires, were assigned to "Global QoL" domain. As a consequence, 13/17 (76.5%) PROMs did not include items regarding the Global QoL domain. Finally, an MCID reference was identified only for 4/17 (23.5%) questionnaires.

Conclusions: Our study led to the establishment of a detailed archive of available lung cancer-specific PROMs. Analysis of distinctive features and characteristics of the various instruments might help scientists and clinicians to select the most appropriate PROM for different research and clinical settings, as well as to develop more homogeneous and standardized methodologies to assess PROs in patients with lung cancer.

Keywords: Patient-reported outcome measures, PROMs, Quality of life

MA15 PARADIGM SHIFTS IN RECURRENCE ASSESSMENT AFTER SURGERY
TUESDAY, SEPTEMBER 10, 2024 - 15:00 - 16:15

MA15.03 Surveillance with [18F]FDG PET/CT of Lung Cancer after Curative Therapy; First Results of a Randomized Trial (SUPE_R)

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Introduction: Lung cancer has a high risk of recurrence after curative treatment, but patient outcomes may be improved if recurrences are detected at an early stage. Therefore, post-treatment surveillance with scheduled computed tomography (CT) for early detection and treatment of relapses is broadly recommended. The purpose of the SUPE_R trial is to assess if surveillance with [^{18}F]Fluorodeoxyglucose positron emission tomography ([^{18}F]FDG PET)/CT can improve recurrence detection, thereby increasing the proportion of recurrences that can be treated with curative intent.

Methods: This national, multi-center randomized controlled trial involved 750 patients who completed definitive therapy for stage IA-IIIC non-small cell lung cancer, recruited from most major hospitals in Denmark, from February 2019 to November 2021. Participants were randomized (1:1) into two groups: the control group, receiving a contrast-enhanced (ce)CT scan every three months (the current standard of care in Denmark), and the PET group, alternating between ceCT and contrast-enhanced [^{18}F]FDG PET/CT scans at three-month intervals. Both groups followed the assigned follow-up schedule for two years or until recurrence was detected.

Results: 373 patients were randomized to the PET group and 377 patients to the control group. Baseline characteristics were comparable across both groups (Table 1). Recurrence was observed in 83 patients (22%) in the PET group and 75 (20%) in the control group (p = 0.43). There was no significant difference in the proportion of recurrences treated with curative intent, with 46% in the PET group and 47% in the control group (p = 0.85). More recurrences were detected outside of scheduled surveillance in the control group compared to the PET group (23% vs 11%, p = 0.045). The 2-year disease-free survival rate was 74.6% (95% CI 71.4-78%) for all patients, with no difference between groups. A secondary, per-protocol analysis confirmed these results. There were fewer reported adverse events from biopsy procedures to diagnose recurrence in the control group, but the difference was not significant (incidence rate ratio = 0.76, 95% CI 0.57-1.01, p = 0.06).

Conclusions: These findings indicate that [^{18}F]FDG PET/CT, despite its increased sensitivity, may not offer a substantial advantage in the early detection of recurrence over standard CT. The impact of [^{18}F]FDG PET/CT on patient quality of life, cost-effectiveness and the role of liquid biopsies in this context remains to be analyzed and will be addressed in future publications. The SUPE_R trial is registered on Clinicaltrials.gov (NCT03740126).

Keywords: surveillance, NSCLC, FDG PET/CT

Table 1. Baseline Characteristics

	PET-Group	Control
N	373	377
Age - mean (SD)	69 (8.3)	69 (8.4)
Female - N (%)	219 (59)	223 (59)
WHO Performance Status - N (%)		
0	182 (49)	187 (50)
1-2	180 (48)	182 (48)
3-4	4 (1)	2 (1)
Unknown	7 (2)	6 (2)
Histology - N (%)		
Adenocarcinoma	274 (73)	272 (72)
Squamous Cell Carcinoma	88 (24)	84 (22)
Other	11 (3)	21 (6)
cTNM - N (%)		
IA	190 (51)	195 (52)
IB	79 (21)	70 (19)
IIA	12 (3)	11 (3)
IIB	45 (12)	44 (12)
IIIA	34 (9)	35 (9)
IIIB	11 (3)	18 (5)
IIIC	2 (1)	4 (1)
Treatment - N (%)		
Resection	289 (77)	302 (80)
w/ adj. chemotherapy	45 (12)	40 (11)
Chemoradiotherapy	25 (7)	26 (7)
Stereotactic body radiotherapy	59 (16)	49 (13)

MA15 PARADIGM SHIFTS IN RECURRENCE ASSESSMENT AFTER SURGERY
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MA15.04 MRD Predicts Clinical Outcomes of Patients with Early-Stage EGFR-Mutant NSCLC: A Post-Hoc Biomarker Analyses of EVIDENCE

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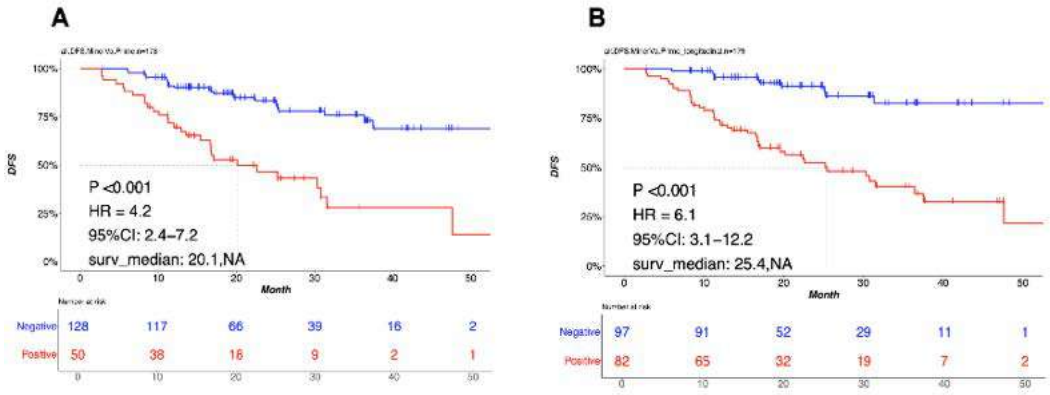
Introduction: EVIDENCE was a randomized, open-label, phase 3 trial that compared icotinib versus chemotherapy as adjuvant treatment for stage II-IIIA, resected EGFR-mutant NSCLC, demonstrating significantly improved DFS with adjuvant icotinib in this patient population. Here, we reported the preliminary post-hoc biomarker analyses of EVIDENCE, to investigate the value of ctDNA-based molecular residual disease (MRD) detection in adjuvant setting among patients with early-stage EGFR-mutant NSCLC.

Methods: A total of 179 patients were included in the biomarker-evaluable population (BEP), consisting of 108 in icotinib arm and 71 in chemotherapy arm. The ctDNA detection was based on a tumor-informed assay (MinerVa Prime) in which SNV, indel and fusion variants detected in tumor tissues using a whole exome panel supplemented with frequent lung cancer fusion genomic regions (WES-lc) were ranked and the top 50 variants per patient were selected in designing of customized panels and tracked in patient postoperative plasma samples to determine the MRD status during and after adjuvant therapy. The ctDNA status was estimated using a statistical model, where a significant difference from the intra-sample background ($p < 0.01$) is considered positive. The MinerVa Prime assay had been analytically validated to possess a specificity of 99.67% and a limit of detection (LoD) of 0.0025% at 30ng of input DNA.

Results: In the BEP, adjuvant icotinib significantly improved DFS compared with chemotherapy (HR 0.4, 95% CI 0.2-0.6). A total of 1432 blood samples from 179 patients were successfully profiled at different time points for further sequencing. In the landmark time point analysis, the positive landmark ctDNA detection rate was 28.6% in chemotherapy arm and 27.8% in icotinib arm, respectively. Patients with detectable MRD at landmark or longitudinal time points had worse DFS than those with undetectable MRD (landmark: HR 4.2, 95% 2.4-7.2, $p < 0.001$; longitudinal: HR 6.1, 95% 3.1-11.2, $p < 0.001$) (Fig 1). Similar results were observed in patients with stage II or stage III diseases or in patients treated with adjuvant icotinib or chemotherapy. Patients with early ctDNA response (landmark detectable MRD transformed to undetectable in first on-therapy time point) had better DFS than those with persistent detectable MRD. The sensitivity for longitudinal MRD for predicting the recurrence was 81.1% and the median lead time for patients with recurrence was 5.6 months.

Conclusions: The current post-hoc biomarker analyses from a phase 3 study highlight the role of MRD in adjuvant setting among patients with stage II-IIIA, completely resected EGFR-mutant NSCLC.

Keywords: molecular residual disease, EGFR-mutant NSCLC, adjuvant therapy



MA15 PARADIGM SHIFTS IN RECURRENCE ASSESSMENT AFTER SURGERY
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MA15.05 Follow-Up Update of Molecular Residual Disease in Localized Non-Small Cell Lung Cancer

J-T. Zhang[1], X. Gao[2], S-Y. Liu[1], Z. Jiao[2], S. Dong[1], Y. Pan[1], Q. Zhou[1], W-Z. Zhong[1], X-N. Yang[1], X. Yi[2], Y-L. Wu[1], [1]Guangdong Provincial People's Hospital, Guangdong Lung Cancer Institute, Guangzhou/CN ,[2]Geneplus-Beijing Institute, Beijing/CN

Introduction: The concept of molecular residual disease (MRD) in solid tumors is progressively gaining traction. Here, we present the updated follow-up from our prior study involving 261 patients with stage I-III non-small cell lung cancer (NSCLC), highlighting the negative predictive value of longitudinal MRD, which was determined to be 96.8%. We aim to validate our previous findings and clarify the clinical application of MRD for NSCLC.

Methods: As of December 31, 2023, the median follow-up for this cohort reached 34.6 months. An additional 296 follow-up blood samples (collected every 3-6 months post-surgery) were obtained for ctDNA-MRD testing, bringing the total number of follow-up blood samples to 1209. Longitudinal time points were defined as intervals of every 3-6 months since the landmark detection. The predictive value and sensitivity of longitudinal MRD were evaluated across various stages and recurrence patterns.

Results: In all, 77 cases (29.5%) recurred at the latest follow-up, with median disease-free survival 18.6 months. 83.1% of them had detectable MRD signals before recurrence, with a median lead time of 5.2 months (95%CI: 3.9-8.9 months). Overall, 190 patients (n=190/261, 72.8%) remained longitudinal undetectable MRD after surgery, and 177 of them kept disease-free, resulting in a negative predictive value of 93.2%. In contrast, 13 patients experienced recurrence while having longitudinal undetectable MRD, potentially influenced by two main clinical and non-clinical factors: brain-only metastases (n=7) and absence of blood samples within six months prior to recurrence (n=4).

Conclusions: With the support of updated follow-up, we strengthen the argument that longitudinal undetectable MRD could serve as a robust indicator for identifying those localized NSCLC patients are cured postoperatively.

Keywords: Circulating tumor DNA, Molecular residual disease, Non-small cell lung cancer

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MA15.07 Preliminary Analysis of Adjuvant Chemotherapy with Atezolizumab in Stage I-III Resected NSCLC and Clearance of ctDNA

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Introduction: The use of adjuvant immune checkpoint blockade (aICB) has demonstrated benefit in patients with early-stage, resectable non-small cell lung cancer (NSCLC) positive for PD-L1 expression. Unanswered questions remain regarding which patients derive benefit from aICB including patients with PD-L1 negative tumors and optimal duration of treatment. The use of circulating tumor DNA (ctDNA), as a measurement of minimal residual disease has been increasingly employed to monitor disease status outside of standard radiographic surveillance and has the potential to inform treatment decision-making and personalize treatment duration, although there is considerable variability in assay methodology and sensitivity.

Methods: We conducted a single-arm, multicenter, phase II trial of adjuvant cisplatin-based chemotherapy with concomitant atezolizumab every 3 weeks for 4 cycles followed by up to 13 additional cycles of atezolizumab alone for patients with resected Stage IB (tumors ≥4cm) - III NSCLC (8th ed) (NCT04367311). ctDNA was collected prior to initiating adjuvant therapy, at 3 months, 6 months, 9 months, and 30-days post completion of the study or every 3 months for 1 year after initiating treatment, for early discontinuation. The AVENIO Oncology Surveillance Test, a tumor-informed, germline-normalized panel-based assay was utilized with ctDNA-positivity (ctDNA+) defined as a detected index ≤0.1. The primary aim of the study was to estimate the percentage of ctDNA+ patients after surgery who had clearance following 4 cycles of adjuvant chemotherapy with atezolizumab plus up to 13 additional cycles of atezolizumab. The study enrollment closed in December 2023.

Results: At the time of this analysis, 59 patients were enrolled in the study with evaluable baseline ctDNA results available for 47 patients. Of the evaluable cohort, 0 (0%), 3 (6%), 20 (43%), 23 (49%), and 1 (2%) patients had Stage IB, IIA, IIB, IIIA and IIIB disease, respectively. 30 (64%) patients were non-squamous while 12 (26%) had squamous histology. 3 (6%) patients had adenosquamous and 2 (4%) patients had NSCLC NOS. PD-L1 expression included PD-L1 <1% (14 patients [30%]), 1-49% (17 patients [36%]) and ≥50% (14 patients [30%]). 2 patients (4%) had unknown PD-L1 expression. Based on the presence of variants identified on the ctDNA panel, 15 (32%) patients had ctDNA positivity at the baseline timepoint after surgical resection. Results from additional analyses, including 6-month disease-free survival and longitudinal on-treatment ctDNA clearance after 3 months will be available on all patients at the time of reporting updated results.

Conclusions: This preliminary analysis shows a substantial portion of patients are ctDNA positive after undergoing curative-intent surgical resection for early-stage NSCLC. Ongoing analysis has the potential to identify patients who obtain benefit from adjuvant systemic therapies and characterize ctDNA kinetics through the course of treatment.

Keywords: Adjuvant, Immune Checkpoint Blockade, circulating tumor DNA

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MA15.08 Ultrasensitive Blood Test for Early Lung Cancer: Integrating Fragmentomics and Mutational Signatures in cfDNA

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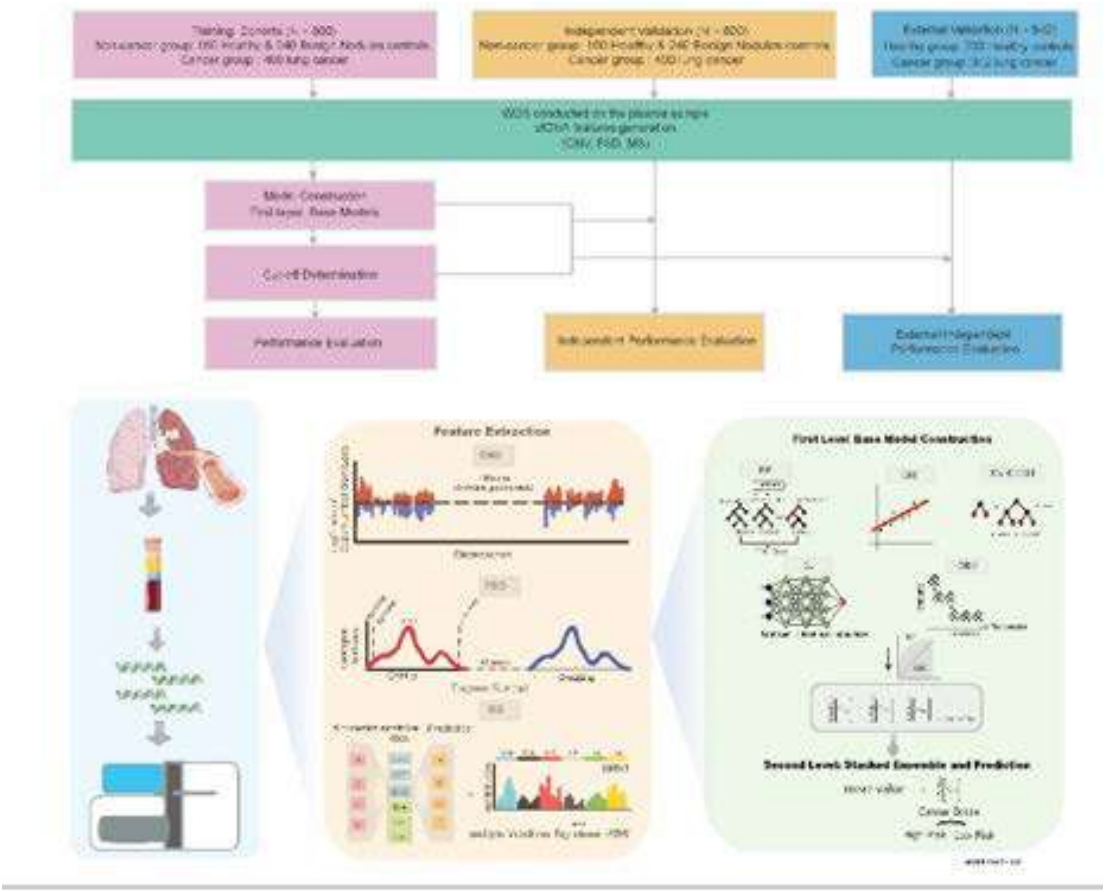
Introduction: Effective detection of lung cancer in the general population is critical to improve treatment outcomes and increase the 5-year survival rate. Despite the utility of Low Dose Computed Tomography (LDCT) as the standard screening method, its limitations in broad population applications necessitate the development of more accessible and sensitive detection strategies.

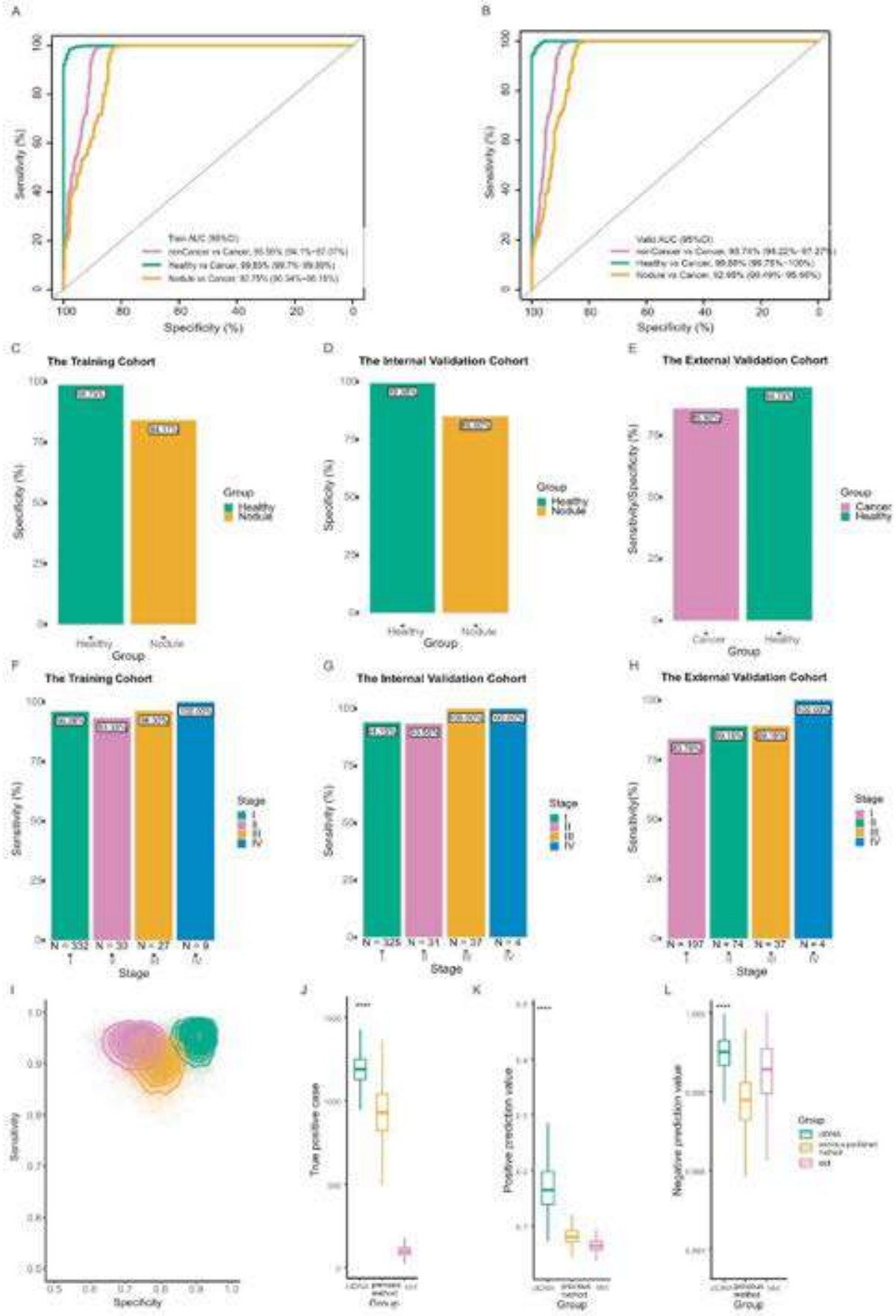
Methods: We explored the multi-omic profiles of circulating tumor DNA (ctDNA) and cell-free DNA (cfDNA) to distinguish between malignant lung cancer patients and non-cancer subjects using a blood-based assay. Employing whole-genome sequencing to characterize cfDNA, we developed a machine learning model based on integrated fragmentomic and mutational signatures (as shown in Figure1). This research encompassed two independent cohorts totaling 1,600 lung cancer patients and an equivalent number of control participants. These cohorts were subsequently divided into training and validation groups.

Results: The developed model demonstrated robust diagnostic performance, evidenced by an area under the curve (AUC) of 95.59% within the training cohort and 95.74% in the validation cohort (ad shown in Figure2). Remarkably, it maintained high efficacy across different cancer stages and histologies. External validation further substantiated the model's utility, achieving 85.9% sensitivity and 94.8% specificity in distinguishing cancer from non-cancer cases. Comparative analyses revealed that our ctDNA assay surpassed both LDCT and a previously established method in simulated population screenings, highlighting its superior diagnostic accuracy.

Conclusions: The developed ctDNA assay represents a groundbreaking advancement in the early detection of lung cancer, showcasing unparalleled sensitivity and specificity. Its ability to efficiently differentiate between cancerous and non-cancerous states in a non-invasive manner suggests a significant potential to complement existing LDCT screening protocols, thereby enhancing early detection rates and potentially improving survival outcomes in lung cancer patients.

Keywords: circulating tumor DNA (ctDNA), early lung cancer, machine learning




A
Sensitivity (%)
Specificity (%)
B
Sensitivity (%)
Specificity (%)
C
The Training Cohort
Specificity (%)
Group
Healthy
Nodule
D
The Internal Validation Cohort
Specificity (%)
Group
Healthy
Nodule
E
The External Validation Cohort
Sensitivity/Specificity (%)
Group
Cancer
Healthy
F
The Training Cohort
Sensitivity (%)
Stage
N = 332
N = 30
N = 27
N = 9
G
The Internal Validation Cohort
Sensitivity (%)
Stage
N = 325
N = 31
N = 27
N = 4
H
The External Validation Cohort
Sensitivity(%)
Stage
N = 107
N = 74
N = 37
N = 4
I
Sensitivity
Specificity
J
True positive case
K
Positive prediction value
Group
L
Negative prediction value
Group

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MA15.09 LCMC3: Long-Term Disease-Free and Overall Survival and their Association with ctDNA After Neoadjuvant Atezolizumab for NSCLC

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Introduction: LCMC3 (NCT02927301) was a Phase II, open-label, single-arm study in patients with resectable NSCLC that met its primary endpoint, with a 20% major pathological response (MPR) rate after neoadjuvant atezolizumab. We report final disease-free survival (DFS) and overall survival (OS) and their association with ctDNA status and clearance.

Methods: Patients who had resectable stage IB-IIIA or select IIIB NSCLC (AJCC, 8th edition), were ≥18 years of age, and had ECOG PS 0-1 received neoadjuvant atezolizumab 1200 mg IV every 3 weeks for 2 cycles, followed by surgery. Adjuvant chemotherapy, radiotherapy and/or adjuvant atezolizumab could then be given to patients without progression per investigator decision. The efficacy population included patients with a complete resection, MPR assessment, and without known EGFR/ALK alterations. ctDNA was collected at baseline, post-neoadjuvant atezolizumab and post-surgery. ctDNA was measured using the tissue-informed AVENIO Oncology Surveillance Test, with ctDNA-positive (ctDNA+) defined as ctDNA detection index ≤0.1. The adjuvant atezolizumab safety analysis population comprised patients who received ≥1 dose of adjuvant atezolizumab.

Results: Of 181 enrolled patients with NSCLC, 137 (76%) composed the efficacy population, of whom 53 (29%) received adjuvant atezolizumab. As of October 13, 2023, median follow-up was 3.1 years (range, 0.2-4.9). The median DFS and OS were not reached and 4-year DFS and OS rates were 70% and 82%, respectively. For patients with stage I/II vs III disease, neither DFS nor OS were statistically different. DFS rates were higher in patients with MPR vs no MPR (4-year, 86% vs 67%; P=0.047) and those receiving adjuvant atezolizumab vs no adjuvant atezolizumab (3-year, 83% vs 64%; P=0.023; Table). Patients with post-surgery ctDNA-negative (ctDNA−) vs ctDNA+ status had improved DFS (HR, 0.29; 95% CI: 0.12, 0.75; P=0.006; n=75). Comparing patients with post-surgery clearance vs no clearance, DFS (HR, 0.25; 95% CI: 0.08, 0.78; P=0.010) and OS (HR, 0.26; 95% CI: 0.07, 0.99; P=0.034; n=53; Table) were both improved. Treatment-related adverse events (TRAEs) in patients receiving adjuvant atezolizumab (n=57) occurred in 65%, with TRAEs leading to adjuvant atezolizumab discontinuation occurring in 18%.

Conclusions: At final analysis, having MPR and receiving adjuvant atezolizumab continued to be associated with DFS benefit. The clinical and survival outcomes for stage III disease were similar to stage I/II. Post-surgery ctDNA clearance was associated with longer OS. Additionally, longer DFS was seen with post-surgery ctDNA− status and clearance. These data suggest that MPR, ctDNA status, and ctDNA clearance may serve as biomarkers for risk stratification.

Keywords: atezolizumab, neoadjuvant, ctDNA

Efficacy population (n=137)[a]					HR (95% CI)	*P* value[b]
DFS						
Clinical stage, 4-y	I or II (n=70) 75%		III (n=67) 64%		0.71 (0.38, 1.34)	0.286
MPR status, 4-y	Yes (n=29) 86%		No (n=108) 67%		0.37 (0.13, 1.03)	**0.047**
Treatment with adjuvant atezolizumab, 3-y	Yes (n=53) 83%		No (n=84) 64%		0.44 (0.21, 0.91)	**0.023**
OS						
Clinical stage, 4-y	I or II (n=70) 82%		III (n=67) 81%		0.93 (0.42, 2.08)	0.864
MPR status, 4-y	Yes (n=29) 93%		No (n=108) 79%		0.30 (0.07, 1.29)	0.088
Treatment with adjuvant atezolizumab, 3-y	Yes (n=53) 89%		No (n=84) 77%		0.48 (0.19, 1.21)	0.112
ctDNA biomarker-evaluable population[c]						
DFS, 3-y						
ctDNA status (at timepoint)	ctDNA−		ctDNA+			
Baseline[d]	n=20 75%		n=70 69%		0.77 (0.29, 2.02)	0.589
Post-neoadjuvant atezolizumab[e]	n=35 80%		n=54 68%		0.58 (0.24, 1.38)	0.210
Post-surgery[f]	n=66 74%		n=9 30%		0.29 (0.12, 0.75)	**0.006**
ctDNA clearance status (from baseline to timepoint)	Clearance		No clearance			
Post-neoadjuvant atezolizumab[g]	n=21 85%		n=44 63%		0.32 (0.09, 1.10)	0.057
Post-surgery[h]	n=47 72%		n=6 33%		0.25 (0.08, 0.78)	**0.010**
Post-surgery ctDNA clearance status by MPR status	MPR yes	MPR no	MPR yes	MPR no	MPR no: ctDNA clearance yes vs no	
	n=10 100%	n=37 64%	n=0 NE	n=6 33%	0.33 (0.11, 1.02)	**0.006**
OS, 3-y						
ctDNA status (at timepoint)	ctDNA−		ctDNA+			
Baseline[d]	n=20 75%		n=70 79%		1.21 (0.44, 3.36)	0.713
Post-neoadjuvant atezolizumab[e]	n=35 82%		n=54 77%		0.76 (0.29, 2.03)	0.582
Post-surgery[f]	n=66 81%		n=9 53%		0.36 (0.12, 1.12)	0.065
ctDNA clearance status (from baseline to timepoint)	Clearance		No clearance			
Post-neoadjuvant atezolizumab[g]	n=21 90%		n=44 74%		0.36 (0.08, 1.61)	0.161
Post-surgery[h]	n=47 82%		n=6 50%		0.26 (0.07, 0.99)	**0.034**
Post-surgery ctDNA clearance status by MPR status	MPR yes	MPR no	MPR yes	MPR no	MPR no: ctDNA clearance yes vs no	
	n=10 100%	n=37 77%	n=0 NE	n=6 50%	0.34 (0.09, 1.30)	**0.039**

NE, not evaluable. [a]For clinical data, 4-y data is reported, except where <10 patients were still alive. [b]Log-rank test. [c]The biomarker-evaluable population included patients in the efficacy population with ≥1 ctDNA sample. [d]Patients had a baseline ctDNA sample (n=90). [e]Patients had a post-neoadjuvant atezolizumab ctDNA sample (n=89). [f]Patients had a ctDNA sample ≤12 weeks post-surgery (n=75). [g]Patients evaluable for post-neoadjuvant atezolizumab ctDNA clearance (n=65). [h]Patients evaluable for post-surgery ctDNA clearance (n=53).

MA15 PARADIGM SHIFTS IN RECURRENCE ASSESSMENT AFTER SURGERY
TUESDAY, SEPTEMBER 10, 2024 - 15:00 - 16:15

MA15.11 Neoadjuvant Sintilimab plus Chemotherapy in EGFR-mutant NSCLC Followed by adjuvant Osimertinib or Observation: A Phase II CTONG2104 Trial

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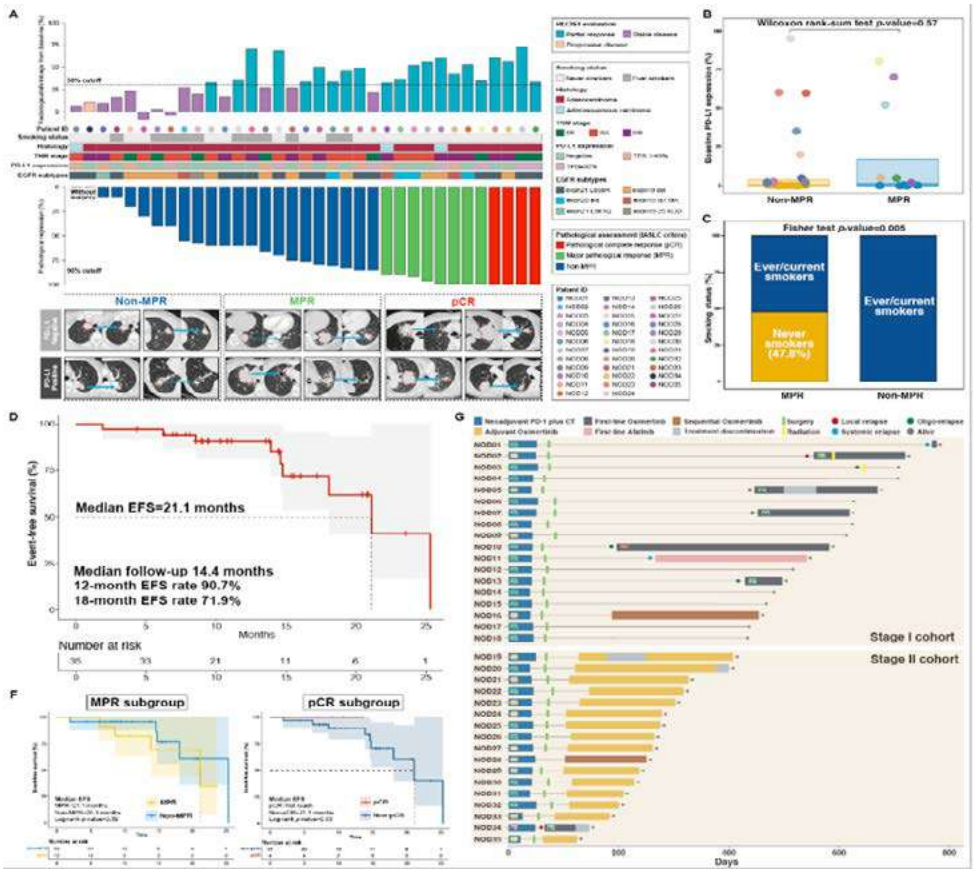
Introduction: Neoadjuvant immunotherapy plus chemotherapy in EGFR-mutant NSCLC remained poorly explored and how it influenced subsequent use of EGFR-TKIs during disease progression or adjuvant setting was unclear. Herein, we report the prespecified analysis of a phase 2 prospective trial (NCT05244213).

Methods: This is an open-label, phase 2 prospective trial with Simon's two-stage design. 35 patients with stage IIB-IIIB (N2) and EGFR mutation including non-sensitive mutations were enrolled, and up to 3 cycles sintilimab plus chemotherapy would be provided followed by surgery and observation for stage I cohort or adjuvant osimertinib for stage II cohort.

Results: As of July 15, 2024, 35 patients had been consecutively enrolled, with 33 completing neoadjuvant treatment and surgery, while the others did not undergo surgery. Common treatment-related adverse events (TRAEs) included alopecia, nausea, and paresthesia, with 17.1% of patients experiencing grade 3-4 granulocytopenia. The confirmed ORR was 60.0% (21/35), with one patient showing PD. Among patients who received neoadjuvant immunochemotherapy, the MPR and pCR rates were 34.3% (12/35) and 11.4% (4/35), respectively. Baseline PD-L1 expression did not correlate with MPR status (p=0.57), but patients without a smoking history exhibited higher MPR rate (p=0.005). With a median follow-up of 14.4 months for the two-stage cohorts, 9 out of 35 (25.7%) patients experienced disease relapse/progression. The median event-free survival (EFS) was 21.1 months, with 12- and 18-month EFS rates of 90.7% and 71.9%, respectively. Despite that no significant difference in EFS based on pathological response status, patients who achieved pCR showed a favorable trend in EFS. No OS events were observed in this study. The ORR for all patients with relapsed/progressive disease who were subsequently treated with EGFR-TKIs was 100%, with one patient achieving CR. The safety profile for patients treated with subsequent EGFR-TKIs or adjuvant osimertinib after neoadjuvant immunochemotherapy was well tolerated. Common TRAEs included diarrhea, rash, and mouth ulcers. In the stage II cohort treated with adjuvant osimertinib, 4 (23.5%) patients experienced grade 3-4 ALT/AST elevation, while no grade 3-4 TRAEs were observed in patients from the stage I cohort treated with osimertinib after disease relapse.

Conclusions: Neoadjuvant sintilimab plus chemotherapy could be an optional treatment modality in selected EGFR-mutant NSCLC without adding severe toxicity to adjuvant or subsequent EGFR-TKIs. Long-term follow-up was warranted to further clarify the role of additional neoadjuvant immunochemotherapy in EGFR-mutant NSCLC.

Keywords: NSCLC, EGFR, Neoadjuvant



MA15 PARADIGM SHIFTS IN RECURRENCE ASSESSMENT AFTER SURGERY
TUESDAY, SEPTEMBER 10, 2024 - 15:00 - 16:15

MA15.12 Aumolertinib as Adjuvant Therapy in Resectable I-III EGFR-Mutant NSCLC : Also Effective in Patients with High-Risk Relapse Factors

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Introduction: Early NSCLC patients(pts) with high-risk relapse factors such as micropapillary/solid tumor/complex glandular component (MP/S/CGC), spread through air space (STAS), visceral pleural invasion (VPI) and vascular invasion (VI) tend to have a poor prognosis. Our study aimed to investigate the efficacy of aumolertinib as adjuvant therapy for stage I-III EGFR-mutant NSCLC undergoing R0 resection, and the impact of high-risk relapse factors on the clinical benefit.

Methods: We enrolled EGFR-mutant NSCLC pts who underwent radical surgery and received a daily dose of aumolertinib 110 mg. The adjuvant duration was 36 months, if tolerable. The results of gene detection and immunohistochemistry were also recorded. We evaluated the disease-free survival (DFS), safety and efficacy of aumolertinib in pts with high-risk relapse factors.

Results: This study analyzed 113 cases of pathologically confirmed adenocarcinoma, EGFR positive mutation (19Del or L858R), and stage I-III NSCLC pts from August 2021 to December 2023. At the data cutoff, 91 pts (80.5%) have been followed up for ≥ 6 months, 21 pts (18.6%) have been followed up for ≥ 18 months. The 1-year DFS rate is 100%, while the 2-year DFS rate is 94.1%. Among them, 44 pts had at least one high-risk relapse factor,including 29 patients with MP/S/CGC (65.9%), 9 patients with STAS (20.5%), 20 patients with VPI (45.5 %), and 5 patients with VI (11.4%). 33 pts (75%) were followed up for ≥ 6 months, 26 pts (59%) were followed up for ≥ 12 months. Median follow-up time was 12.5 months. At 12 months, 100% pts were alive and disease-free. Based on adjuvant targeted therapy, there was no significant difference in postoperative recurrence between the population with the high-risk relapse factors and the overall population in one year. During the treatment, 24 pts (21.2%) had treatment-related adverse events (TRAEs) of any grade, such as mild rash and diarrhea. No grade≥3 adverse events occurred. No pts withdrew from therapy due to adverse drug reactions.

Conclusions: This study suggested that aumolertinib had good efficacy and a tolerable safety profile as adjuvant therapy in resectable EGFR-mutant NSCLC,specially in patients with high-risk relapse factors. Our study is still ongoing to expand the cohort of pts with high-risk pathologic factors and extend the follow-up period to determine longer-term outcomes.

Keywords: Adjuvant Targeted Therapy, High-risk Relapse Factors, Aumolertinib

MA15 PARADIGM SHIFTS IN RECURRENCE ASSESSMENT AFTER SURGERY
TUESDAY, SEPTEMBER 10, 2024 - 15:00 - 16:15

MA15.13 Furmonertinib as Adjuvant Therapy for Completely Resected Stage IA with High-Risk Factors and IB NSCLC Patients with EGFR Mutations

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Introduction: Furmonertinib (AST2818) is a highly brain-penetrant, third-generation EGFR tyrosine kinase inhibitor (TKI), which has been approved for the first-line treatment of patients with 19Del or L858R mutations and treatment of patients with T790M mutations whose disease has progressed on or after EGFR TKI therapy. A retrospective analysis has indicated good efficacy and safety of furmonertinib as adjuvant therapy for completely resected stage IA2 to IIIB NSCLC patients with EGFR mutations (19Del, L858R, G719A and Ex20ins), but there are no prospective evidence of furmonertinib as adjuvant therapy for completely resected NSCLC. Here we firstly report the efficacy and safety of furmonertinib as adjuvant therapy for completely resected stage IA with high-risk factors and IB NSCLC patients with EGFR mutations in a prospective, multi-center, single-arm study (NCT05445310).

Methods: In this prospective, multi-center, single-arm, phase II study, 114 patients will be enrolled, completely resected stage IA with high-risk factors and stage IB NSCLC patients with EGFR mutations (19Del, L858R and uncommon mutations except for Ex20ins) will receive furmonertinib 80mg orally once daily for 3 years. Staging is determined according to the eighth edition of the Cancer Staging Manual of the AJCC. The primary endpoint is the disease-free survival (DFS) rate at 3 years. The secondary endpoints are median DFS, overall survival (OS) rate at 3 years, median OS, and safety. The exploratory endpoints are the changes of molecular residual disease (MRD) and the relations between the efficacy and MRD status.

Results: From August 2022 to March 2024, there were 32 completely resected NSCLC patients enrolled. The median follow-up was 311.5 days, baseline characteristics were as follows, the median age was 60 years (range: 44-70), male 43.8%, stage IA 56.3% (IA1 3.1%, IA2 34.4%, IA3 18.8%), all stage IA patients had at least one high-risk factor, the high-risk factors mainly included micropapillary (55.6%), solid component (33.3%) and spread through air spaces (33.3%), EGFR mutations were 19Del (25.0%), L858R (65.6%), G719A (3.1%) and L861Q (6.3%). At data cut-off March 20.2024, all patients continued to receive furmonertinib and no disease recurrence. There were 12 postoperative patients successfully detected by MRD assay, all the patients' MRD were negative. No grade 3 or higher treatment related adverse events (TRAEs) occurred. The most common TRAEs (≥10%) were skin chapping 25.0%, rash 21.9%, and oral ulcer 18.8%. Dose interruption due to TRAE was reported in one patient. There was no incidence of dose reductions, treatment discontinuation or deaths due to TRAEs.

Conclusions: Furmonertinib 80mg orally once daily has shown potential efficacy and excellent safety as adjuvant therapy for completely resected stage IA with high-risk factors and IB NSCLC patients with EGFR mutations. Patients were well tolerated and the TRAEs were consistent with previous studies.

Keywords: Furmonertinib, Stage I NSCLC, Adjuvant therapy

MA16 STRATEGIES BEYOND CURRENT IMMUNOTHERAPIES
TUESDAY, SEPTEMBER 10, 2024 - 15:00 - 16:15

MA16.03 Survival Outcomes in Single Versus Double Immune Checkpoint Inhibitor in Advanced Non-Small Cell Lung Cancer: A Meta-Analysis

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Introduction: Immune checkpoint inhibitors (ICI) with or without chemotherapy (CMT) are the initial standard of care in patients with advanced non-small cell lung cancer (NSCLC) without actionable mutations. This meta-analysis was conducted to evaluate the survival benefit of ICIs based on the number of ICIs used in the first-line regimen.

Methods: Articles with search terms related to ICI and NSCLC were evaluated from Medline, Embase, and CENTRAL databases. Eligible studies must be randomized controlled studies of patients with advanced NSCLC in the first-line setting. At least one arm must receive ICI with or without CMT, and the other must receive CMT alone. Hazard ratios (HR) for overall survival (OS) and progression-free survival (PFS), along with their 95% confidence intervals (CI), were collected and pooled using the generic-inverse variance method. Subgroup analyses were performed based on the number of ICIs used (single vs double).

Results: In total, 21 studies were included in the meta-analysis. OS and PFS in patients with negative PD-L1 were similar for single versus double for squamous (pooled HR for OS 0.82; 95%CI 0.71-0.96 and 0.72; 95%CI 0.57-0.91, and PFS 0.63; 95CI 0.53-0.75 and 0.60; 95%CI 0.42-0.86, respectively) and nonsquamous (pooled HR for OS 0.82; 95%CI 0.74-0.91 and 0.72; 95%CI 0.61-0.86, and PFS 0.70; 95%CI 0.62-0.78 and 0.76; 95%CI 0.62-0.94, respectively) histological subtypes. Similarly, no survival outcome distinctions based on the number of ICI in the regimen were noted in the positive PD-L1 subgroup in both histological subtypes (Figure 1A-B). OS and PFS benefits also did not differ based on any KRAS, KRAS G12C, or STK11 mutations. However, patients with KEAP1 mutation had improved OS and PFS with double ICI (pooled HR for OS 0.41; 95%CI 0.25-0.67 and PFS 0.48; 95%CI 0.26-0.88) but not single ICI (pooled HR for OS 0.84; 95%CI 0.58-1.22 and PFS 0.97; 95%CI 0.72-1.32) (Figure 1C).

Conclusions: Double ICI did not confer improved survival outcomes compared to single ICI for advanced non-small cell lung cancer based on PD-L1 status, histological subtype, or KRAS and STK11 mutations. However, patients with KEAP1 mutations may benefit from double ICI therapy.

Keywords: Immunotherapy, Advanced NSCLC, Dual immune checkpoint inhibitor

MA16 STRATEGIES BEYOND CURRENT IMMUNOTHERAPIES
TUESDAY, SEPTEMBER 10, 2024 - 15:00 - 16:15

MA16.04 Radiomic Biomarkers Predict Response to Immunotherapy Rechallenge in Recurrent NSCLC after Chemoradiation and Durvalumab

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Introduction: Over 50% of patients with unresectable stage III non-small cell lung cancer (NSCLC) experience recurrence within two years of receiving chemoradiation (CRT) and consolidative durvalumab. Our prior study revealed a median progression-free survival (mPFS) of 6.1 months in those rechallenged with pembrolizumab-based regimens, suggesting suboptimal responses with IO for recurrent NSCLC (rNSCLC). However, PFS varied widely (0.2 to 36.8 months) without discernible differences in patient characteristics or biomarkers (e.g., PD-L1 expression, KRAS mutation status, etc.), indicating that a subset of patients with rNSCLC derive benefit from pembrolizumab. We therefore sought to identify radiomic biomarkers derived from CT images at the time of recurrence that are capable of predicting response to IO rechallenge.

Methods: In this retrospective study at the Cleveland Clinic Foundation, 45 cases of rNSCLC with measurable lung lesions on CT scans were analyzed. All patients were treated with CRT and durvalumab prior to disease recurrence and subsequently received pembrolizumab ± chemotherapy. CT images at the time of recurrence were scrutinized for radiomic signatures predicting response to IO rechallenge. Based on PFS, patients were categorized as “responders” (PFS ≥ 6 months) or “non-responders” (PFS < 6 months). Utilizing 860 texture features, a linear discriminant analysis classifier (LDA) predicted response through 100 iterations of threefold cross-validation, with performance assessed using the area under the curve (AUC). A LASSO Cox regression model, for PFS prediction, derived a multivariate radiomic signature, providing risk scores to categorize patients as high or low risk based on the median.

Results: The mRMR method identified the top five predictive intra/peritumoral radiomic features. An LDA classifier, utilizing these features, effectively discriminated between responders and non-responders (AUC 0.87). The radiomic risk score was determined by applying a linear combination of the five most significant features selected through the LASSO method, each assigned corresponding coefficients. Employing a multivariate Cox proportional hazards model that incorporates clinicopathologic variables (including age, sex, race, smoking history, pack-year, and tumor histologic subtype) along with radiomic features, the radiomics signature demonstrated a significant association with PFS (HR: 4.5; 95% CI: 2.84-6.7; P = 0.003).

Conclusions: Textural features extracted from both within and outside malignant nodules on CT images of individuals with rNSCLC, who previously received concurrent CRT and consolidative durvalumab, proved to be predictive of PFS and responses to pembrolizumab ± chemotherapy. Radiomic biomarkers may play a key role in identifying a subset of patients with rNSCLC who would derive benefit from IO rechallenge while sparing others from unnecessary toxicity. Further validation of these quantitative image-based biomarkers in multiple, independent, multi-institutional cohorts is essential.

Keywords: Radiomics, Immunotherapy, Non small cell lung cancer

MA16 STRATEGIES BEYOND CURRENT IMMUNOTHERAPIES
TUESDAY, SEPTEMBER 10, 2024 - 15:00 - 16:15

MA16.05 PIEZO1+ Caner-associated Fibroblasts Shape an Inert Microenvironment to Suppress Anticancer Immunity in Non-Small Cell Lung Cancer

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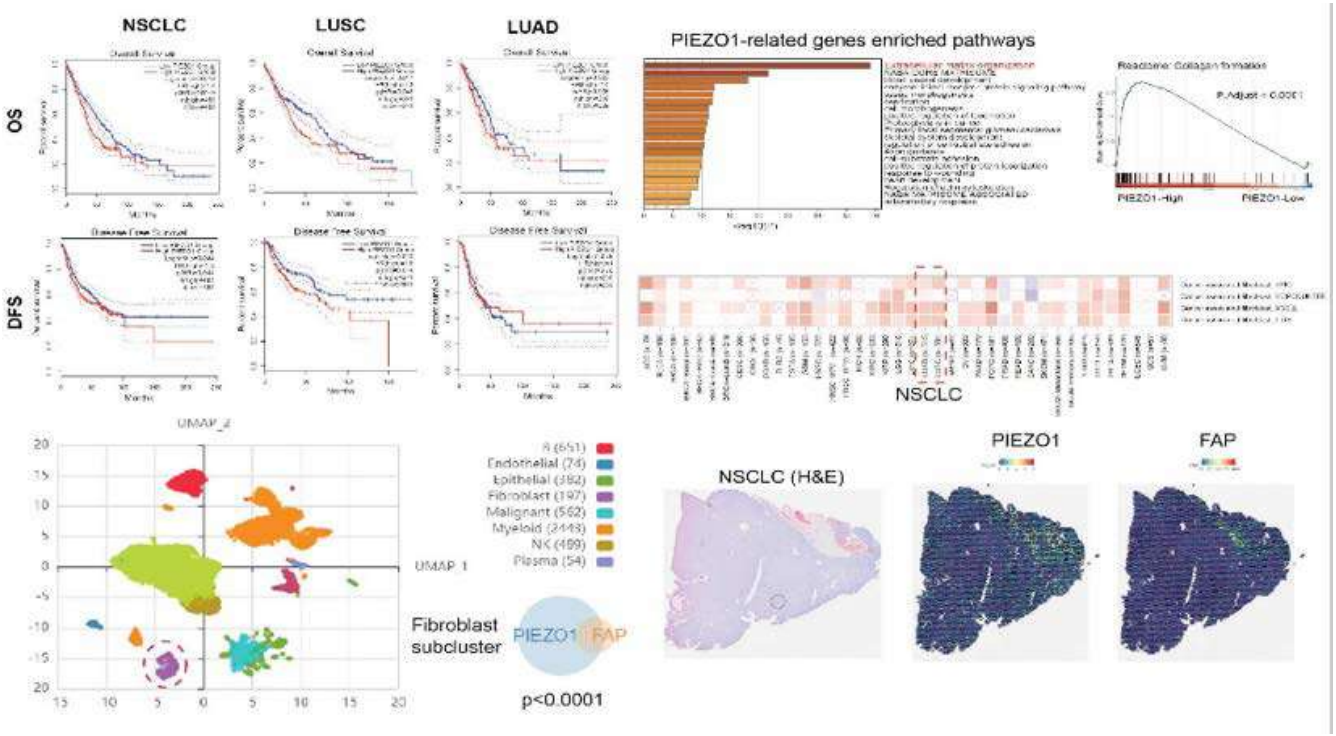
Introduction: Immune checkpoint inhibitors (ICIs) have shown significant improvements over chemotherapy in non-small cell lung cancer (NSCLC). However, cancer-associated fibroblasts (CAFs) can lead to immunotherapy resistance, and PIEZO1 is highly expressed in CAFs. Therefore, we aim to explore the impact of PIEZO1+ CAFs on the antitumor immunity in NSCLC.

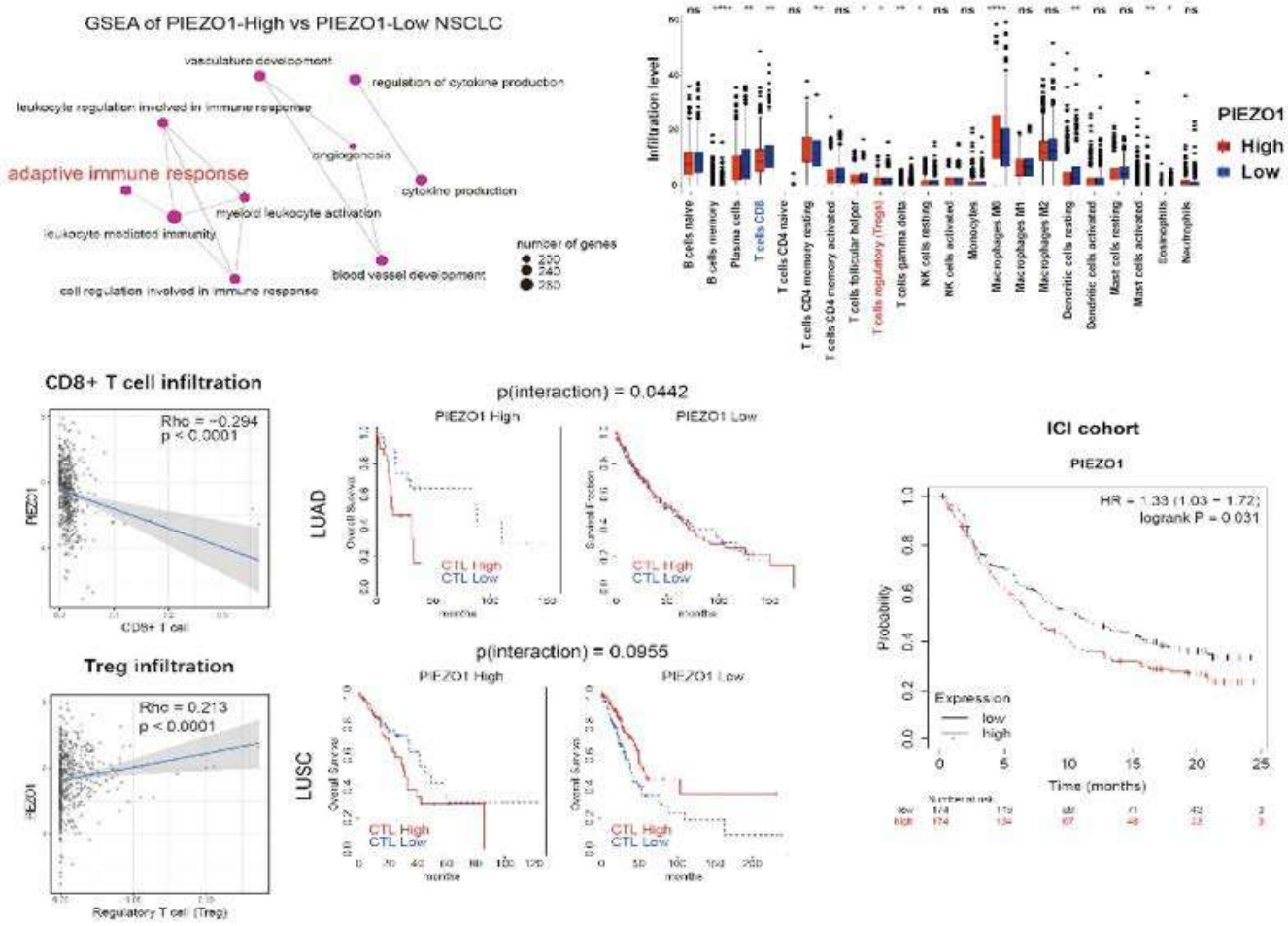
Methods: Transcriptomic data were utilized to analyze the prognostic effect of PIEZO1 in NSCLC, followed by pathway enrichment and immune infiltration analysis to explore downstream signalings. Spatial and cellular distribution of PIEZO1 in NSCLC microenvironment was investigated using single-cell and spatial transcriptomics data. The interaction between PIEZO1 and cytotoxic lymphocyte activity was analyzed to explore its immunoregulatory effect. An immunotherapy clinical cohort was collected to explore the relationship between PIEZO1 and ICI response.

Results: High PIEZO1 expression yielded poor prognosis in NSCLC, regardless of overall survival and disease-free survival. PIEZO1-related genes were significantly enriched in extracellular matrix remodeling and collagen biosynthesis pathways. Tumors with higher PIEZO1 expression yielded more CAF infiltration compared with PIEZO-low counterparts. Single-cell profiling of NSCLC revealed co-expression between PIEZO1 and CAF-secreting protein FAP. Spatial transcriptomics data suggested that PIEZO1 and FAP were co-localized in the fibrous components of NSCLC microenvironment (Fig 1). The infiltration of CD8+ T cells was significantly reduced in PIEZO1-high tumors, accompanied by an increase of regulatory T cells. Interaction analysis between PIEZO1 and cytotoxic lymphocyte activity indicated that the antitumor effect of cytotoxic lymphocytes was dependent on PIEZO1 expression. Survival analysis of the ICI cohort demonstrated significantly shorter overall survival in PIEZO1-high patients compared to those with low expression (Fig 2).

Conclusions: In NSCLC, PIEZO1+ CAFs shaped an inert microenvironment by potentially reversing the antitumor effect of cytotoxic lymphocytes, thereby inducing poor prognosis and immunotherapy resistance in NSCLC. Interventions targeting PIEZO1+ CAFs may represent a new strategy to enhance ICI efficacy in NSCLC.

Keywords: non-small cell lung cancer (NSCLC), cancer associated fibroblast (CAF), tumor microenvironment (TME)




GSEA of PIEZO1-High vs PIEZO1-Low NSCLC
vasculature development
regulation of cytokine production
leukocyte regulation involved in immune response
angiogenesis
adaptive immune response
cytokine production
myeloid leukocyte activation
leukocyte mediated immunity
blood vessel development
cell regulation involved in immune response
number of genes
Infiltration level
PIEZO1
High
Low
B cells naive
B cells memory
Plasma cells
T cells CD8
T cells CD4 naive
T cells CD4 memory resting
T cells CD4 memory activated
T cells follicular helper
T cells regulatory (Tregs)
T cells gamma delta
NK cells resting
NK cells activated
Monocytes
Macrophages M0
Macrophages M1
Macrophages M2
Dendritic cells resting
Dendritic cells activated
Mast cells resting
Mast cells activated
Eosinophils
Neutrophils
CD8+ T cell infiltration
Rho = −0.294
p < 0.0001
PIEZO1
CD8+ T cell
p(interaction) = 0.0442
PIEZO1 High
PIEZO1 Low
LUAD
Overall Survival
Survival Fraction
CTL High
CTL Low
months
Treg infiltration
Rho = 0.213
p < 0.0001
Regulatory T cell (Treg)
p(interaction) = 0.0955
LUSC
ICI cohort
PIEZO1
HR = 1.33 (1.03 − 1.72)
logrank P = 0.031
Probability
Expression
low
high
Time (months)

MA16 STRATEGIES BEYOND CURRENT IMMUNOTHERAPIES
TUESDAY, SEPTEMBER 10, 2024 - 15:00 - 16:15

MA16.07 A First in Human (FIH), Phase 1 Open Label, Dose Escalation and Expansion Study of CTM103, a LNP MRNA Encoding an IL2Rß? Selective Il-2v, As Monotherapy and in Combination with Pembrolizumab, in Patients with Advanced Solid Tumors

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Introduction: CTM103 is an LNP mRNA encoding an IL2R$\beta\gamma$ selective IL-2v derivative fused with Human Serum Album. Preclinically, the novel LNP mRNA platform allowed expression and therefore extended plasma half-life of IL2v in animal models, which is not achieved with other protein-based IL-2 drugs. CTM103 stimulated significant and sustained expansion of CD8 T cells for more than three weeks, with minimal expansion of regulatory T cells. Moreover, CTM103 demonstrated superior efficacy than IL-2 based drugs in multiple cancer models and has an excellent safety profile in rodents and non-human primates. Therefore, the novel design of CTM103 has the potential to fully unleash the antitumor effects of the IL-2 pathway while mitigating unwanted toxicity.

Methods: This first-in-human, open label phase 1 study evaluates the safety, tolerability, and initial efficacy of CTM103 with or without pembrolizumab in patients with advanced solid tumors. The design includes two portions of the study: Parts A, CTM103 monotherapy in which patients receive intravenous CTM103 once every 3 weeks (Q3W) and Part B in which patients receive CTM103 in combination with pembrolizumab (200 mg on day 1), both intravenous Q3W. Both portions of the study consist of 3+3 escalation cohorts to define maximum tolerated dose (MTD). If response signal is observed in a given dose cohort, additional 10-20 patients will be enrolled in the expansion portion of the study to further evaluate the safety and efficacy. The trial is ongoing and data as of 7/24/2024 is presented in this abstract.

Results: In Part A, 9 patients in three dose cohorts received CTM103. All patients demonstrated high and prolonged plasma level of IL-2, and remarkable elevation of CD8 T cells (upto 5 folds) and NK cells (upto 25 folds), which can last through the 3-week-period until next injection. No dose-limiting toxicities (DLT) were observed. In Part B, 13 patients in two dose cohorts were enrolled, 10 of which are treatment naïve PDL1+ advanced NSCLC. All patients showed increased CD8 T cells (upto 12 folds) and NK cells (upto 22 folds), and most AEs were at grade 1-2, and were all transient and recovered in less than 7 days. At the cut-off date, 8 of the 10 PD1 treatment naïve PDL1+ NSCLC patients in Part B reached at least the 1st tumor evaluation time-point, 6 of which were evaluated to be PR, and the other 2 were SD. ORR is 75%.

Conclusions: CTM103 was generally well tolerated at the current dose level, which already demonstrated high and prolonged plasma level of IL-2, and robust immune stimulatory activity in promoting CD8 T cells and NK cells proliferation.

Keywords: IL-2, mRNA LNP, PD-1

MA16 STRATEGIES BEYOND CURRENT IMMUNOTHERAPIES
TUESDAY, SEPTEMBER 10, 2024 - 15:00 - 16:15

MA16.08 Impact of Site of CAN-2409 Injection Plus Continued Immune Checkpoint Inhibitor (ICI) In CI-resistant stage III/IV NSCLC

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Introduction: NCT04495153 is an open-label, phase 2 clinical trial of CAN-2409+valacyclovir in combination with continued ICI treatment in patients with non-resectable, stage III/IV NSCLC following an inadequate response to anti-PD-(L)1 treatment. Here, we explore the impact of the specific site of injection of CAN-2409 on overall survival (OS) and immunological biomarkers.

Methods: Patients were enrolled in 2 cohorts (C) depending on disease status at enrolment. C1: patients with stable disease despite ICI treatment, and C2: patients with progressive disease despite ICI treatment. Two doses of CAN-2409 (5x10^11vp) were injected 5-7w apart via bronchoscopic or percutaneous injections into lung tumor (LT), lymph nodes (LN), or peripheral metastases (PM), each followed by valacyclovir.

Results: As of 16Jan2024, 73 patients were treated (safety population: ≥1 dose of CAN-2409) and 44 were evaluable per protocol (received 2 doses of CAN-2409+valacyclovir and 12-week CT scan). 18 patients received both injections into LT, 13 LN, 8 PM, and 5 in combination of different lesions (LT and LN). Lesions were mainly injected via bronchoscopy (>60%). There were no significant differences between grade 3 events by site of injection; most common TRAEs (≥5%) were fatigue and pyrexia. Median OS (mOS) for C1 (n=5) was not reached (mFU 15.2mos; 4 patients were still alive at follow-up); mOS for C2 was 20.6 months (mFU 19.2mos). The proportion of patients surviving through 12, 14, or 18 months was not significantly different when comparing patients injected into LT versus LN. However, survival was significantly shorter in patients injected into PM compared to combined LT and LN injected patients (P = 0.029 and P = 0.04 for 12 and 14 months, respectively). Importantly, none of the patients injected into PM developed a partial RECIST response; the number of patients with progressive disease was higher in this subgroup compared to patients injected into LN or LT. CyTOF analysis revealed that LN injections were associated with a greater increase in exhausted B cells, CD8+ Tim3+ T cells, and CD4+ PDL1+ T cells after the first CAN-2409 injection compared to LT injections (p=0.024, p=0.002, and p=0.027, respectively). LT injections were associated with an increase in CD69+ Naïve CD4+ T cells, Tim3+ Central Memory CD4+ T cells, and CD11C+ Naïve CD4+ T cells (p=0.001, p=0.023, and p=0.040, respectively after second injection), whereas LN injections were associated with a decrease in these cell populations. LT injections elicited an increase in plasma levels of granzyme H and CCL20, which were significantly greater than changes observed after LN injections (p=0.046 and p=0.039). Due to limited biospecimen availability, PM specimens were excluded from the analysis.

Conclusions: CAN-2409 can be safely delivered intratumorally into LT, LN, and PM in patients with NSCLC. Injection into LT and/or LN is associated with improved survival compared to injection into PM. Administration of CAN-2409 into LT and/or LN is associated with systemic immune activation.

Keywords: Intratumoral immunotherapy, Intranodal immunotherapy, Systemic immune response

MA17.03 30 Years of International Real World Outcomes in Patients with Limited Disease Small Cell Lung Cancer

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Introduction: The landscape of limited disease small cell lung cancer (LD-SCLC) management has changed little over 30 years. The standard of care treatment remains platinum-doublet chemotherapy with radiation concurrently or sequentially as the standard of care since the early 1990s. Some patients also receive prophylactic cranial radiation subsequently. This treatment pattern may change in the coming months as outcomes of phase 3 randomized clinical trials combining chemotherapy and immunotherapy with radiation in LD-SCLC are reported.

Methods: We analyzed data from the international lung cancer consortium (ILCCO) across 20 sites in Europe, North America, and Asia. This analysis included 1,503 patients who were diagnosed with LD-SCLC between 1990 and 2020 who had complete clinicodemographic data available (e.g., age, sex, smoking status, education level, ethnicity and stage). A subset also had cardiometabolic/respiratory co-morbidity data. Cox regression models were generated evaluating potential prognostic variables on overall survival (OS). Median follow-up time was measured in years using the reverse Kaplan-Meier method.

Results: The consortium harmonized patient data from 12 North American, 6 European and 2 Asian studies. The median age was 65 years (interquartile range: 58-72), 54% were male, 96% were ever-smokers, 88% were White, 6% Asian, 45% had a cardiometabolic comorbidity in which 13% had diabetes, 41% had a respiratory comorbidity, including 26% with COPD. The median follow-up of this mature dataset was 11.4 years and median OS was 19.0 months (95% CI: 17.3, 20.6). OS probabilities at 1, 2, and 4 years are provided in Table 1. In univariable analyses, men (HR=1.14, 95% CI: 1.02, 1.27), low education (HR 1.27, 1.07, 1.51), 70+ years old (HR 1.66, 1.48, 1.87), or European (HR 1.24, 1.07, 1.43), were associated with inferior prognosis (p <0.05). In multivariable analysis, poorer OS was associated for male sex, HR=1.18 (1.03, 1.34; p=0.019) and older age revealed a HR per 10 y -increase of 1.33 (1.23-1.44; p<0.001). In contrast, the year of diagnosis was not associated with median OS or survival probabilities.

Conclusions: When compared to historical data, 2-year survival was reported as 44% (radiation given once or twice daily; Turrisi A.T, et al NEJM 1999), which is similar to all time periods in our 30-year international dataset, with expectedly high comorbidity rates. There has not been a significant change in outcome in over 3 decades. Our real-world outcome data in LD-SCLC will be important to compare with the control-arm outcomes of upcoming immunotherapy studies such as ADRIATIC.

Keywords: Small cell lung cancer, Real world outcomes, Overall survival

Subset	N (%)	overall survival probability (95% CI)		
		1-year	2-years	4-years
All	1503 (100%)	0.67 (0.65, 0.69)	0.41 (0.38, 0.43)	0.23 (0.21, 0.25)
Female	686 (46%)	0.71 (0.68, 0.75)	0.44 (0.40, 0.48)	0.26 (0.22, 0.29)
Male	817 (54%)	0.63 (0.60, 0.67)	0.38 (0.35, 0.42)	0.20 (0.18, 0.24)
Never-smoker	61 (4%)	0.76 (0.66, 0.88)	0.47 (0.35, 0.62)	0.32 (0.21, 0.49)
Ever-smoker	1442 (96%)	0.67 (0.64, 0.69)	0.40 (0.38, 0.43)	0.22 (0.20, 0.25)
Education-moderate-high	895 (88%)	0.52 (0.45, 0.60)	0.30 (0.23, 0.37)	0.19 (0.14, 0.26)
Education-low	172 (12%)	0.70 (0.67, 0.73)	0.42 (0.39, 0.46)	0.24 (0.22, 0.28)
Age < 70 years	1010 (67%)	0.74 (0.71, 0.77)	0.46 (0.43, 0.50)	0.27 (0.24, 0.30)
Age = 70+ years	493 (33%)	0.53 (0.49, 0.58)	0.29 (0.25, 0.34)	0.15 (0.12, 0.19)
North America	1170 (78%)	0.70 (0.68, 0.73)	0.43 (0.41, 0.46)	0.24 (0.22, 0.27)
Asia	60 (4%)	0.65 (0.54, 0.79)	0.39 (0.28, 0.55)	0.39 (0.28, 0.55)
Europe	273 (18%)	0.54 (0.48, 0.6)	0.29 (0.24, 0.36)	0.16 (0.12, 0.21)
Diagnosis year (1990-2003)	551 (37%)	0.65 (0.61, 0.69)	0.38 (0.34, 0.42)	0.22 (0.19, 0.26)
Diagnosis year (2004-2008)	511 (35%)	0.68 (0.64, 0.72)	0.41 (0.37, 0.46)	0.23 (0.20, 0.27)
Diagnosis year (2009-2020)	415 (28%)	0.69 (0.64, 0.73)	0.44 (0.39, 0.49)	0.23 (0.19, 0.28)

MA17 LIMITED-STAGE SCLC, NOVEL IMMUNOTHERAPY COMBINATIONS AND BIOMARKERS IN SCLC
TUESDAY, SEPTEMBER 10, 2024 - 15:00 - 16:15

MA17.04 Patient-Reported Outcomes (PROs) With Consolidation Durvalumab Versus Placebo Following cCRT in Limited-Stage SCLC: ADRIATIC

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Introduction: There is a paucity of relevant PRO data reported for patients with small-cell lung cancer (SCLC), particularly in the limited-stage (LS) setting. In the double-blind, phase 3 ADRIATIC study (NCT03703297), consolidation durvalumab after concurrent chemoradiotherapy (cCRT) significantly improved the dual primary endpoints of overall survival and progression-free survival versus placebo in patients with LS-SCLC. Durvalumab was well tolerated, with no new safety signals observed. Here we report results from the secondary PRO endpoints.

Methods: Eligible patients had stage I–III LS-SCLC (stage I/II inoperable), WHO performance status 0/1, and had not progressed after cCRT. Patients (N=530) were randomized 1-42 days after cCRT to durvalumab 1500mg or placebo Q4W until investigator-determined disease progression, intolerable toxicity, or a maximum of 24 months. Secondary endpoints included change in symptoms, functioning and global health status/quality of life (GHS/QoL) using European Organisation for Research and Treatment of Cancer QLQ-C30 and QLQ-LC13 electronic questionnaires. Change from baseline for prespecified key subscales was examined using mixed-effect model repeat measurement analysis. Time to deterioration (TTD) and improvement rates (for prespecified key subscales and other subscales) were analyzed using stratified Cox proportional hazards models and logistic regression, respectively. A score change of ≥10 from baseline was considered clinically meaningful.

Results: Compliance with QLQ-C30/LC13 questionnaires was 79.7-82.2% at baseline and remained >70% through Week 16 in both durvalumab (n=264) and placebo (n=266) arms. Mean baseline scores were comparable between the two arms. In both arms, mean changes from baseline in prespecified key subscales averaged over 24 months were small and not clinically meaningful for any subscale. For prespecified key subscales (Table) and other subscales (QLQ-C30: emotional, cognitive and social functioning, pain, nausea/vomiting, dyspnea, insomnia, constipation, diarrhea; QLQ-LC13: hemoptysis, arm/shoulder pain, other pain, sore mouth, dysphagia, peripheral neuropathy, alopecia), there were no between-arm differences in TTD except for arm/shoulder pain (LC13), which was delayed with durvalumab versus placebo (median 25.7 versus 9.1 months [hazard ratio 0.70; 95% CI 0.51-0.94]). Similar improvement rates were reported in both arms for prespecified key subscales (Table) and other subscales; the only difference observed was for chest pain (LC13; 67.3% versus 47.8% for durvalumab versus placebo [odds ratio 2.28; 95% CI 1.08-4.95]).

Conclusions: In ADRIATIC, treatment with durvalumab for up to 2 years improved survival outcomes versus placebo without a clinically meaningful impact on PROs for GHS/QoL, functioning or symptoms, further supporting consolidation durvalumab as a new standard of care in LS-SCLC.

Keywords: Durvalumab, Patient-reported outcomes, ADRIATIC

Prespecified key PRO subscale	Median time to deterioration (months)*		Improvement rate (%)†	
	Durvalumab	Placebo	Durvalumab	Placebo
GHS/QoL (C30)	10.2	10.2	30.4	33.5
	HR 0.93 (95% CI 0.71, 1.23)		OR 0.85 (95% CI 0.54, 1.34)	
Physical functioning (C30)	10.1	16.6	35.4	38.1
	HR 1.10 (95% CI 0.83, 1.47)		OR 0.87 (95% CI 0.51, 1.48)	
Role functioning (C30)	12.8	9.1	52.1	54.1
	HR 0.77 (95% CI 0.58, 1.01)		OR 0.92 (95% CI 0.48, 1.76)	
Fatigue (C30)	4.5	5.6	51.2	44.9
	HR 1.12 (95% CI 0.87, 1.44)		OR 1.30 (95% CI 0.84, 2.01)	
Appetite loss (C30)	20.2	17.5	66.3	65.1
	HR 1.09 (95% CI 0.80, 1.49)		OR 1.04 (95% CI 0.55, 1.95)	
Dyspnea (LC13)	3.7	5.5	55.6	49.4
	HR 1.11 (95% CI 0.86, 1.43)		OR 1.28 (95% CI 0.82, 1.99)	
Cough (LC13)	22.9	14.7	46.9	40.1
	HR 1.12 (95% CI 0.83, 1.52)		OR 1.36 (95% CI 0.83, 2.22)	
Chest pain (LC13)	30.4	14.7	67.3	47.8
	HR 0.79 (95% CI 0.57, 1.08)		OR 2.28 (95% CI 1.08, 4.95)	

*An HR <1 favors durvalumab over placebo
†Percentage of patients with a minimum of 2 consecutive assessments at least 14 days apart that show a clinically meaningful improvement from baseline; an OR >1 favors durvalumab over placebo
CI, confidence interval; HR, hazard ratio; OR, odds ratio

MA17 LIMITED-STAGE SCLC, NOVEL IMMUNOTHERAPY COMBINATIONS AND BIOMARKERS IN SCLC
TUESDAY, SEPTEMBER 10, 2024 - 15:00 - 16:15

MA17.05 Longitudinal MRD Monitoring Enhances Prognosis Prediction in 105 Patients with Limited-Stage SCLC Receiving Concurrent Chemoradiotherapy

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Introduction: Limited-stage small-cell lung cancer (LS-SCLC) accounts for approximately one third of newly diagnosed small-cell lung cancer cases. Chemoradiotherapy with/without following prophylactic cranial irradiation (PCI) serves as the standard of care for unresectable LS-SCLC, and poor clinical outcomes underscore an urgent need to develop noninvasive biomarkers for prognostic prediction. Given few studies systematically investigating circulating tumor DNA (ctDNA) applicability in LS-SCLC, our prospective study aims to evaluate the prognostic value of minimal residual disease (MRD) through ctDNA monitoring.

Methods: Patients with unresectable LS-SCLC who received 1-2 cycles of chemotherapy followed by concurrent chemoradiotherapy were prospectively enrolled. Plasma ctDNA samples were collected at multiple time points, including the baseline, after 1-2 cycles of induction chemotherapy and before thoracic radiotherapy (pre-RT), within one month after completing thoracic RT (post-RT), and on the last day of PCI (post-PCI). The MRD status integrating single nucleotide variants, copy number alterations, and fusions was identified by a next-generation sequencing panel covering 139 lung cancer-relevant genes with an average sequencing depth of approximately 30000×. Kaplan-Meier curves and log-rank tests were performed in survival analyses, with hazard ratios (HRs) and 95 % confidence intervals (CIs) estimated by Cox proportional hazards models.

Results: A total of 105 eligible patients were consecutively enrolled between June 2018 and December 2022 (median age: 59 [31-74]; male: 81.9%; stage III: 86.7%; smoker: 70.5%; median follow-up: 24.93 months). ctDNA positivity was observed in all baseline samples, and the positivity rate decreased dramatically to 54% after 1-2 cycles of chemotherapy (p=0.002). Patients with positive pre-RT ctDNA status exhibited inferior PFS (median: 14.40 months vs. 42.20 months; HR: 1.81; 95% CI: 1.07-3.05; p=0.03) and OS (median: 29.53 months vs. not reached [NR]; HR: 1.95; 95% CI: 1.02-3.74; p=0.04) to pre-RT ctDNA negative patients. Given that clearance of MRD within one month after thoracic RT was observed in 60% of patients with detectable pre-RT ctDNA, patients were classified into the pre-RT ctDNA negative (N=48), post-RT MRD clearance (N=21), or post-RT MRD sustained subgroup (N=14). Superior PFS (median: 16.53 months vs.9.70 months; HR: 0.37; 95% CI: 0.17-0.82; p=0.01) was observed in the post-RT MRD clearance subgroup in comparison to the post-RT MRD sustained subgroup, with similar result obtained in OS (median: NR vs. 22.77 months; HR: 0.26; 95% CI: 0.09-0.76; p=0.01). In contrast, no significant differences in PFS and OS were observed between the pre-RT ctDNA negative and the post-RT MRD clearance subgroups. It should be noted that of 46 MRD negative patients at post-RT, only 2 patients regained MRD positivity at the post-PCI time point confirmed disease progression soon, with 2.47 and 2.65 months preceding radiographic progression respectively, demonstrating higher recurrence risks than post-PCI MRD negative patients (log-rank p<0.001).

Conclusions: This is the first prospective study to evaluate ctDNA MRD systematically in a large LS-SCLC cohort receiving chemoradiotherapy. ctDNA-derived MRD can identify LS-SCLC with a high disease progression risk at concurrent chemoradiotherapy initiation or through longitudinal monitoring. Moreover, MRD status after PCI is useful to detect recurrence prior to radiological assessment.

Keywords: limited-stage small-cell lung cancer, minimal residual disease, prognosis prediction

MA17 LIMITED-STAGE SCLC, NOVEL IMMUNOTHERAPY COMBINATIONS AND BIOMARKERS IN SCLC
TUESDAY, SEPTEMBER 10, 2024 - 15:00 - 16:15

MA17.07 Durvalumab Plus Anlotinib Versus Durvalumab as Maintenance Treatment in ES-SCLC (DURABLE): A Randomized, Phase 2 Trial

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Introduction: The phase 3 CASPIAN trial established durvalumab plus chemotherapy as first-line standard of care for extensive-stage small-cell lung cancer (ES-SCLC) patients. However, approaches that can boost long-term survival are still needed. Antiangiogenic therapy has the potential to alleviate immunosuppression and showed synergetic effect with immune check-point inhibitors (ICIs). Anlotinib is an oral novel anti-vascular agent, and recent study have showed that adding anlotinib into ICIs plus chemotherapy could improve patients outcomes compare with chemotherapy alone. In the DURABLE study, we aimed to assess the efficacy and safety of durvalumab plus anlotinib versus durvalumab alone as maintenance treatment for ES-SCLC patients.

Methods: This randomized, open-label, phase 2 trial was done at 5 sites in China. Eligible patients were adults (aged 18-75) ES-SCLC patients with ECOG PS 0-1. Patients with no disease progression after 4 cycles of first-line durvalumab plus platinum-etoposide were randomized to durvalumab (1500 mg, q4w) plus anlotinib (12 mg, 1-14 days, q3w) or durvalumab alone (1500 mg, q4w) until disease progression or unacceptable toxicity. The primary endpoint was PFS (from maintenance); secondary endpoints included overall survival (OS), PFS (from first dose of treatment) and safety.

Results: From December 2021 to September 2023, 66 patients were randomized to durvalumab plus anlotinib arm (n=34) or durvalumab alone arm (n=32). Baseline demographics were generally well balanced between treatment arms. At data cut-off (1st March. 2024), the median follow-up was 15.1months (range 6.8-26.9). Durvalumab plus anlotinib significantly improved PFS compared with durvalumab alone (median PFS [from maintenance]: 5.3 vs 1.9 months, HR=0.66 [80% CI: 0.46, 0.95],median PFS [from first dose of treatment]: 8.4 vs 5.6 months, HR=0.67 [80% CI: 0.46, 0.97]). Median OS for durvalumab plus anlotinib arm and durvalumab alone arm was not reached vs 12.9 months, HR 0.56 [80% CI: 0.34, 0.91]),12-month OS rates were 63.3% vs. 57.5%. Grade≥ 3 treatment-emergent adverse events (TEAEs) occurred in 17.6% patients in the durvalumab plus anlotinib arm vs.12.5% in the durvalumab alone arm, with the most common grade ≥ 3 TEAEs being hematological toxicity in both arms. TEAE leading to treatment discontinuation occurred in 2.9% patients vs. 3.1%. 17 patients remained on treatment. Further assessment is ongoing.

Conclusions: Durvalumab in combination with anlotinib as maintenance therapy demonstrated significant PFS benefit (about 3 months) and trend of improved OS compared with durvalumab alone in in ES-SCLC patients not progressed from durvalumab plus platinum-etoposide. No new safety signal was observed. Further investigation is warranted.

Keywords: extensive-stage small-cell lung cancer, maintenance treatment, anti-vascular agent

MA17 LIMITED-STAGE SCLC, NOVEL IMMUNOTHERAPY COMBINATIONS AND BIOMARKERS IN SCLC
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MA17.08 Safety and Efficacy of Tifcemalimab Combined with Toripalimab in Refractory Extensive Stage Small Cell Lung Cancer

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Introduction: Tifcemalimab (JS004 or TAB004) is a humanized IgG4 monoclonal antibody with a hinge mutation (S228P) that binds BTLA and blocks its interaction with its ligand HVEM. In an I/II study (NCT05000684) as we previously reported at 2023 ASCO Annual Meeting, tifcemalimab in combination with toripalimab (anti-PD-1) showed preliminary anti-tumor activities with a manageable safety profile in refractory extensive stage small cell lung cancer (ES-SCLC). Here, we report the updated efficacy and safety results from the intent-to-treatment population.

Methods: Patients with pathologically confirmed ES-SCLC and refractory to prior systemic therapies were enrolled. Eligible patients received 200mg tifcemalimab and 240mg toripalimab intravenously once every three weeks until disease progression, intolerable toxicity or up to 2 years of treatment. Primary endpoints included safety and objective response rate (ORR) evaluated by investigator per RECIST v1.1.

Results: From 8/27/2021 to 1/13/2023, a total of 43 patients with ES-SCLC were enrolled. As of March 14, 2024, the median follow-up duration was 11.17 months. The median age was 59.0 (range 38-75) years, and 34 (79.1%) were males. Nineteen (44.2%) patients had received ≥2 lines of prior therapies. By the data cut-off date, 39 (90.7%) patients experienced treatment-emergent adverse events (TEAEs); 17 (39.5%) experienced grade >=3 TEAEs. The most common TEAEs included anemia (25.6%), blood creatine phosphokinase increase (25.6%), alanine aminotransferase increase (23.3%), COVID-19 (23.3%), hyperglycemia (23.3%), hyponatremia (20.9%), and hypothyroidism (20.9%). Eleven (25.6%) patients experienced TEAEs led to interruption of study drugs and no TEAEs led to discontinuation of study drugs were reported. Eighteen (41.9%) patients experienced immune related AE (irAEs), and 4 (9.3%) experienced CTCAE grade >=3 irAEs. Among 43 patients, 40 were efficacy evaluable, the ORR was 32.6%, the disease control rate (DCR) was 51.2%. The duration of response was 5.7 (95%CI 2.0, 14.6) months. The median progression free survival was 2.8 (95% CI 1.4, 4.4) months, the median overall survival was 12.3 (95% CI 7.8, 15.7) months. The preliminary biomarker analysis of available tumor tissue suggested that higher ORR and DCR were observed among patients with PD-L1 or HVEM positive expression. Further biomarker analysis will be updated.

Conclusions: Tifcemalimab in combination with toripalimab showed promising antitumor activity with manageable toxicity in patients with refractory ES-SCLC. Further clinical evaluation of this combination treatment in SCLC is warranted.

Keywords: Tifcemalimab, Toripalimab, Extensive Stage Small Cell Lung Cancer

MA17.09 Efficacy and Safety of Tislelizumab Plus Anlotinib and 2-Cycle Irinotecan as Second-Line Treatment for ES-Small Cell Lung Cancer(ESTAIL)

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Introduction: Second-line treatment for ES-SCLC is mainly chemotherapy, but the efficacy needs to be improved. In recent years, immune checkpoint inhibitors and anti-angiogenic drugs have become important treatments for ES-SCLC. Herein, we hypothesis that Tislelizumab (Tis) combined with Anlotinib (Anlo) and 2-cycle Irinotecan can improve efficacy and tolerability in second-line treatment for ES-SCLC.

Methods: This is a single-arm, Phase II study (NCT05027100). Pts failed to first-line treatment with EP or EC or PD-L1 inhibitor +EP/EC are permitted. Pts are treated with Tis plus Anlo and Irinotecan for up to 2cycles, followed by Tis plus Anlo maintenance therapy. Primary endpoint was objective response rate, and second endpoints included PFS, OS, DOR, DCR and safety. The planned sample size was 32 with a historical control of 16%, an expected value of 35%, a one-sided α of 0.05, and a power of 80%, One Arm Binomial design.

Results: Between July 27,2021 and November 29,2023,32 patients were enrolled. Fifteen pts (46.9%) had stable brain metastases. There were 23 pts received first-line EP/EC treatment and 9 pts received PD-L1 inhibitor +EP/EC. As of March 1 ,2024, the median follow-up was 9.6 months. Among the 32 patients in the efficacy analysis set, the ORR was 50%, which met the primary endpoint, median DOR was 5.72 months. The median PFS was 7.1months and 6m-PFS rate was53.2% (95%CI:28.9%-72.6%). The subgroup analysis of median PFS according to first-line EP/EC or PD-L1 inhibitor +EP/EC were 8.4 months and 3 months, 6m-PFS rate were 63.5% (95%CI:33.1%-83%) and 22.2% (95%CI:0.9%-61.8%). The median overall survival was 7.5 months, The subgroup analysis of median OS according to first-line EP/EC or PD-L1+EP/EC were 9.0months and 5.6months,respectively .The median OS2 from first-line to data cutoff was 17.2months and 1y-OS2 rate was 63.9% (95%CI:42.9%-78.9%).The subgroup analysis of 1y-OS2 rate according to first-line EP/EC or PD-L1+EP/EC were 67.6% (95%CI:43.7%-83.1%) and 47.4% (95%CI:7.8%-82.3%),respectively. The overall safety was manageable, Grade 3 or higher treatment related AEs and immune-related AEs occurred in 8 patients (8/32, 25%) and 3patients (3/32, 9.3%), respectively. The most frequently reported grade 3 or higher TRAEs were hyperglycemia,thrombocytopenia and Neutropenia.

Conclusions: Tislelizumab combined with Anlotinib and 2-cycle Irinotecan as second-line Treatment for ES-SCLC demonstrated promising efficacy and safety, especially pts who failed to first-line treatment of PD-L1 inhibitor +EP/EC could benefit from it.

The key subgroup analysis of ORR

Keywords: Efficacy and Safety, second-line Treatment, ES-Small Cell Lung Cancer

Response	Total (N=32)	brain metastases (yes)	brain metastases(No)	First-line treatment(EP/EC)	First-line treatment(PD-L1+EP/EC)	Time of First line platinum to relapse(>3months)	Time of First line platinum to relapse(<3months)
BoR,n (%)							
PR	16	9	7	13	3	5	8
SD	12	5	7	7	5	1	6
PD	1	0	1	0	1	0	0
NE	3	1	2	3	0	1	2
ORR,n(%)	16(50)	9(60)	7(41.2)	13(56.5)	3(33.3)	5(71.4)	8(50)
DCR,n(%)	28(87.5)	14(93)	14(82)	20(87)	8(88.9)	6(85.7)	14(87.5)

MA17 LIMITED-STAGE SCLC, NOVEL IMMUNOTHERAPY COMBINATIONS AND BIOMARKERS IN SCLC
TUESDAY, SEPTEMBER 10, 2024 - 15:00 - 16:15

MA17.11 NOTCH1 Expression Is Associated with Overall Survival in Small Cell Lung Cancer Patients Treated with Atezolizumab in IMpower133

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Introduction: Small cell lung cancer (SCLC) resists response to immune checkpoint blockade (ICB) and predictive biomarkers to guide ICB treatment in the SCLC clinic are lacking. We hypothesized major Notch pathway genes may correlate with survival with first-line ICB treated SCLC patients based on our prior work linking Notch signaling with ICB efficacy in relapsed SCLC (Roper et al. Nature Communications 2021).

Methods: We analyzed expression of major Notch signaling genes NOTCH1, NOTCH2, REST, and HES1 in relation to overall survival (OS) in the phase 3 IMpower133 extensive-stage SCLC clinical trial in which first-line atezolizumab (atezo) plus etoposide and platinum (EP) significantly improved OS (HR 0.70, 95% CI, 0.54-0.91, P = 0.007) compared to placebo (pbo) plus EP. Analysis was performed using recently defined transcriptional subsets (Nabet et al. Cancer Cell 2024): SCLC-N (NEUROD1) (31%, n=85/271), SCLC-A (ASCL1)+SCLC-I-NE (Inflamed, neuroendocrine) (47%, n=127/271), and SCLC-I-nNE (Inflamed, non-neuroendocrine) (22%, n=59/271). High and low expression were defined as greater than or equal to median or less than median expression, respectively, within each subset. Cleaved NOTCH1 (Val1744) antibody was used for immunohistochemistry (IHC).

Results: Within the SCLC-A+SCLC-I-NE subset, high NOTCH1 expression was strongly associated with OS with atezo compared to pbo (HR 0.39, 95% CI, 0.22 to 0.69; P=0.0012) whereas low NOTCH1 expression was not (HR 1.21, 95% CI, 0.67-2.18, P=0.536). Comparing treatment arms, atezo favored high NOTCH1 expression (HR 0.51; 95% CI, 0.29 to 0.88; P=0.02), while pbo favored low NOTCH1 expression (HR 2.04; 95% CI, 1.13 to 3.67; P=0.02). Within the SCLC-N subset, high NOTCH1 expression was also associated with OS with atezo compared to pbo (HR 0.44; 95% CI, 0.21-0.92; P=0.024), but low NOTCH1 expression was not (HR 0.79; 95% CI, 0.40-1.55; P=0.49). There was no difference in OS between atezo and pbo based on NOTCH2, REST, and HES1 expression. Active NOTCH1 signaling by IHC was evident across subsets in 29% (n=56/193) of SCLC tissues.

Conclusions: High NOTCH1 expression is associated with longer OS with the addition of ICB to EP in the major subsets of SCLC whereas low NOTCH1 expression is not. Our results implicate NOTCH1 as a potential predictive biomarker for ICB in SCLC.

Keywords: small cell lung cancer, immunotherapy, NOTCH1

MA17 LIMITED-STAGE SCLC, NOVEL IMMUNOTHERAPY COMBINATIONS AND BIOMARKERS IN SCLC
TUESDAY, SEPTEMBER 10, 2024 - 15:00 - 16:15

MA17.12 Delineating the Mechanism of Resistance to Targeted Therapy via Cellular Transdifferentiation

P. Gopal, M. Abazeed, Northwestern University, Chicago/IL/USA

Introduction: Patients with oncogene-directed targetable mutations (i.e., EGFR) experience better outcomes in non-small cell lung cancers (NSCLC). Most tumors treated with targeted therapies ultimately relapse. Repeat biopsies of relapsing tumors have identified a phenomenon, referred to as cellular transdifferentiation. A subset of NSCLC tumors, lung adenocarcinomas (LUADs) upon treatment with targeted therapy, transdifferentiate into small cell lung cancer (t-SCLC). As more selective and potent targeted therapies for LUAD enter the clinic, including anti-Ras therapies, this phenomenon takes on even greater significance. Survival after neuroendocrine transdifferentiation is poor since targeted therapies are not effective against high-grade neuroendocrine tumors. However, the mechanisms of transdifferentiation from one cancer type to another remain very poorly understood.

Methods: We have combined patient derived xenografts (PDX) and PDX-derived ex vivo lines with multi-omic characterization, high-content image-based morphometry and fluorescence tracking, and single-cell barcode tracing to better understand the process of lung tumor transdifferentiation.

Results: We have developed a first-of-its-kind t-SCLC model that reconstitutes in real-time (in ex vivo culture) LUAD to SCLC transdifferentiation. Genomic and transcriptomic analyses of our NSCLC PDX collection identified multiple tumors with mutations in TP53 and RB1, two genes that are biallelically altered in virtually all de novo SCLCs. PDX sample CBX336 and CBX282 have been identified as having mutations in both TP53 and RB1, in addition to expressing the KRASG12C oncogene. Upon treatment with Sotorasib, tumors initially demonstrated slow tumor growth. This was followed by a dramatic increase in the growth trajectory after prolonged drug exposure. We characterized the resultant resistant tumors and showed that they contained expression of canonical markers of the neuroendocrine lineage, including NEUROD1. We show that in CBX336 the t-SCLC that emerges has high levels of NEUROD1 expression. Immunohistochemical (IHC) characterization revealed evidence of histological transformation to a NeuroD1-expressing SCLC. Our experimental (fluorescence tracking) and computational data suggest a synchronized procession toward transdifferentiation with the upregulation of the neuroendocrine transcription factor NEUROD1.Our experimental and computational data suggest a highly coordinated procession toward transdifferentiation with the parallel upregulation of the neuroendocrine transcription factor NEUROD1 across numerous epithelial cellular clones.

Conclusions: We have developed a new experimental system and framework for the study of lung t-SCLC at the single-cell level. Ongoing work includes the integration of new resources to study lineage reprogramming, the regulation of transdifferentiation by the cancer genome, and advancing new therapeutic strategies that combat plasticity by deploying unique drug combinatorial strategies.

Keywords: lung cancer, transdifferentiation, plasticity

MA17 LIMITED-STAGE SCLC, NOVEL IMMUNOTHERAPY COMBINATIONS AND BIOMARKERS IN SCLC
TUESDAY, SEPTEMBER 10, 2024 - 15:00 - 16:15

MA17.13 DLL3-targeted CAR-T Therapy of Small Cell Lung Cancer Utilizing Circular RNA

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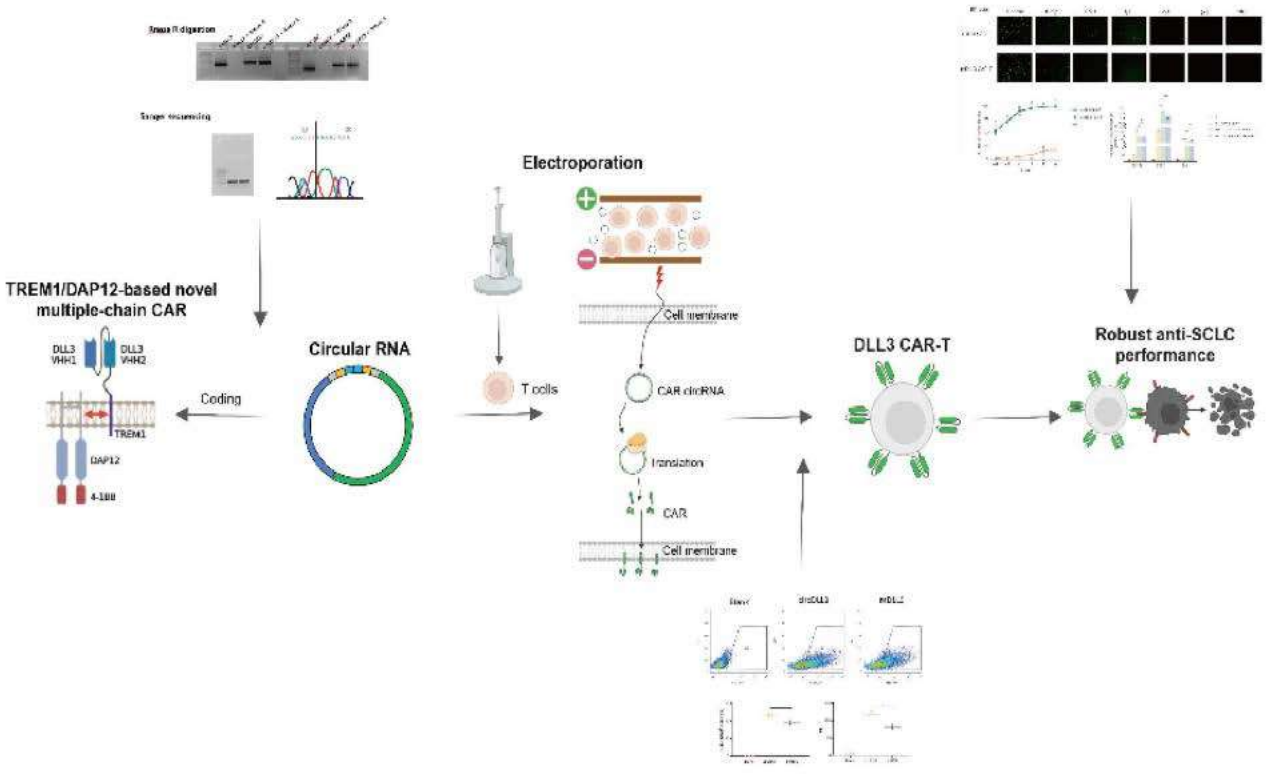
Introduction: The survival of small cell lung cancer (SCLC) is discouraging, necessitating the development of novel targets and effective therapeutic approaches. Delta-Like Ligand 3 (DLL3) represents a promising target for the treatment of SCLC, with ongoing vigorous therapeutic strategies. Here, we report DLL3-targeted CAR-T therapy constructed by circular RNA (circRNA), yielding promising therapeutic results of treating SCLC.

Methods: Circular RNAs (circRNAs) are covalently closed single-stranded RNAs that are resistant to exonuclease-mediated degradation. Compared with linear mRNA, circular RNA is more stable and efficient as translate templates, thus circRNA has been considered as "the next generation" of mRNA. By splicing CVB3 IRES into 2 parts, we developed a new Group I permuted intron-exon (PIE) self-splicing system (named NeoAna) for in vitro circRNA synthesis. Thus, circRNA transcripts encoding the DLL3-targeted CAR structure were synthesized with the NeoAna platform. By employing electroporation, DLL3-targeted CAR-T cells were constructed directly using T cells from healthy volunteers.

Results: We have previously reported a highly efficient TREM1/DAP12-based novel multiple-chain CAR structure. In current study, we successfully synthesized and validated the feasibility of circRNA encoding DLL3-targeted CAR. Through comparative comparison with messenger RNA (mRNA), we observed distinct advantages of circRNA, particularly in terms of stability and sustained DLL3 CAR expression. Moreover, we fine-tuned the electroporation conditions and RNA dosage, achieving a CAR-T positivity rate of approximately 47%. Subsequent in vitro co-culture experiments revealed the potent cytotoxicity of CAR-T cells against SCLC cells, with ELISA and RT-PCR analyses providing further validation. Lastly, using mice subcutaneous, orthotopic, and metastatic models, we demonstrated the efficacy of circRNA-based CAR-T therapy in SCLC tumor eradication, significantly extending survival.

Conclusions: Leveraging electroporation and circRNA, we have effectively engineered DLL3-targeted CAR-T cells with effective cytotoxicity against SCLC. This research offers a promising avenue for advancing SCLC therapeutics.

Keywords: Delta-Like Ligand 3, CAR-T therapy, circular RNA



MA18 NEW PARADIGMS IN LUNG CANCER SCREENING
TUESDAY, SEPTEMBER 10, 2024 - 15:00 - 16:15

MA18.03 Participant Eligibility for Lung Cancer Screening in Australia: An Analysis of Proposed Criteria

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Introduction: Eligibility for the proposed Australian National Lung Cancer Screening Program (NLCSP) is based around categorical smoking and tobacco exposure recommendations from the Medical Services Advisory Committee (MSAC). Canadian provinces have adopted screening using PLCOm2012 risk model, with UK adopting a combination of the PLCOm2012 and LLPv2 risk models. The aim of this study was to investigate the proportion of International Lung Screening Trial (ILST) participants who could have been eligible, and lung cancers that would have been detected, by the MSAC criteria in an Australian NLCSP setting.

Methods: All individuals between 50-80 years of age, who underwent baseline eligibility assessment under the ILST were included (regardless of screening enrolment). This included participants from Canada, Australia and Hong Kong. Eligibility under MSAC criteria (aged 50-70 years; ≥30 pack-years, ≤10 years since cessation) were compared against USPSTF2021 (aged 50-80 years, ≥20 pack-years, ≤15 years since cessation) criteria and the PLCOm2012 and LLPv2 risk models at ≥1.51%, 6 year-risk and ≥2.5%, 5-year risk thresholds, respectively.

Results: A total of 9,725 participants were included (of which 4,053 were eventually enrolled in ILST). The cohort was 48% (n=4,670) female, with the majority having quit smoking (61.7%, n=5,997). The median (IQR) age was 63 (59-69) years, with a mean smoking duration and quit time of 34.9 and 17.2 years, respectively. 173 lung cancers were detected in total.

Regarding eligibility, the USPSTF2021 criteria selected the largest proportion of participants (59%, n=5,761), followed by PLCOm2012 (54%, n=5,223) and LLPv2 (49%, n=4,759), with MSAC criteria selecting the least (37%, n=3,612; see Figure 1).

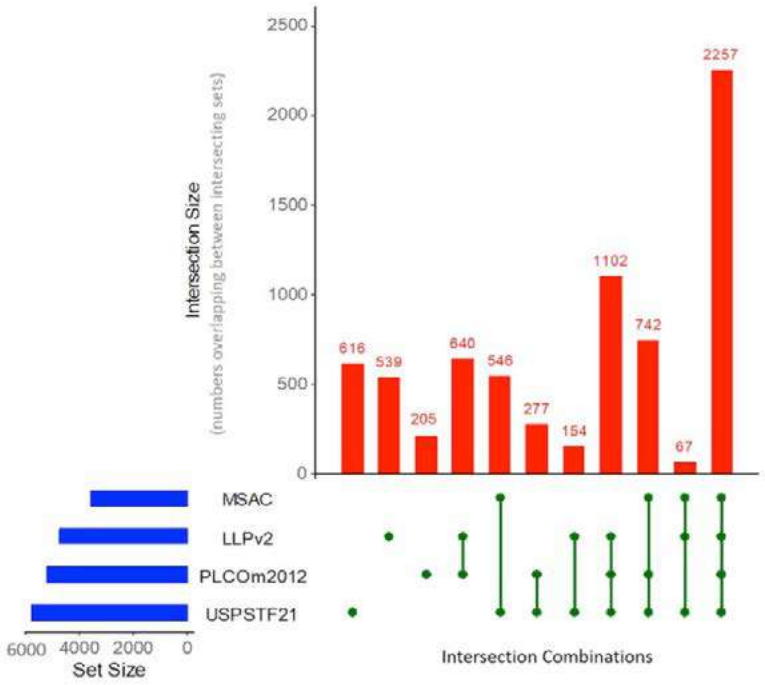
For detected lung cancers, the PLCOm2012 model identified the largest proportion (92%, n=159), while MSAC criteria identified half the cases (52%, n=90). The USPSTF2021 and the LLPv2 identified 83% (n=143) and 78% (n=134) of lung cancers, respectively.

The MSAC criteria demonstrated poor sensitivity (0.52, 95%CI 0.44-0.60), when compared to USPSTF2021 (0.83, 95%CI 0.76-0.88) criteria, and LLPv2 (0.77, 95%CI 0.7-0.83) and PLCOm2012 (0.92, 95%CI 0.87-0.96) risk models, at selected thresholds.

Conclusions: Compared to other selection criteria and risk-prediction models for assessment of lung cancer screening eligibility, the proposed MSAC criteria lacks sensitivity. Under MSAC criteria fewer individuals are eligible and fewer lung cancers would be detected. Continuing evaluation of MSAC optimal selection criteria for the Australian NLCSP will be required after establishment in 2025.

Keywords: Lung Cancer Screening, Participant Eligibility, Selection Criteria

Figure 1. The UpSet plot below describes the size of the screening cohort selected by each eligibility criteria in the blue bar plot (bottom-left), with the intersections (i.e. overlap of individuals selected for eligibility) indicated by the green dot matrix, described by size in the red bar plot.



MA18 NEW PARADIGMS IN LUNG CANCER SCREENING
TUESDAY, SEPTEMBER 10, 2024 - 15:00 - 16:15

MA18.04 Evaluating Early-Stage Lung Cancer Survival Based on Age and Morbidity to Inform the Upper Age Limit for Screening

M.T. Warkentin[1], E. Vakil[1], E.L.R. Bedard[2], W.Y. Cheung[1], D.R. Brenner[1], A. Tremblay[1], [1]University of Calgary, Calgary/AB/CA ,[2]University of Alberta, Edmonton/AB/CA

Introduction: Lung cancer is the leading cause of cancer-related mortality globally. Older individuals have an elevated lung cancer risk, but those with significant comorbidities also have greater competing risks for mortality. This could preclude curative treatment options and reduce the survival benefits of screening. The objective of this study was to inform the upper age limit for lung cancer screening by assessing early-stage lung cancer survival based on comorbidities and fitness for surgery.

Methods: We used the Alberta Cancer Registry (ACR) to identify all lung cancers diagnosed in Alberta, Canada between 2010 and 2020. Only early stage (I or II) lung cancers were included. We defined five age groups based on the following categories: <70, 70-74, 75-79, 80-84, and 85+. Overall survival was based on the time from the date of lung cancer diagnosis until the date of death (any cause) or a censoring date based on the last known date of follow-up. We estimated overall survival using the Kaplan-Meier method. We present the five-year overall survival with 95% confidence intervals (CI) for each age group and sex and stratified by Charlson Comorbidity Index and receipt of surgery.

Results: There were 6,401 patients with early-stage lung cancers (71% stage I, 29% stage II) in the ACR between 2010 and 2020, of which 43% and 57% were among males and females, respectively. For females, the five-year survival was 54.7% (CI: 50.6-58.8), 47.2% (CI: 42.7-51.7) and 33.7% (CI: 28.4-38.9) for ages 70-74, 75-79, and 80-84, respectively. For males, five-year survival was 47.7% (CI: 43.1-52.3), 38.0% (CI:33.2-42.8), and 24.2% (CI: 19.2-29.3) for ages 70-74, 75-79 and 80-84, respectively. Across all age groups, the five-year survival was higher for those with fewer comorbidities and who received surgery as part of their treatment strategy (Figure 1). Five-year survival for males and females ages 75-79 and 80-84 was still high and may suggest that lung cancer screening among selected individuals in these age groups may confer substantial survival benefit.

Conclusions: Some older age patients have reasonable survival and may still benefit from screening despite being ineligible according to most guidelines. Application of upper age limits to lung cancer screening should consider comorbidity and fitness for surgery since these can significantly influence the survival benefit derived from early detection. The criticisms of risk-based approaches for preferentially selecting older individuals for screening may only be warranted among those with significant comorbidities that would limit their survival benefit.

Keywords: Lung cancer screening, Early detection, Screening guidelines

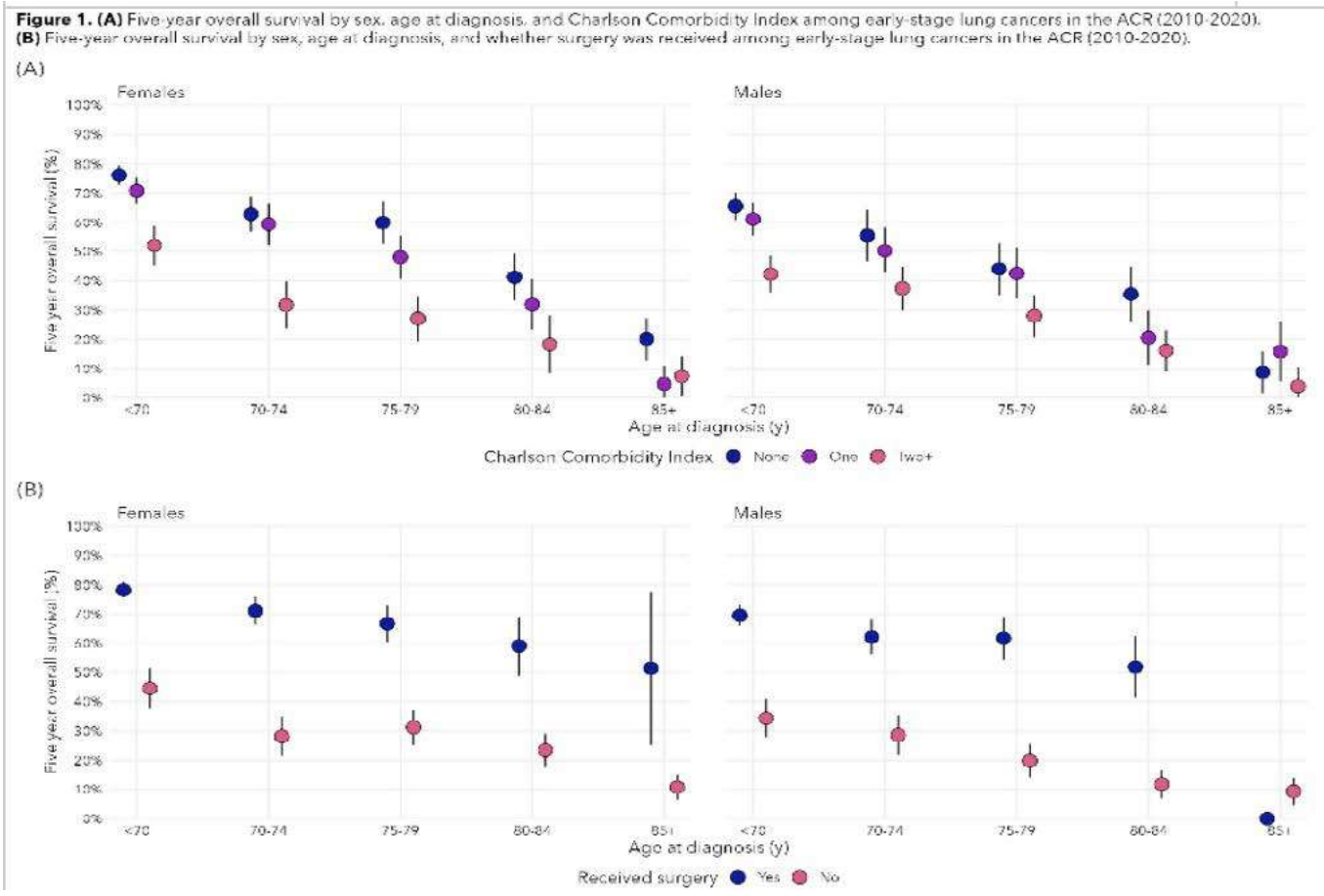


Figure 1. (A) Five-year overall survival by sex, age at diagnosis, and Charlson Comorbidity Index among early-stage lung cancers in the ACR (2010-2020). **(B)** Five-year overall survival by sex, age at diagnosis, and whether surgery was received among early-stage lung cancers in the ACR (2010-2020).

MA18 NEW PARADIGMS IN LUNG CANCER SCREENING
TUESDAY, SEPTEMBER 10, 2024 - 15:00 - 16:15

MA18.05 Effectiveness of NELSON vs PLCOm2012 Lung Cancer Screening Eligibility Criteria: Final Analysis of the Prospective German HANSE Study

J. Vogel-Claussen[1], B. Bollmann[1], K. May[2], S. Stiebeler[3], S. Dettmer[1], A. Faron[3], A. Kuhlmann[4], G. Schmid-Bindert[5], R. Kaaks[6], J. Barkhausen[2], S. Bohnet[2], M. Reck[7], [1]Hannover Medical School, Hannover/DE ,[2]UNIVERSITÄTSKLINIKUM Schleswig-Holstein Campus Lübeck, Lübeck/DE ,[3]Radiologische Allianz GbR, Grosshansdorf/DE ,[4]Universitätsmedizin Halle, Hannover/DE ,[5]Medizinische Fakultät Mannheim, Universität Heidelberg, Mannheim/DE ,[6]Deutsches Krebsforschungszentrum, Heidelberg/DE, [7]Lungeenclinic Grosshansdorf, Grosshansdorf/DE

Introduction: Lung cancer is a major health problem. CT lung screening can reduce lung cancer mortality through early diagnosis. Retrospective analyses and one prospective trial using the USPSTF2013 criteria suggest that identifying individuals for screening by accurate prediction models is more efficient than using categorical age-smoking criteria. This study prospectively compared the effectiveness of the Netherlands Leuvens Longkanker Screenings Onderzoek (NELSON) and PLCOm2012 model eligibility criteria.

Methods: In this prospective northern German cohort study (HANSE), participants, aged 55-79 years, who were current or former smokers and who met either NELSON risk criteria (smoking quit time ≤10 years, >15 cigarettes/day for >25 years or >10 cigarettes/day for >30 years) or a PLCOm2012 risk threshold of at least 1.58% within 6 years of screening, were recruited from 3 certified lung cancer sites (Hannover, Grosshansdorf, Lübeck) and received baseline and one year follow-up low-dose CT screening (Rofo. 2022 Dec;194(12):1333-1345). Main outcome was the comparison of the positive predictive values (PPV) for lung cancers detected in PLCO m2012-selected vs. NELSON-selected high-risk groups. For testing the null hypothesis of equal PPVs for lung cancer detected in PLCOm2012-selected versus NELSON-selected individuals, the weighted generalized score statistic by Kosinski was used (ClinicalTrials.gov, NCT04913155).

Results: The cancer detection rate of participants with lung cancer was significantly higher using the >1.58 % at 6 years of PLCOm2012 risk score compared to the NELSON inclusion criteria (108 [97.3%] of 111 individuals vs 85 [76.6%] individuals; p<0.0001). When the sample was supplemented with the low risk population, who did not meet the high-risk criteria and consented to participate in the HANSE study (n=7463), the calculated lung cancer detection rates (sensitivity) of the NELSON criteria and the PLCOm2012 threshold of >1.58% at 6 years were 60.7 % and 77.1%, respectively. Accordingly, the HANSE study showed a 19.4% relative increase of the PPV for screen detected lung cancers in the PLCOm2012-selected group (PPV=108/4167 [2.59%] compared to the NELSON-selected group (PPV=85/3916 [2.17%], p=0.004). After adjusting the PLCOm2012 risk score cutoff to > 1.68 % at 6 years to achieve equal sized groups the specificity values were not significantly different (69.4% vs 69.6%, p=0.68), while sensitivity remained significantly higher (106/109, [97.3%]) and PPV even increased to 106/ 3916 (2.71%, relative difference 24.7%) in the PLCOm2012 risk vs the NELSON criteria group. Cumulative estimated life expectancies from baseline for those subsequently diagnosed with lung cancer were higher in those who had PLCOm2012 risk of > 1.68 % at 6 years than in individuals who were NELSON-positive (1650.3 years vs 1405.5 years; difference 244.8 years, p=0.021). Despite no differences in the PLCOm2012 score (p=0.44), a significant higher rate of lung cancer was detected in females (2.63%) vs. males (1.78%, p=0.04) in the high-risk HANSE cohort.

Conclusions: PLCOm2012 is reliable and more efficient than the NELSON criteria for selecting individuals to be enrolled into a lung cancer-screening program and should be used for identifying high-risk individuals based on the results of the HANSE Study. Further research adjusting risk scores for gender should be considered.

Keywords: lung cancer screening, low dose CT, risk score

MA18 NEW PARADIGMS IN LUNG CANCER SCREENING
TUESDAY, SEPTEMBER 10, 2024 - 15:00 - 16:15

MA18.07 Missing Variables and the Utility of Lung Cancer and Lung Nodule Risk Calculators

W. Liao[1], A.T. Matthews[2], J.U. Goss[1], T.U. Qureshi[1], S.U. Peppers[1], A.U. Harris[1], A.U. Porter[1], K.U. Dortch[1], C. Fehnel[1], K. Tonkin[3], M.A. Ray[4], A. Mehrotra[3], S. Ely[5], M.P. Smeltzer[4], R.U. Osarogiagbon[1], [1]Baptist Cancer Center, Memphis/TN/USA ,[2]Baptist Memorial Health Care, Memphis/TN/USA ,[3]Baptist Memorial Hospital, Memphis/TN/USA ,[4]University of Memphis, Memphis/TN/USA ,[5]George Washington University, Washington/DC/USA

Introduction: Early lung cancer detection depends on screening healthy high-risk individuals, and assessing the malignancy probability of lung nodules (LNs). Validated risk calculators help identify candidates for lung cancer screening (LCS), and triage individuals with LNs. We evaluated variables required in three LCS, and two LN malignancy risk calculators, to assess the feasibility of using natural language searches to automate their use.

Methods: We analyzed a prospective observational LCS and incidental LN program (P) database abstracted from routinely generated clinical records. Using information at initial enrollment, we evaluated the availability of component variables for three LCS risk calculators- PLCOm2012, Lung Cancer Death Risk Assessment Tool (LCDRAT), and the Bach model- and two LN malignancy risk calculators- the Brock University and Solitary Pulmonary Nodule Malignancy Risk (Herder) models. The three LCS risk calculators were examined in all LCS patients and LNP enrollees age-eligible for LCS; the two LN risk calculators were examined in all LNP enrollees and LCS patients with Lung-RADS 2 - 4 (indicating presence of a lung lesion).

Results: From 2015 to 2023, 13,823 and 29,712 persons were enrolled into LCS and LNP. Among the LCS cohort, 8,576 (62%) had a Lung-RADS score of 2 or greater; 20,507 (69%) of LNP enrollees met age criteria for LCS. Overall, 1,328 (9.61%), 1,325 (9.59%), and 3,926 (28.4%) of LCS enrollees had all variables needed for the PLCOm2012, LCDRAT and Bach models, respectively; 137 (0.46%) and 1,491 (5.02%) of LNP enrollees had all variables needed for the Brock and Herder models, respectively. Missing information on education and family history of lung cancer impaired use of the PLCOm2012 and LCDRAT; the Bach Model suffered less than 10% missing data. Missing data on nodule attenuation (85%) and edge characteristics (93%) impaired use of the Brock and Herder models. Among the LNP cohort age-eligible for LCS, 2,414 (11.77%), 2,414 (11.77%) and 10792 (52.63%) had all the variables needed to use the PLCOm2012, LCDRAT and Bach models, respectively; among the LCS cohort with Lung-RADS 2-4, 949 (11.07%) and 1,636 (19.08%) had all the variables needed to use the Brock and Herder models, respectively (Table).

Conclusions: Although validated risk calculators can be useful in triaging patients into risk-based pathways of care, they require variables not routinely provided during care delivery, limiting their practical utility. Key nodule descriptors were most frequently missing from radiology reports, likely preventing the automation of their use for natural language processing algorithms.

Keywords: Radiologist, Missing Data Variables, Screening

Percentage of missing variables in Lung Cancer Screening (LCS) and Lung Nodule Program (LNP) cohorts at initial enrollment		
Risk model and component variables	**LCS* N = 8576**	**LNP* N = 20507**
PLCOm2012: Proportion with all variables available, n (%)	**777 (9.06)**	**2414 (11.77)**
Age	0	0
Race	1.47	1.19
Education	68.24	78.07
BMI	2.29	4.11
COPD	0	0
Personal history of cancer	0	0
Family history of lung cancer	23.01	28.41
Smoking status	0.2	4.05
Smoking intensity (packs per day)	6.17	27.49
Duration of smoking	8.54	37.38
Duration of quitting	2.42	27.32
LCDRAT: Proportion with all variables available, n (%)	**776 (9.05)**	**2414 (11.77)**
Age	0	0
Gender	0	0.01
Heigh & Weight/BMI	2.29	4.11
Race/Ethnicity	1.47	1.19
Education	68.24	78.07
History of Lung Disease	0	0
Family History of Lung Cancer	23.01	28.41
Smoking Status	0.2	4.05
Age on Set	9.01	39.92
PPD	6.17	27.49
Quit Years	2.42	27.32
Bach Model: Proportion with all variables available, n (%)	**2429 (28.32)**	**10792 (52.63)**
Cigarettes per day	6.17	27.49
Duration of smoking	8.54	37.38
Duration of quitting	2.42	27.32
Age	0	0
Asbestos exposure	0	0
Sex	0	0.01
Brock Model: Proportion with all variables available, n (%)	**949 (11.07)**	**112 (0.55)**
Age	0	0
Sex	0	0.05
Family history of lung cancer	23.01	29.92
Emphysema	0	0
Nodule size	3.4	7.75
Nodule type (density or attenuation)	81.84	84.58
Nodule location	1.75	3.28
Nodule count	0.03	11.34
Nodule edge characteristics (spiculation)	93.8	93.14
Herder Model: Proportion with all variables available, n (%)	**1636 (19.08)**	**1135 (5.53)**
Age	0	0
Smoking status (current/former)	0.2	4.05
Extra-thoracic cancer more than 5-years?	0	0
Nodule diameter	3.4	7.75
Nodule location	1.75	3.28
Nodule edge characteristics (speculation)	93.8	93.14
PET scan	0	0.81

MA18 NEW PARADIGMS IN LUNG CANCER SCREENING
TUESDAY, SEPTEMBER 10, 2024 - 15:00 - 16:15

MA18.08 Risk and Timing of Second Primary Lung Cancer Among Young Women with a History of Breast Cancer in the United States

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Introduction: Young women with a history of breast cancer may benefit from lung cancer screening, despite not meeting requisite age or smoking pack-year eligibility criteria. However, the risk of lung cancer diagnosed among young women with a history of breast cancer has never been studied. Our objective was to evaluate the incidence, timing, and predictors of lung cancer diagnosed among young women with a history of breast cancer.

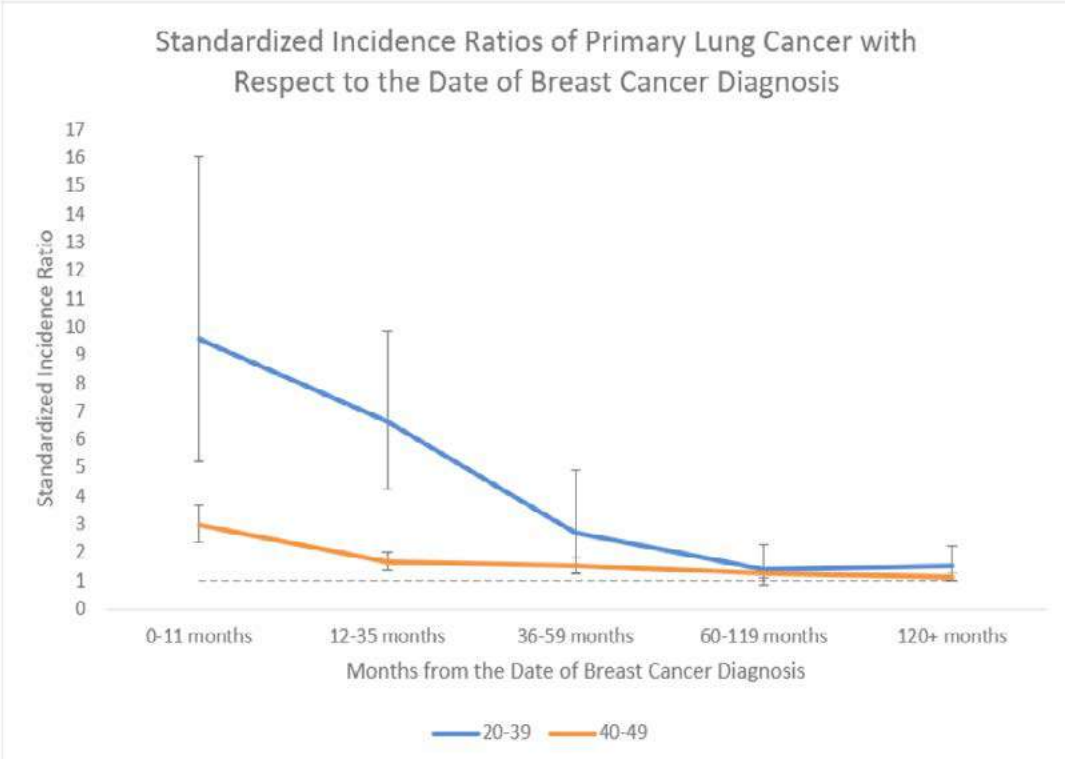
Methods: Women aged <50 years diagnosed with breast cancer from 2000-2018 in the Surveillance Epidemiology End Results database were identified for analysis. The incidence of primary lung cancer among women in the study cohort was compared to the incidence of primary lung cancer among an age, sex, race, and calendar year-matched cohort in the general U.S. population using standardized incidence ratios. Patterns in the time from breast cancer diagnosis to lung cancer diagnosis were examined. Fine-Gray competing risks regression was used to identify predictors of an increased risk of primary lung cancer among young women in the study cohort. Five-year survival after lung cancer diagnosis was examined by stage using the Kaplan-Meier method.

Results: From 2000-2018, 891 women aged <50 diagnosed with breast cancer developed lung cancer. The incidence of lung cancer among young women with a prior breast cancer diagnosis, compared to young women in the general population, was significantly elevated for 5 years after breast cancer diagnosis (Figure). The median time from breast cancer to lung cancer diagnosis was 6.58 (IQR: 2.83-11.0) years. Of lung cancers diagnosed, the stage distribution was 27% stage I, 7% stage II, 23% stage III, and 43% stage IV. There were disparities in the stage of lung cancer diagnosed, and 55% of Black women were diagnosed with stage IV disease compared to 42% of White women. Predictors of increased risk of lung cancer included older age and patients living in rural compared to urban regions. Five-year survival from the date of diagnosis of stage I, II, III, and IV lung cancer was 77%, 61%, 34%, and 9%, respectively.

Conclusions: Young women diagnosed with breast cancer had a significantly increased risk of developing primary lung cancer. Over 40% of lung cancers were diagnosed at stage IV when five-year survival was 9%. These findings suggest the need to explore the possibility of lung cancer screening in this patient population, especially among women whose demographic and tumor characteristics are associated with highest risk of second primary lung cancer.

Keywords: lung cancer, breast cancer, women

Figure. Standardized Incidence Ratios of Primary Lung Cancer During the First Year, 1-3 Years, 3-5 Years, 5-10 Years, and 10+ Years After Breast Cancer Diagnosis Among Women Aged 20-39 and 40-49



MA18 NEW PARADIGMS IN LUNG CANCER SCREENING
TUESDAY, SEPTEMBER 10, 2024 - 15:00 - 16:15

MA18.09 Comparing Efficient Lung Cancer Screening Strategies for Black and White Americans

S. Skolnick[1], P. Cao[2], J. Jeon[1], R. Meza[3],[4], [1]University of Michigan, Ann Arbor/MI/USA ,[2]MD Anderson Cancer Center, Houston/TX/USA ,[3]BC Cancer Research Institute, Vancouver/BC/CA ,[4]University of British Columbia, Vancouver/BC/CA

Introduction: In 2021, the United States Preventative Services Task Force (USPSTF) updated their lung cancer screening guidelines, in part, to address documented disparities in eligibility. Black individuals are proportionally less eligible for screening compared to their White counterparts, despite having higher lung cancer risk. It is thus critical to assess the relative effectiveness of current and alternative lung screening strategies for Black individuals using race-specific data and analyses.

Methods: We used a well-validated microsimulation model of the natural history of lung cancer, CISNET MichiganLung, to evaluate screening strategies by race and identify and compare optimal strategies for the US Black and White populations. The CISNET MichiganLung model was originally developed for the whole US population, so it was adapted to the Black and White sub-populations. For both populations, we evaluated a range of screening scenarios with varying factors such as age at start and stop of screening and pack-year history. We then assessed life years gained, lung cancer deaths averted, screening harms, such as false positive screens and overdiagnosis, and identified efficient screening scenarios for Black and White Americans. Efficient scenarios were those that had the highest life years gained and/or lung cancer deaths averted for a given number of screens.

Results: Overall, efficient screening strategies for Black Americans were less restrictive (lower starting age and fewer packyears required) compared to those for White Americans. The 2021 USPSTF guidelines were found to be efficient for both populations, but the 2013 recommendations were efficient only for White Americans. Regardless, current and previous USPSTF screening recommendations appear to be substantially more beneficial for White than for Black Americans.

Conclusions: Our results suggest that screening strategies that are efficient for Black Americans are different from those for White Americans. Race-specific guidelines might be needed with a lower packyear threshold for eligibility for Black individuals.

Keywords: lung screening, disparities, decision analysis

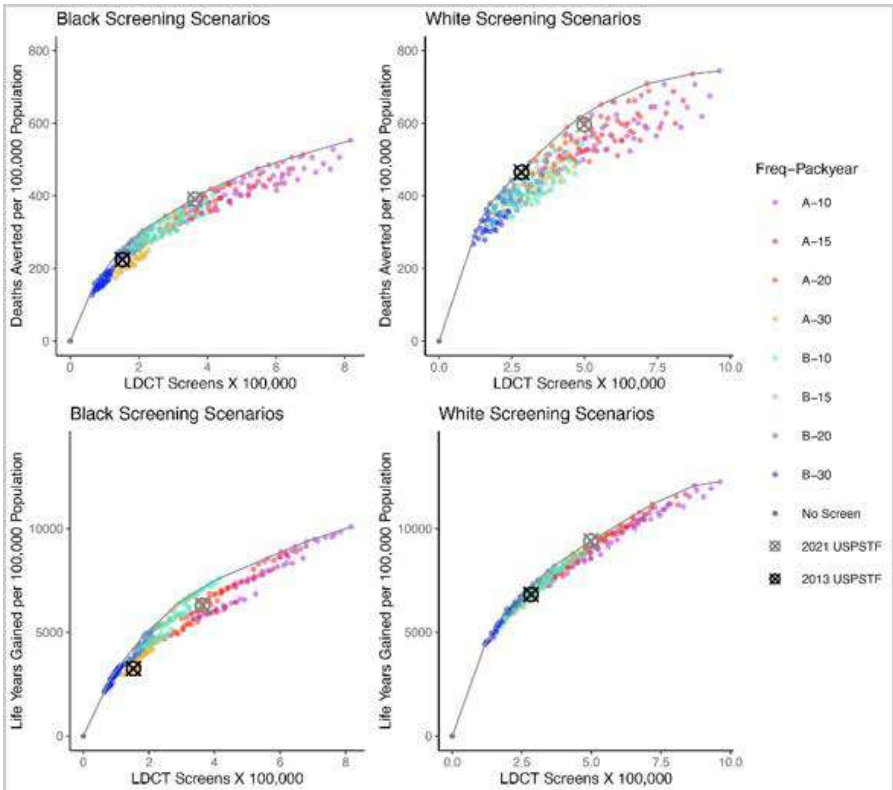


Figure 1. Low-Dose Computed Tomography (LDCT) vs. lung cancer deaths averted and life years gained for Black and White populations. Displaying patterns by frequency and pack-years.

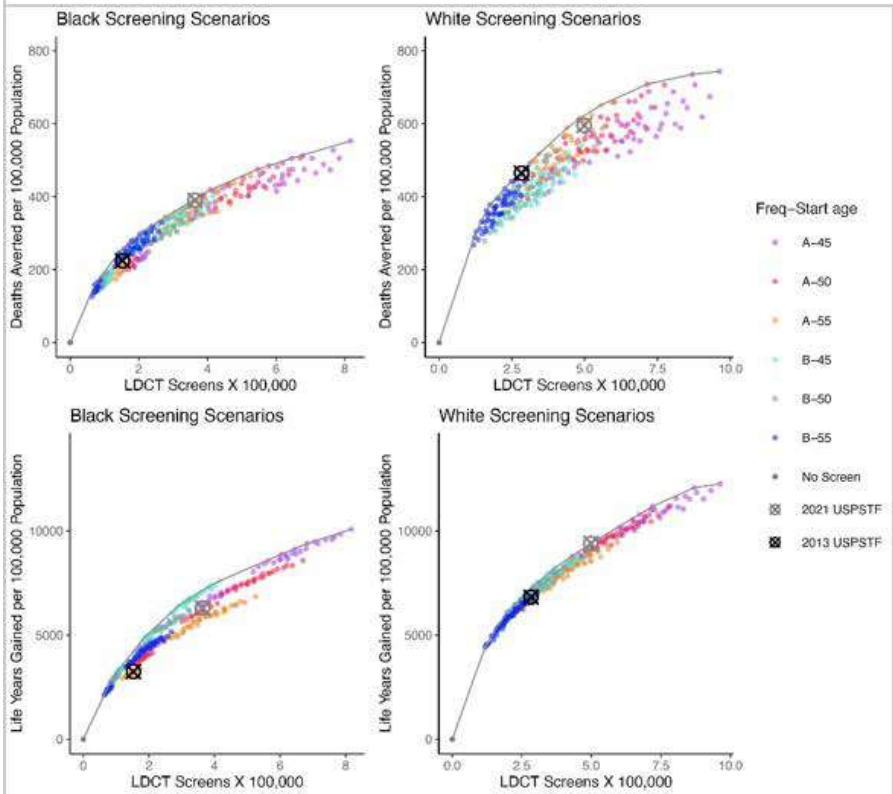


Figure 2. Low-Dose Computed Tomography (LDCT) vs. lung cancer deaths averted and life years gained for Black and White populations. Displaying patterns by frequency and age at start.

MA18 NEW PARADIGMS IN LUNG CANCER SCREENING
TUESDAY, SEPTEMBER 10, 2024 - 15:00 - 16:15

MA18.11 The Evolution of the Lung Screening Network: Uniting to Strengthen Community and Share Best Practices Among Navigators

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Introduction: Lung cancer is the leading cancer of cancer mortality accounting for about 20% of cancer deaths1. The United States Preventive Services Task Force3 and Centers for Medicare and Medicaid Services2 approved coverage of lung cancer screening (LCS) following the National Lung Cancer Screening Trial, which demonstrated that LCS reduces lung cancer mortality3. Following these approvals, healthcare organizations began to develop LCS programs with navigators assuming these roles without formal education or training on LCS. A LCS navigator from Chicago, Illinois observed that in healthcare institutions, a single navigator was responsible for coordination of all care and education in this new position. She recognized an opportunity to locally collaborate and network which prompted the convening of an October 2019 in-person meeting of navigators to discuss their respective LCS programs. At that initial meeting, navigators working for competing healthcare organizations voiced the need to share and learn from each other. From there, the Lung Screening Network (LSN) was founded. Its mission was to create a consortium of professionals involved in LCS to strengthen individual programs and bring greater awareness to the emerging discipline of LCS.

Methods: Broad use of virtual platforms during the Covid-19 pandemic allowed for the first virtual LSN meeting in late 2020. The LSN has since continued to meet virtually every other month. A steering committee comprised of five navigators with over 30 years combined screening experience was established to lead the LSN. The committee meets at least twice per month focusing on delivering relevant best practices and educational content at every LSN meeting.

Results: Growth: LSN Member Volumes by Year: 2019: 27; 2020: 54; 2021: 83; 2022: 106; 2023: 122; LSN Member Geographic Reach: 2019: Illinois, Indiana; 2024: Illinois, Arizona, California, Iowa, Indiana, Kentucky, Michigan, North Carolina, New Jersey, Wisconsin, Georgia, United Kingdom, US Partners with national reach Advocacy and Community: Prior to updated LCS guidelines in 2021, 18 LSN members representing nearly 100,000 LCS exams submitted commentary to CMS endorsing expansion of LCS eligibility criteria. Partnerships: National Lung Cancer Round Table, American College of Radiology, American Lung Association, GO2 Foundation for Lung Cancer Focus on LCS Navigator Needs: LSN members completed a survey in 2023 to understand the LSN audience and to provide meaningful content and support. The results include: 64% from the LSN home state of Illinois. 25% of programs began in 2015 while 21% began in 2020 or later. 70% are nurse navigators, 60% have responsibilities beyond LCS. Members requested further support in retention, communication, and data management.

Conclusions: The LSN adds value to LCS navigators as evidenced by growth, increased advocacy, and the need to address common issues among diverse programs. Currently, the LSN committee volunteers time and uses platforms borrowed from healthcare systems to plan and host meetings. The group continues to evolve with limited infrastructure or monetary support. Future considerations include exploring new opportunities for LSN growth and navigator support.

Keywords: Screening, Navigators, Advocacy

MA18 NEW PARADIGMS IN LUNG CANCER SCREENING
TUESDAY, SEPTEMBER 10, 2024 - 15:00 - 16:15

MA18.12 Innovations in Lung Cancer Screening: Adoption of the Pink and Pearl Campaign

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Introduction: Lung cancer is an often-overlooked women's health concern. According to the American Lung Association, only 8% of adults recognize lung cancer as the #1 cancer killer of women. Lung cancer screening (LCS) is the only approved method for screening patients identified as high risk for lung cancer; however, LCS faces distinctive barriers including complicated eligibility criteria, lack of awareness, and stigma. In the United States roughly 80% of women eligible for mammography complete the recommended screening, while only 7% of people eligible for LCS complete screening. Tennessee's Department of Health launched the first Pink and Pearl Campaign to raise awareness for breast and lung cancer screening, simultaneously. Building upon this initiative, our institution tailored and implemented a similar campaign to identify patients undergoing mammography who might also qualify for LCS. Our campaign's objective is to identify, educate, and facilitate LCS among women already engaged in preventative care mammography.

Methods: Our multidisciplinary team, consisting of thoracic surgeons, primary care providers, radiologists, and breast surgeons, led by a LCS nurse navigator convened to plan and implement Pink and Pearl. Several in-person and virtual patient and provider facing educational events were held during the months of October and November 2023, which respectively coincided with Breast Cancer Awareness Month and Lung Cancer Awareness Month. These events were promoted internally via email, fliers, and posters. A continuous outreach program was developed to directly target women undergoing mammography. An existing screening tool routinely completed at mammogram appointments was modified to identify patients that may be eligible for LCS. Patients identified were contacted by lung screening nurse navigators to facilitate LCS. The navigators assessed LCS eligibility, discussed shared decision-making including tobacco cessation, and facilitated ordering LCS with the patient's primary care provider. Eligibility status, eligible patient follow-up plan, and reason for ineligibility were recorded by the navigators.

Results: 8 total events were hosted during October and November 2023. Format: 6 in person, 2 virtual; Audience: 4 patients, 1 healthcare providers, 3 both. Over a 5-month period, 225 patients were identified to receive outreach by LCS nurse navigators. 65 Not reached, 36 Ineligible for LCS, 124 Eligible for LCS: 56 Already enrolled in a LCS program, 27 Declined LCS, 41 LCS Orders requested.

Conclusions: Utilizing a multidisciplinary approach to target at risk patient populations already engaged in preventive care is an effective method for healthcare institutions to try to increase LCS rates. It is important to consider the complicated and inconsistent guidelines for LCS that will likely contribute to the persistent low uptake of LCS.

Keywords: Screening, Nursing, Collaboration

MA18 NEW PARADIGMS IN LUNG CANCER SCREENING
TUESDAY, SEPTEMBER 10, 2024 - 15:00 - 16:15

MA18.13 Comparison of Sybil with Brock and PLCOm2012 Models Among Screening Participants with Positive and Negative Baseline Screens

R. Meza[1,2], C. Durney[1], Y. Mok[1], S. Atkar-Khattra[1], R. Phellan Aro[3], M.T. Warkentin[4], M. Tammemagi[5], R. Myers[1,2], R.J. Hung[3], S. Lam[1], [1]BC Cancer Research Institute, Vancouver/BC/CA ,[2]University of British Columbia, Vancouver/BC/CA ,[3]Lunenfeld-Tanenbaum Research Institute, Sinai Health, Toronto/ON/CA ,[4]University of Calgary, Calgary/AB/CA ,[5]Brock University, St. Catharines/ON/CA

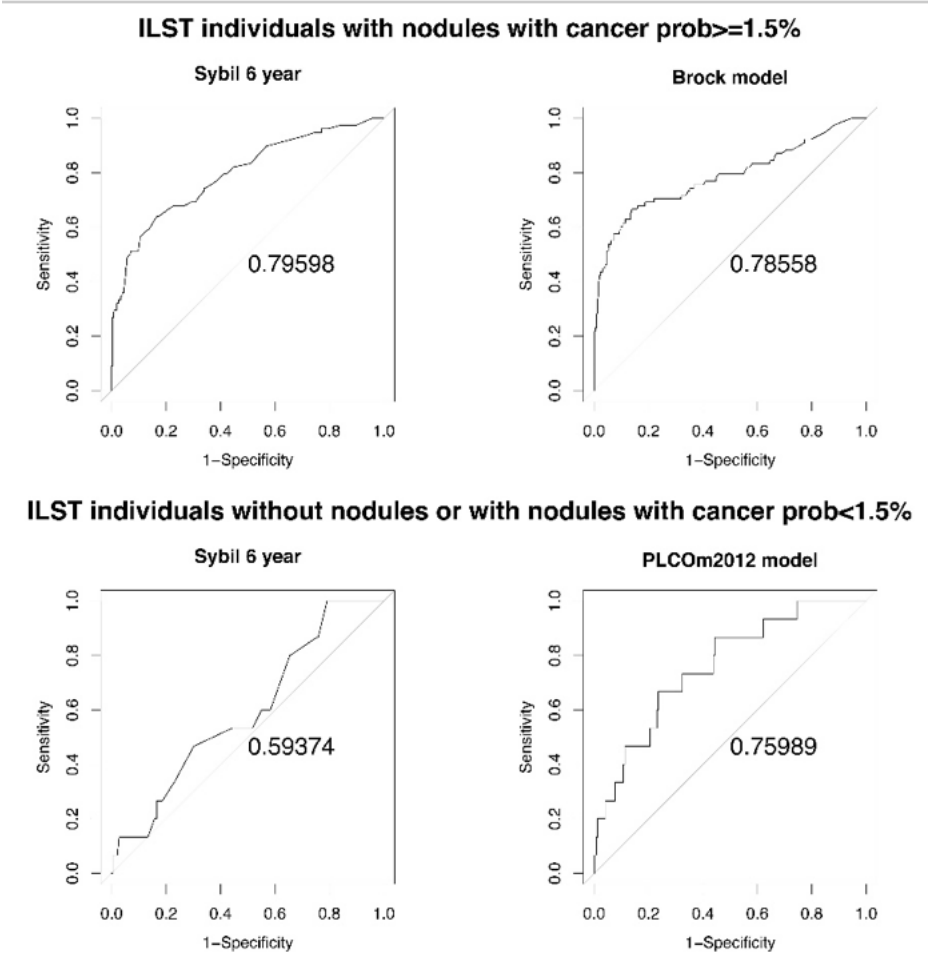
Introduction: There is growing interest in using artificial intelligence (AI) decision-support tools to enhance lung cancer risk prediction. A deep learning model (Sybil) has been proposed to predict future lung cancer risk for up to six years from a single low-dose computed tomography (LDCT) to personalize lung cancer screening. The ability to accurately stratify screen participants with lower risk who can have their next screening or surveillance CT in 2 to 6 years has significant implications for health care resource utilization, radiation exposure and costs. The purpose of our study is to evaluate the performance of Sybil versus the International Lung Screening Trial (ILST) protocol, where participants with no nodules detected on the first LDCT or with nodules with <1.5% lung cancer probability based on the Brock malignancy score (PanCan model) were triaged to have their next LDCT in 24 months (71% of the entire screened cohort belong to this negative screen category with 0.19% of them diagnosed with lung cancer within 24 months).

Methods: Baseline LDCTs from the ILST Vancouver (N=2121) and the Pan-Canadian Early Detection of Lung Cancer Study (PanCan, N=2192) were analyzed with Sybil. The performance of Sybil was compared with the PLCOm2012 lung cancer risk prediction model for individuals with no nodules or with nodules <1.5% Brock lung cancer probability (termed here as negative screens). We also compare the performance of Sybil versus the Brock model in participants with lung nodules with lung cancer probability greater than 1.5%. Model performance was assessed using the area under (AUC) the receiver-operating-characteristic (ROC) curve.

Results: Among patients with negative screens, PLCOm2012 performed better with AUCs of 0.760 in ILST versus 0.59 for Sybil (Figure 1). The Brock model and Sybil had similar performance in patients with lung nodules with malignancy risk >1.5%. The AUCs were 0.786 and 0.796 for Brock and Sybil respectively. Similar results were obtained when the comparisons were performed using the PanCan dataset (AUCs 0.633 in PanCan, 0.560 for Sybil in the negative screens; 0.753 in PanCan versus 0.743 in Sybil for scans with nodule malignancy risk scores >1.5%). The performance of all models improved after recalibration with additional smoking covariates.

Conclusions: The performance of AI tools needs to be compared with existing lung cancer risk prediction tools using cohorts with adequate follow-up and known outcomes before prospective evaluation in clinical settings.

Keywords: lung cancer screening, artificial-intelligence, risk prediction



MA19 INNOVATIVE THERAPEUTIC APPROACHES AND MOLECULAR INSIGHTS IN LUNG CANCER
TUESDAY, SEPTEMBER 10, 2024 - 15:00 - 16:15

MA19.03 SMARCA4 Controls State Plasticity in SCLC Through Regulation of Neuroendocrine Transcription Factors and REST Splicing

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Introduction: Small Cell Lung Cancer (SCLC) accounts for 15% of all lung cancer cases and is classified into transcriptional subtypes with distinct degrees of neuroendocrine (NE) differentiation. The majority (~75%) of SCLC tumors, including those of the SCLC-A (ASCL1+) and -N (NEUROD1+) subtypes, exhibit a high-NE profile. Recent evidence supports plasticity among subtypes with a bias toward adoption of low-NE states during disease progression or upon acquired chemotherapy resistance. Notably, the regulators involved in SCLC subtype switching have not been fully defined. Pharmacologically tractable targets to constrain subtype plasticity in SCLC could have substantial clinical utility. Here, we evaluated the role of SMARCA4, the catalytic subunit of the SWI/SNF complex, in tumor plasticity and as a therapeutic target in SCLC.

Methods: SMARCA4 expression levels were assessed at the CCLE and public patient databases. ATACseq and RNAseq experiments were performed in SCLC cells after treatment with FHD-286, a SMARCA4/2 dual ATPase inhibitor. DNA binding profile of SMARCA4 was characterized by ChIPseq in high-NE SCLC Patient Derived Xenografts (PDXs). Combination of FHD-286 and afatinib was tested in vitro and in a set of chemo-resistant SCLC PDXs in vivo.

Results: SMARCA4 expression positively correlates with NE genes in both SCLC cell lines and patient databases. Pharmacological inhibition of SMARCA4 with FHD-286 induces the loss of NE features and downregulates neuroendocrine and neuronal signaling pathways while activating non-NE factors. Mechanistically, SMARCA4 binds to the promoter of the NE-lineage transcription factors ASCL1 and NEUROD1, and to other NE genes, including SYP, FOXA1, FOXA2, INSM1, CHGA and DLL3. Enrichment analysis of high-confidence SMARCA4 targets, identified by integrating ChIPseq and RNAseq data, revealed neuron related pathways among the top GO Biological processes regulated by SMARCA4 in SCLC. Additionally, ATAC-seq experiments showed that SMARCA4 inactivation alters chromatin accessibility, predominantly at enhancer regions, to suppress NE programs. In parallel, SMARCA4 also controls REST, a known suppressor of the NE phenotype. We found that the RNA splicing factor of REST, SRRM4, is only expressed in tumor types with both high SMARCA4 and NE/neuronal features. Interestingly, SMARCA4 binds to the transcription starting site of SRRM4 and promotes the splicing of REST into the inactive neuron-specific isoform, REST4, to sustain the NE state in SCLC. Furthermore, SMARCA4 inhibition with FHD-286 inhibits the proliferation of SCLC NE cells at nanomolar doses (median IC50=90). Pharmacological inhibition of SMARCA4 drives the activation of ERBB and Neuroregulin-1 (NRG1) pathways by upregulating the expression of ERBB family members and subsequent downstream targets ERK and AKT. FHD-286 in combination with the pan-ERBB inhibitor, afatinib, demonstrates strong synergy in SCLC cell lines and induces greater cell death relative to single agent treatments. Dual targeting of SMARCA4 and ERBBs also exhibits a potent anti-tumor effect on chemo-resistant SCLC PDXs.

Conclusions: In summary we provide evidence for a critical role of SMARCA4 as a key regulator of the NE phenotype, as well as a potential therapeutic target for the treatment of SCLC.

Keywords: SCLC, Tumor Plasticity, Targeted therapy

MA19 INNOVATIVE THERAPEUTIC APPROACHES AND MOLECULAR INSIGHTS IN LUNG CANCER
TUESDAY, SEPTEMBER 10, 2024 - 15:00 - 16:15

MA19.04 Teriflunomide in Vitro or Leflunomide in Vivo Treatment Increases the Efficacy of Lurbinectedin in SCLC

T. Mirzapoiazova, L. Tseng, I. Mambetsariev, H. Li, B. Armstrong, S. Singhal, P. Kulkarni, R. Salgia, City of Hope National Medical Center, Duarte/CA/USA

Introduction: Inhibition of transcription is one of the strategies for targeting SCLC. Lurbinectedin is a selective inhibitor of RNA pol II, which is commonly hyperactivated in SCLC. Lurbinectedin has shown promise in treating SCLC patients after failure to first-line systemic therapy (Dumoulin et. al, 2022). Nevertheless, the 5-year survival rate remains around 6% (Koinis et. al, 2016). Previous studies have shown that Teriflunomide and Leflunomide have potent anticancer effects on human bladder cancer and NSCLC cells (Cheng et. Al, 2020; Jiang et. Al, 2018). We hypothesized that treatment with Leflunomide or a combination of Teriflunomide and Lurbinectedin can be a novel therapeutic approach to treat SCLC.

Methods: SBC3 and H446 SCLC cells were used for spheroid formation. LDH assay was used to detect drug cytotoxicity effect. Immunoblotting was performed to evaluate drug-induced cellular damage. Mitochondrial dysfunction of the spheroids was assessed by MitoSOX and ATP assays. Immunofluorescent staining and confocal microscopy were used to quantify spheroid mitochondria. RNA-seq analysis of spheroids was performed after Teriflunomide/Lurbinectedin treatment. Xenograft study was performed to test therapeutic efficacy of the Leflunomide/Lurbinectedin combination.

Results: Treatment of SBC3 spheroids with Teriflunomide/Lurbinectedin low-dose combination synergistically inhibited spheroid viability. The combination of Teriflunomide/Lurbinectedin inhibited RNA pol II activity and increased the levels of proteins related to DNA damage and replication stress. The expression of MDM2, p21, and E2F1 proteins, which are regulators of p53 and cell cycle associated cyclins, was downregulated upon combination treatment. Combination treatment also induced an increase of mitochondrial superoxide and decreased ATP production. Moreover, the combination treatment significantly decreased the level of round mitochondria and was associated with inhibition of mitochondrial fission DRP1 protein. RNA-seq results indicated a robust effect of combination treatment on critical cancer pathways in the SCLC spheroid model. Finally, the efficacy of Teriflunomide/Lurbinectedin combination was tested in SBC3 mouse xenograft model. While Leflunomide and Lurbinectedin alone inhibited tumor growth by 22 and 39%, respectively the Teriflunomide/Lurbinectedin combination acted synergistically and significantly reduced tumor growth by 83% compared to the untreated control.

Conclusions: Collectively, our data suggest combinations of Lurbinectedin with Teriflunomide or Leflunomide are a potential therapeutic approach to suppress SCLC progression. These novel results pave the way for clinical trials in the future to validate these treatment strategies in patients with SCLC.

Keywords: SCLC, Lurbinectedin, Leflunomide/Teriflunomide

MA19 INNOVATIVE THERAPEUTIC APPROACHES AND MOLECULAR INSIGHTS IN LUNG CANCER
TUESDAY, SEPTEMBER 10, 2024 - 15:00 - 16:15

MA19.05 Dynamic Immune Profile of Peripheral Blood Predicts Immunotherapy Efficacy and Prognosis in Small Cell Lung Cancer

L. Wu, J. Wang, B. Chen, X. Pu, J. Li, Y. Xu, L. Xu, Y. Kong, F. Xu, K. Li, Q. Wang, L. Liu, Hunan Cancer Hospital, Changsha/CN

Introduction: The immune profile of peripheral blood can provide abundant data on efficacy and prognosis, which is expected to provide more biomarkers and related mechanisms for exploring tumour treatment. However, the lack of biomarkers that can accurately predict efficacy and prognosis in immunotherapy for extensive small cell lung cancer(ES-SCLC) is an urgent problem.

Methods: In this study, 81 dynamic peripheral blood samples (baseline, after two cycles of treatment[C2], and progressive disease) were collected from ES-SCLC patients who received first-line immunotherapy combined with chemotherapy (n=20) and chemotherapy alone (n=7). The following proteins were performed on peripheral blood mononuclear cells cytometry by time of flight (CyTOF): CD45, CD3, CD4, CD8, CD25, CD127, CD45RA, CD45RO, CCR7, TCR$_{\gamma\delta}$, CD19, CD66b, CD14, CD56, CD16, CD11c, CD123, HLA-DR, CD38, CD57, CXCR3, CCR6, CCR4, CXCR5, CD95/Fas, LAG-3, Tim-3, CTLA-4, PD-L1, PD-1, CD278/ICOS, and TIGIT. Peripheral blood immune cells from ES-SCLC patients were finely typed, and the activation/depletion status and immune checkpoint expression levels of different immune cells were detected. We further explored the dynamic immune profile of peripheral blood that could predict the efficacy and prognosis of SCLC immunotherapy in combination with efficacy assessment and survival indicators.

Results: In the immunotherapy group, a high percentage of senescent CD4+TEM/CD4+TEM at baseline (P=0.0206) was significantly associated with longer PFS. A high percentage of $\gamma\delta$T cells (P<0.0001) and high expression of TIGIT on CD4+T cells (P=0.021) at baseline were significantly associated with shorter PFS. In contrast, in the chemotherapy group, the above peripheral blood immune profiles were not predictors of PFS with chemotherapy. In addition, dynamic changes in immune checkpoint showed that CTLA-4 and ICOS expression in total cells at disease progression was significantly higher compared with C2 in the immunotherapy group. In contrast, no such dynamic changes were observed in the chemotherapy group, suggesting that elevated CTLA-4 and ICOS expression may be related to immunotherapy resistance.A high percentage of CD8+TEM/T cells at baseline (P=0.003) and C2 (P=0.024) and a high percentage of DCs at baseline (P=0.006) were significantly negatively correlated with OS only in the immunotherapy group. PD-1 (B cells, P=0.031; NK, P=0.008; cDCs, P=0.026; pDCs, P=0.030; Early NK, P=0.007; Late NK, P=0.008; CD4+TCM, P=0.009; Naive CD4+T, P=0.014) and TIGIT (NK, P=0.037; Late NK, P=0.028) expression was significantly negatively correlated with OS in several cell subsets.

Conclusions: In SCLC peripheral blood immune cell subsets, a high percentage of senescent CD4+TEM cells and a low percentage of $\gamma\delta$T cells suggested better immunotherapy efficacy, while a high percentage of CD8+TEM cells and DC cells suggested poorer immunotherapy prognosis. Elevated expression of CTLA-4 and ICOS was associated with immunotherapy resistance. High expression of TIGIT and PD-1 was associated with a worse immunotherapy prognosis.

Keywords: small cell lung cancer, immunotherapy, biomarker

MA19 INNOVATIVE THERAPEUTIC APPROACHES AND MOLECULAR INSIGHTS IN LUNG CANCER
TUESDAY, SEPTEMBER 10, 2024 - 15:00 - 16:15

MA19.07 Targeting USP22 Suppressed Carcinogenesis and Enhanced Immune Response in KRAS-Induced Lung Cancer

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Introduction: Ubiquitin-specific peptidase 22 (USP22), a putative cancer stem cell biomarker, primarily controls key epigenetic modifications by catalyzing the removal of the mono-ubiquitin moiety from histone H2B to control gene expression. It also stabilizes proteins or regulates activities of those critical cancer drivers including SIRT1, cMyc, and CCND1, inhibits many p53 host-protective functions. Overexpression of USP22 is frequently found in various human cancers and is strongly associated with aggressive cancer growth, metastasis, recurrence, and resistance to treatment. Notably, recent studies have further revealed that USP22 stabilizes programmed-death ligand-1 (PD-L1) in cancer cells and Foxp3 in T regulatory cells (Tregs), which substantially contribute to immunosuppression in the tumor microenvironment (TME). Therefore, USP22 is also a promising target for cancer immunotherapy. In addition, mutant Kras upregulates PD-L1 in lung cancer, Kras-induced inflammation and immunosuppression play a critical role in cancer progression.

Methods: A transgenic mouse model with conditional knockout of USP22, Kras-G12D mutation, and p53 loss (USP22-Ko) was created and compared to mice bearing Kras G12D mutation and p53 loss alone (Kp) to characterize the impact of USP22 depletion on the carcinogenesis and immune response in lung adenocarcinoma. Tumor volume was assessed via micro-CT scanning. The immune infiltration in TME was displayed by immunohistochemistry and multiple immunofluorescence (mIF) analysis of immune cell specific markers of T cells and microphages. Modulated signaling pathways and immune landscape by USP22-Ko were examined by RNAseq, Spatial transcriptomics analysis, and validated by immunofluorescence and Western-blot analysis. The response of USP22-Ko lung cancer to anti-PD-L1 therapy was assessed by in vivo therapeutic experiment and was compared to treatment in Kp mice.

Results: USP22-Ko drastically suppressed the in vivo growth and progression of lung cancers and significantly prolonged the survival of cancer-bearing mice compared with Kp mice. Morphological and immunohistochemistry analysis demonstrated that USP22-Ko was associated with better differentiation, enhanced T cell immune infiltration, and decreased FOXP3+ Tregs and PD-L1 expression in mouse lung adenocarcinomas compared with Kp mice. Importantly, RNAseq and gene set enrichment analysis indicated that USP22-Ko significantly inhibited Kras signaling pathway and enhanced p53 signaling pathway, suggesting that targeting USP22 may attenuate oncogenic Kras potential and partially rescue p53 tumor suppressor function. Furthermore, Spatial transcriptomics analysis and mIF analysis demonstrated that USP22-Ko dramatically decreased macrophage cells infiltration, suppressed TGF-beta 1 signaling pathway in TME of lung adenocarcinoma compared to Kp mice. In addition, USP22-Ko potentially enhanced the therapeutic efficacy of anti-PD-1 immune checkpoint blockade on mouse lung adenocarcinoma, indicating targeting USP22 may improve immunosuppression in TME, enhance sensitivity to immunotherapy, and exerts synergistic anticancer effects.

Conclusions: Intrinsic USP22 in cancer is critical for carcinogenesis and immunosuppressive TME in Kras-mutant lung cancer; and targeting USP22 will suppress cancer progression, partially break immunosuppression in TME, and sensitize Kras-mutant lung cancer to anti-PD-L1 therapy.

Keywords: USP22, Kras-mutant lung cancer, immune response

MA19 INNOVATIVE THERAPEUTIC APPROACHES AND MOLECULAR INSIGHTS IN LUNG CANCER
TUESDAY, SEPTEMBER 10, 2024 - 15:00 - 16:15

MA19.08 Transcriptomic Features of Circulating CX3CR1+CD8+ Temra Cells as a Predictor of Chemo-Immunotherapy Response in NSCLC Patients

J. Wu[1], X. Xu[2], H. Si[1], Y. Li[2], L. Xu[1], Y. She[1], X. Hu[2], C. Chen[1], Y. Dong[3], [1]Shanghai Pulmonary Hospital, Tongji University School of Medicine, Shanghai/CN ,[2]Abiosciences, Beijing/CN ,[3]Shanghai Pulmonary Hospital, No. [507], Yangpu District, Shanghai, China, Shanghai/CN

Introduction: Our previously study (Zheng L et al. Science. 2021) on pan-cancer single-cell landscape of tumor-infiltrating T cells revealed that circulating CX3CR1+CD8+ Temra Cells harbored tumor-specific TCRs and had the highest mobility between blood and tumor microenvironment in most cancer types. Here, we further explore the transcriptomic features of CX3CR1+CD8+ Temra cells for predicting the efficacy of chemoimmunotherapy in NSCLC.

Methods: We conducted 12 single-cell RNA and TCRs sequencing for 6 paired tumor and peripheral blood samples from NSCLC patients treated with neoadjuvant chemo-immunotherapy (3 Pathological complete response vs 3 Non-pathological response). After annotating CD8+ T cell subsets, we validated whether CX3CR1+CD8+ Temra cells in peripheral blood following chemoimmunotherapy exhibit tumor-specific TCRs. Subsequently, we integrated three published datasets along with our own peripheral blood single-cell transcriptomic data of CX3CR1+CD8+ Temra cells to construct a machine learning model (logistic regression model) for predicting the efficacy of chemo-immunotherapy. Patients identified as responders if they achieved PR or CR on the first radiological assessment. Others (PD and SD) were classified as non-responders in the machine learning model. Finally, we prospectively established a multi-centers cohort with metastatic NSCLC patients treated with first line chemo-immunotherapy from April to December 2023 (NCT 06054152). The collected peripheral blood samples were subjected to fluorescence-activated cell sorting (CD45+CD8+CX3CR1+) followed by Bulk-RNA sequencing.

Results: CX3CR1+CD8+ Temra cells exhibit high expansion (ASCL2, KLF2, KLF3, ZEB2, TBX21), migration (CXCR2, CXCR1) and strong effector molecule (GZMB) and significantly enrich in patients acquired pathological complete response. In the three training datasets (Sade-Feldman M, et al. Cell. 2018, Zhang Y, et al. Cancer Cell. 2021, Liu B, et al. Nat Cancer. 2022.), the accuracy of logistic regression-based machine learning model is 94.7% to 100% in a total of 38 patients. Specifically, 88 transcriptomic features were identified in our model, such as CD9, COPE, SFRP4t and so on. Furthermore, we prospectively collected 131 samples from NSCLC patients and conducted the Bulk-RNA sequencing for sorted CX3CR1+CD8+ Temra cells. Finally, we used this cohort as the validated dataset for the machine learning model. Importantly, the overall accuracy is 81.3% with 81.8% recall rate. Due to the relatively short follow-up period (Median follow-up time: 7.8 months), we are currently unable to conduct prognostic stratification analysis.

Conclusions: Overall, our study highlights the potential utility of transcriptomic Features of circulating CX3CR1+CD8+ Temra cells as a blood-based biomarker for chemo-immunotherapy and a marker to identify frequent circulating tumor-infiltrating lymphocyte repertoires.

Keywords: CX3CR1+CD8+ Temra Cells, Chemo-Immunotherapy, Logistic regression-based machine learning model

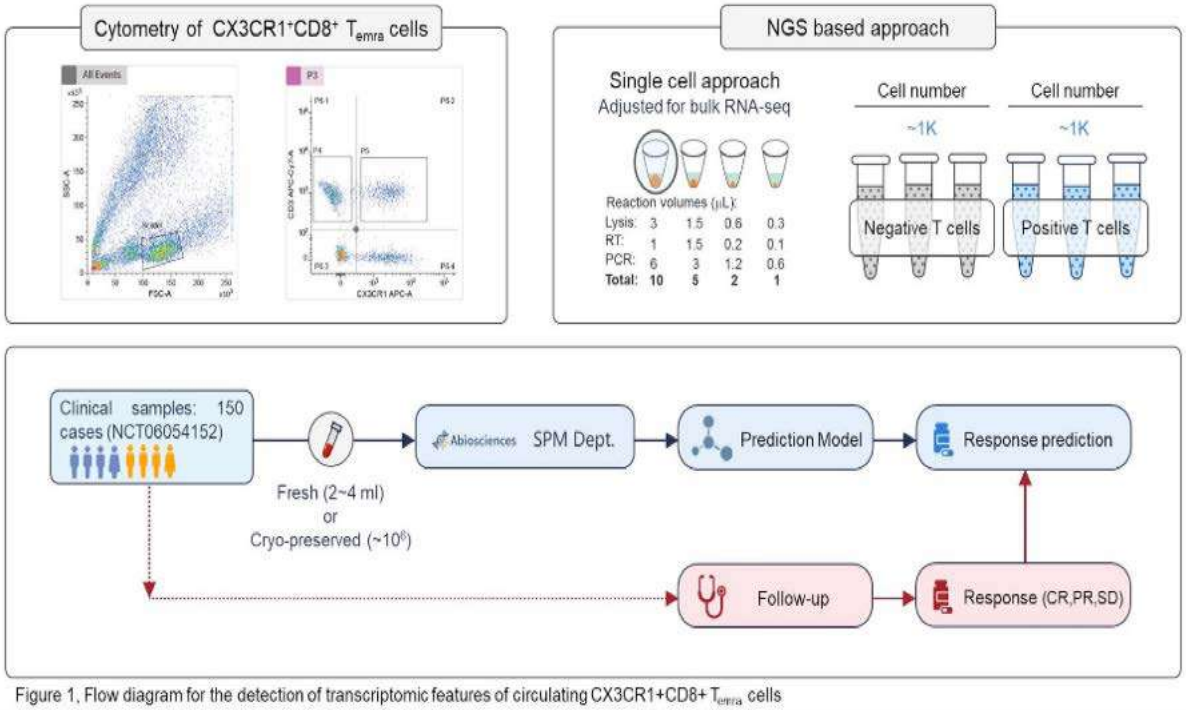

Figure 1. Flow diagram for the detection of transcriptomic features of circulating CX3CR1+CD8+ T_{emra} cells

MA19 INNOVATIVE THERAPEUTIC APPROACHES AND MOLECULAR INSIGHTS IN LUNG CANCER
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MA19.09 Q&A

MA19 INNOVATIVE THERAPEUTIC APPROACHES AND MOLECULAR INSIGHTS IN LUNG CANCER
TUESDAY, SEPTEMBER 10, 2024 - 15:00 - 16:15

MA19.10 The Tracerx 421 Cohort Provides Insights to Key Pathological Features of Lung Squamous Cell Cancer

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Introduction: Lung squamous cell carcinoma (LUSC) can present pathologically with diverse histomorphologies, principally reflecting the presence or absence of keratinization, but also reflecting other histological features. The biological basis for these variations in morphology are poorly understood. TRACERx is a multi-centre prospective observational cohort study that examines cancer evolution in non-small cell carcinoma from diagnosis to treatment. We sought to understand the genomic and evolutionary events that govern keratinization and invasiveness in LUSC within the TRACERx cohort.

Methods: By performing multi-region whole exome sequencing in 136 patients diagnosed with LUSC from the TRACERx 421 cohort, encompassing 498 tumoural regions, we examined the genomic and transcriptomic events that underlie keratinization and subclonal evolution in LUSC. Geneset enrichment analyses were performed to examine the signaling pathways associated with tumour keratinization and invasiveness. Paired primary and metastasis samples were studied to estimate the timing of metastasis divergence. The pathological and genomic features were compared for survival differences in LUSC patients.

Results: LUSC is characterized by an abundance of truncal chromosomal events across the genome. High clonal tumour mutation burden and neoantigen load is a feature of non-keratinized LUSC compared to keratinized LUSC. In a subset of keratinized LUSC where ancestor/descendent-like relationships were identified between regional samples, transition from keratinized to non-keratinized histology was frequently observed and this is associated with an increase in loss of heterozygosity events. The diverse pathological manifestations in LUSC are associated with distinct transcriptomic profiles with invasive features being associated with epithelial-mesenchymal transition and stromal breakdown-related genesets. Early metastatic divergent tumours, defined as metastatic clones diverged before the last clonal sweep within the primary tumour, dominated the cohort, suggesting that metastasis may frequently occur in LUSC before the primary tumour become clinically detectable in the imaging studies. Clinically, the interplay between keratinization, tumour budding, and the reduction in tumour infiltrating lymphocytes in LUSC may influence the patient outcome.

Conclusions: Taken together, LUSC keratinization and specific features of invasiveness are associated with distinct genomic and transcriptomic features. These data highlight the potential clinical relevance of such findings and the impact of regional histological features within those tumours demonstrating morphological heterogeneity.

Keywords: Squamous cell lung cancer, Cancer evolution, Thoracic pathology

MA19 INNOVATIVE THERAPEUTIC APPROACHES AND MOLECULAR INSIGHTS IN LUNG CANCER
TUESDAY, SEPTEMBER 10, 2024 - 15:00 - 16:15

MA19.11 In Vivo CRISPR/Cas9 Library Screening for Target Genes of SCLC Brain Metastasis

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Introduction: Immunotherapy has come of age for lung cancers, especially lung squamous cancer (LUSC) which is lack of targeted therapies. However, the efficacy of immunotherapy needs improvement, given its frequent primary and adaptive resistance.

Methods: A new strategy to generate LUSC models in mice was developed with genetically engineered lung organoids, followed with orthotopic transplant into the lung of C57B/l6 recipient mice. Histopathological assays were performed to validate these models for LUSC. Then, tumor organoids were developed from these mouse models for genome wide CRISPR/cas9 library screening. Once the sgRNA library was introduced into the tumor organoids, they were transplanted into secondary C57B/l6 recipient mice or nude mice as a control and treated with anti-PD1 antibodies. When the recipients were succumbed to the disease, tumors were harvested and the relative enrichments and depletions of sgRNAs were detected by high throughput sequencing, comparing the tumors from the C57B/l6 mice to those from the nude mice. The candidate target genes are under validation and their potential molecular mechanisms will be investigated.

Results: A serial of LUSC mouse models with different genetic drivers were established. Histopathological analyses showed that these models represented the features of human disease. Tumor organoids were successfully developed from these models and serial transplantation confirmed that these organoids remained the characteristics of the original models. A sgRNA library of 120,000 sgRNAs targeting all the coding genes of the whole genome was introduced into the organoids. Dozens of hits for ICI sensitizers were revealed by high throughput sequencing.

Conclusions: The new models would be of value for translational studies on LUSC. And the genome wide CRISPR/cas9 library screening would identify new therapeutic targets to co-operate with immunotherapy.

Keywords: LUSC, immunotherapy, CRISPR/cas9 library screening

MA19 INNOVATIVE THERAPEUTIC APPROACHES AND MOLECULAR INSIGHTS IN LUNG CANCER
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MA19.12 Identification of Novel Therapeutic Targets for SOX2 Driven Lung Squamous Cell Carcinoma

R. Navab, M-S. Tsao, B. Raught, N. Moghal, Princess Margaret Cancer Centre, Toronto/ON/CA

Introduction: Lung cancer is the leading cause of cancer mortality in Canada (25% of all deaths, Canadian Cancer Statistics, 2019) and the world. The predominant forms are adeno (50%), squamous cell (LUSC) (25%), and small cell (15%) carcinomas. Two-thirds of LUSC patients are diagnosed at advanced, nonresectable stages. The major driver mechanism of LUSC involves amplification of 3q26-28, with the SOX2 transcription factor being a key player in this amplicon, along with one of its partners, TP63. Many LUSC models have lost SOX2 and TP63 expression, making it challenging to study clinically relevant mechanisms of SOX2-mediated pathogenesis.

Methods: To better model clinical LUSC pathogenesis, we generated the MGH7 LUSC cell line and 4 long-term LUSC organoid models (XDO's) from patient and PDX tumors. These models have been characterized for mRNA expression using RNAseq and for SOX2 and TP63 expression by IHC. They were also validated to be dependent on SOX2 and TP63 by shRNA knockdown. SOX2-interacting proteins were identified by BioID in MGH7 cells grown under standard 2D culture conditions and the XDO377 organoid model grown in 3D culture. SOX2-interactors were tested for their involvement in LUSC growth through a CRISPR-Cas9 dropout screen in MGH7 cells. SOX2 target genes were also identified in MGH7 cells through shRNA-mediated SOX2 knockdown and RNAseq.

Results: Our 2D and 3D LUSC models were found to not only maintain SOX2 and TP63 expression, as observed in clinical tumors, but to also show growth dependency on these transcription factors. SOX2 BioID identified 443 and 479 SOX2-interactors in MGH7 and XDO377 organoid cells, respectively. Overall, 60% of the SOX2-interactors were common to both models. However, among many classes of well-defined transcriptional regulators (eg. chromatin remodelers, chromatin modifiers, coactivators, corepressors), the overlap was >80%. 319/443 (73%) of the SOX2-interactors identified in MGH7 cells promoted growth of these cells, as revealed in the CRISPR-Cas9 dropout screen. Many of the SOX2-interactors that promote MGH7 growth are not annotated as common essential genes in the DepMap, supporting cancer-specific functions. Experiments are currently underway to validate the non-common essential SOX2-interactors found to be hits in the CRISPR screen, and to determine how they may impact SOX2 function, and whether their function can be generalized across multiple SOX2-expressing LUSC models.

Conclusions: Compared to 2D cell culture, organoid culture may increase the likelihood that LUSC cancer cells cultured from patient tumors retain SOX2 and TP63 expression and growth dependency. However, if established to maintain SOX2 and TP63 expression, even some 2D LUSC cell lines may be equally good to 3D models, as evidenced by highly similar SOX2-interactomes. A number of SOX2-interactors that are not common essential genes promote growth of LUSC cancer models, supporting the notion that they could be good surrogate therapeutic targets for SOX2 to develop new treatment strategies for LUSC.

Keywords: Transcription Factor, Gene Expression, Organoid

POSTER PRESENTATIONS

P1.01A RISK FACTORS, RISK REDUCTION & TOBACCO CONTROL - CLINICAL TRIALS IN PROGRESS
SUNDAY, SEPTEMBER 8, 2024 - 12:00 - 14:00

P1.01A.01 The INHERIT Study - Investigating Hereditary Risk in Thoracic Cancers (NCT05587439)

J. LoPiccolo[1], V.G. Williamson[1], D.R. Koeller[1], D.R. Haradon[1], A. Harper[2], V. Kotait[2], E. Izzo[2], A. Ciupek[3], B. Addario[4], J.C. King[5], R. Erwin[2], C.A. Granville[3], J.E. Garber[1], P.A. Jänne[1], [1]Dana Farber Cancer Institute, Boston/MA/USA ,[2]Addario Lung Cancer Medical Institute, San Carlos/CA/USA ,[3]GO[2] for Lung Cancer, Washington/DC/USA ,[4]GO[2] for Lung Cancer, San Carlos/CA/USA ,[5]IASLC, Denver/CO/USA

Introduction: The contribution of inherited susceptibility to lung cancer is not well understood, particularly among those without significant tobacco exposure. Studies of germline/inherited susceptibility to lung cancer and identification of pathogenic germline mutations associated with lung cancer risk may increase understanding of potential genetic modifiers of somatic alterations in lung cancer oncogenes. Indeed, germline EGFR mutations have been identified as one cause of familial lung cancer, and previous research has outlined a syndrome of familial EGFR-mutant lung cancer predisposition across multiple unrelated kindreds (Oxnard GR, et. al., JCO, 2023). The INHERIT (Investigating Hereditary Risk In Thoracic Cancers) study (NCT05587439) aims to ascertain genetic contributors to lung tumorigenesis and establish a repository for clinicopathologic information and biologic specimens from individuals with inherited lung cancer predisposition.

Methods: INHERIT will create a data and specimen repository and follow patients with potential germline risk over time. Eligible patients fall into one of three cohorts: 1) Individuals with personal or family history of lung cancer who carry or are at high risk of carrying an EGFR T790M or other EGFR germline variant identified in blood or saliva, including via somatic single or multi-gene panel testing (MGPT), 2) Individuals with personal or family history of lung cancer who carry or are at high risk of carrying non-EGFR germline variants (e.g., HER2, TP53, ATM, BRCA1/2, CHEK2, PTEN, YAP1, and others that will be identified) that may contribute to inherited lung cancer risk, identified in blood or saliva, including via somatic single MGPT, and 3) individuals with lung cancer or family history of lung cancer who are not known to carry a pathogenic germline variant and with one of the following: more than one first-degree relative diagnosed with lung cancer, multi-generational family history of lung cancer, or personal history of multiple primary lung cancers or other neoplasms. Eligible participants are asked to complete study questionnaires to obtain lung cancer history, other medical history, social history, occupational and environmental exposure history, and detailed family history of cancer. All participants provide a research blood specimen, either at clinical centers or via remote collection using mobile phlebotomy, for whole-genome and RNA sequencing, as well as banking of serum, along with optional clinical germline multi-gene panel testing (MGPT) through a commercial laboratory. Participants with positive MGPT results (pathogenic/likely pathogenic variants) are offered genetic education and counseling and cascade testing for family members. Computed tomography (CT)-based screening will be performed in EGFR T790M carriers, who represent the largest and ideal population for screening and follow up, to better determine risk of lung cancer and age of disease onset. A multi-pronged recruitment and enrollment method is utilized to increase diversity of participants including locally at partnered clinical sites, remotely as referred by local clinical contacts, and self-referral via an IRB-approved study website (www.inheritstudy.org) with consent and enrollment by centralized study staff and remote blood collection via mobile phlebotomy. Data and specimens will be utilized primarily to create an ongoing data and specimen repository for future IRB-approved research.

Keywords: germline/inherited risk, familial lung cancer, EGFR-mutant lung cancer

P1.01A RISK FACTORS, RISK REDUCTION & TOBACCO CONTROL - CLINICAL TRIALS IN PROGRESS
SUNDAY, SEPTEMBER 8, 2024 - 12:00 - 14:00

P1.01A.02 Monitoring Inflammatory Response Secondary to Air Pollution Exposure Through Volatile Organic Compounds

R.L. Myers[1], A. Smolinska[2], C. Bartolomeu[3], F. Ricciardi[2], B. O'Brien[2], S. Thompson[2], M. Allsworth[2], B. Boyle[2], C. Carlsten[4], S. Lam[1], [1]BC Cancer, Vancouver/BC/CA ,[2]Owlstone, Cambridge/GB ,[3]BC Cancer Research Institute, Vancouver/BC/CA ,[4]Vancouver Coastal Health, Vancouver/BC/CA

Introduction: Outdoor air pollution, specifically particulate matter less than 2.5 µg/m3 (PM2.5) is known as a Group 1 carcinogen and a significant contributor to lung cancer and respiratory disease world-wide. It elevates the risk of mortality due to conditions like heart disease, stroke, and is the 5th ranking mortality risk factor as of 2015. Inflammation in the lungs is a common response to pollutants, releasing volatile organic compounds (VOCs) in breath, which can potentially serve as non-invasive markers for assessing inflammation. The aim of this study is to examine the changes over 24 hours in exhaled breath compounds and blood after an acute exposure 300µg/m3 of PM2.5.

Methods: The study uses a randomized controlled double-blind crossover design. Twenty non-smoking, healthy individuals underwent 2 separate exposures in the UBC Air Pollution Exposure Lab booth. Sessions were 4 weeks apart and consisted of diesel exhaust (DE) diluted to 300g/m3 of PM2.5 or to filtered air (FA; sham), exposures demonstrated to be indistinguishable to participants. Breath samples were analyzed using gas chromatography coupled with high-resolution mass spectrometry (Breath Biopsy®) at various time points: before exposure, immediately after, and at 0.5, 1,3, 6-, and 24-hours post-exposure. The samples were compared to blank samples to identify VOCs originating from breath rather than ambient air. Blood samples were collected at baseline, 1h 3h and 24h post exposure. Both untargeted and targeted analyses of inflammation-related VOC compounds were analyzed. Blood was analyzed via Mesoscale™, CRP, TNFµ and 8-isoprostane. Data analysis included univariate analysis using linear mixed models and multivariate techniques such as principal component analysis and ANOVA simultaneous component analysis (ASCA).

Results: ASCA revealed a significant effect of exposure type (DE vs FA, $p < 0.01$) and a significant interaction ($p < 0.05$) between post-exposure time and exposure type. Compounds related to inflammation, such as hexadecane and butanal increased significantly in the breath of individuals exposed to PM2.5 in DE vs FA. However, all samples collected 24 hours post-exposure resembled baseline samples, indicating that the observed changes post-exposure diminished within 24 hours, which corresponded with the blood panels.

Conclusions: This study demonstrates that a distinct multi-VOC profile is detectable in breath from individuals exposed to air pollution, inflammatory response was confirmed via blood panels. These findings suggest that VOCs in exhaled breath may offer a non-invasive means to detect acute airway inflammation, providing valuable insights into detecting, monitoring and treating respiratory disease (and potentially downstream effects) secondary to air pollution.

Keywords: Volatile Organic Compounds, Air Pollution, Particulate Matter

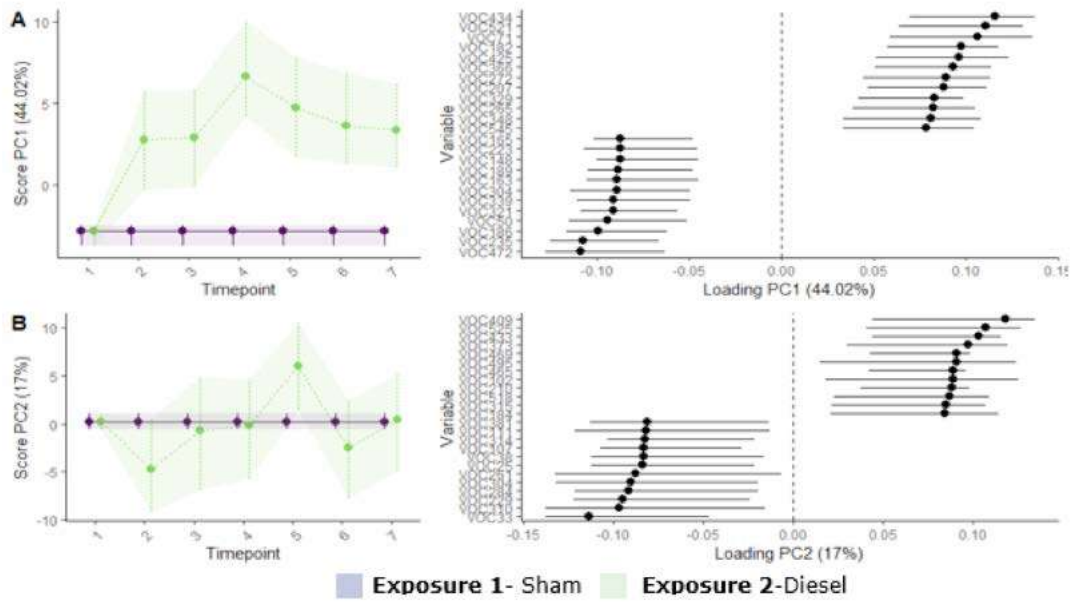


Figure 1 Multivariate analysis of measured VOCs produced during a sham vs diesel exposure over a 24-hour period.

P1.01A RISK FACTORS, RISK REDUCTION & TOBACCO CONTROL - CLINICAL TRIALS IN PROGRESS
SUNDAY, SEPTEMBER 8, 2024 - 12:00 - 14:00

P1.01A.03 Can-Prevent-Lung Trial-Canakinumab for the Prevention of Lung Cancer: Updated Interim Clinical and Biomarker Analysis

J.J. Zhang, M. Salehjahromi, S. Heeke, M. Godoy, H. Tran, M. Antonoff, B. Carter, E. Ostrin, X. Le, C. Gay, M. Vailati Negrao, L. Byers, C. Lu, G. Blumenschein, D. Rice, G. Walsh, R. Rajaram, S. Lin, W. Hofstetter, R. Mehran, A. Vaporciyan, S. Moghaddam, J.J. Lee, J. Wu, J. Heymach, MD
Anderson Cancer Center, Houston/TX/USA

Introduction: Preclinical work has demonstrated anti-interleukin-1beta (IL-1B) can delay the progression of precancers into invasive lung adenocarcinomas. Canakinumab, a humanized anti-ILB antibody has been reported to decrease lung cancer incidence by ~70% in CANTOS trial. Can-Prevent-Lung is single arm Phase II trial aiming to test whether canakinumab can increase regression rate of persistent high-risk lung nodules and prevent lung cancer.

Methods: Patients with persistent high-risk pulmonary nodules (at least 2 CT scans 3 months apart showing no evidence of regression; predicted risk exceeding 10% according to the Brock model for those without personal history of lung cancer or exceeding 5% for those with localized lung cancer who complete standard-of-care therapy) are eligible to receive canakinumab 200mg subcutaneously every 3 weeks for up to 8 doses. CT scans are scheduled after 2 doses, 4 doses, and 8 doses. Therapeutic response are evaluated using modified RECIST criteria (mRECIST), which assess both solid and ground-glass opacity components as well as 3D volumetric analysis. A control group of patients identified through propensity matching is analyzed in a similar manner. Peripheral blood T cell receptor (TCR) sequencing, cytokine profiling, and plasma cell-free DNA (cfDNA) methylation profiling, are conducted at various time points, including baseline before treatment initiation, 3 weeks and 6 months after the first dose of treatment.

Results: At the updated analysis, 15 patients have completed treatment and safety follow-up. Canakinumab has been well tolerated, with no toxicities of Grade 3 or higher. The most common toxicity was Grade 2 neutropenia (n=4) with no active infections. According to mRECIST criteria, 11 patients demonstrated shrinkage of lung nodules, with the best response being a reduction of -27%, while 13 patients exhibited a slower growth trajectory following canakinumab treatment compared to before treatment initiation. In 3D volumetric analysis, the treatment group showed volume shrinkage, with a median growth rate of -6.7% per year, in contrast to a growth rate of +14.8% per year observed in the control group. Additionally, compared to the control group, lesions in the treatment group tended to have a significantly smaller number of cells (P=0.024), lower degree of intra-lesion spatial heterogeneity (P=0.049), and lower average CT density (P<0.001). Interestingly, the concentration of cfDNA negatively correlated with treatment response, and distinct methylation patterns were associated with the diagnosis of lung cancer in longitudinal analysis. T-cell receptor (TCR) profiling and peripheral blood cytokine profiling are currently ongoing.

Conclusions: Canakinumab has exhibited a favorable safety profile and promising efficacy in the treatment of patients with high-risk lung nodules. Methylation changes in ctDNA may offer valuable insight for lung cancer interception trials. Can-Prevent-Lung trial has been amended to administer canakinumab at a dosage of 300mg subcutaneously every 3 months for up to 4 doses to mitigate the risk of neutropenia and reduce patient travel requirements in the interception setting.

Keywords: Prevention, Precancer, canakinumab

P1.01A RISK FACTORS, RISK REDUCTION & TOBACCO CONTROL - CLINICAL TRIALS IN PROGRESS
SUNDAY, SEPTEMBER 8, 2024 - 12:00 - 14:00

P1.01A.04 Point-of-care Nicotine Replacement for the Treatment of Nicotine Addiction in a Provincial Cancer System

R.L. Myers[1], C. Colby[2], M. Crosby[3], B. Freeman[3], C. Bartolomeu[4], S. Lam[1], F. Feldman[1], [1]BC Cancer, Vancouver/BC/CA ,[2]BC Cancer, Abbotsford/BC/CA ,[3]BC Cancer, Prince George/BC/CA ,[4]BC Cancer Research Institute, Vancouver/BC/CA

Introduction: Smoking Cessation at the time of a cancer diagnosis is an integral part of cancer treatment. In 2014 the Surgeon General's Report (SGR) concluded that cessation at diagnosis was associated with reductions in; cancer-specific mortality, overall mortality, cancer recurrence and improved treatment response. The 2020 SGR concluded that cessation exacts a 40% reduction in mortality, improving well-being, is cost-effective and is a vital part of cancer treatment. In 2022, IASLC issued a position statement on tobacco cessation after a cancer diagnosis, outlining the importance of screening and treating all cancer patients at the time of a cancer diagnosis. Comprehensive tobacco cessation pathways are required at all cancer institutions, starting with screening for use and providing evidence-based cessation support. Despite the initiation of these programs, cessation rates remain low, indicating novel ideas to break the status quo are required. We describe a point-of-care nicotine replacement pilot program nested within a larger cessation program.

Methods: BC Cancer initiated an Ask, Advise, Refer (AAR) tobacco cessation program at 6 sites across British Columbia, Canada, where all cancer patients presenting for their first visit are screened for tobacco use and offered treatment specific advice on cessation and an opt-out referral to a telephone quit line and provincial nicotine replacement program (NRP). The NRP supplies 3 months of nicotine replacement therapy (NRT) at no cost to the patient. Adoption, reach and effectiveness indicators were recorded from 2019 to 2024. Based on low quit rates, a pilot point-of-care NRT program was initiated at a single center, where patients who were still smoking would leave the cancer clinic, after their first visit, with a NRT (patch) applied to the arm and a 7-day supply of dual NRT therapy (patch and gum), and referral to NRP. Given the challenging geographic area, patients that were reviewed virtually had dual NRT shipped to their home.

Results: Between 2019-2021, 45,348 patients presented for cancer treatment throughout all 6 sites. 11,832 of these patients were screened for tobacco use, identifying 1,974 (17%) current tobacco users; 46% female, and 67% Caucasian. 1102 (56%) were offered a referral to the telephone quit line and the NRP, 580 (53%) accepted. Of these, 223 (38%) quit, attempted to quit or reduced tobacco consumption. The point-of-care NRP pilot was initiated in Oct 2023, a total of 21 patients (48% female, median 30 pk-yrs (min 9.75, max 90) have received NRT at point-of-care, 76% received dual NRT, 71% accepted referral to a telephone quit-line. Eight patients were remotely located, with an average distance of 463 km from the nearest centre. The average cost of shipping NRT was $25.14. Quit rates will be recorded at 6 and 12 months.

Conclusions: Tobacco cessation is an integral part of cancer treatment but is often overlooked. Broader access to effective and novel methods of screening and treatment is required, particularly for those in rural/remote communities. We describe a novel point-of-care pathway to service all patients, including those in rural/remote communities who generally experience decreased access to in-person care.

Keywords: Smoking Cessation, Nicotine Replacement Therapy, Point-of-care

P1.01B RISK FACTORS, RISK REDUCTION & TOBACCO CONTROL - DISEASE - PROFILE
SUNDAY, SEPTEMBER 8, 2024 - 12:00 - 14:00

P1.01B.01 Derivation and Validation of Nomogram to Predict Outcomes of Patients with Simultaneous Multiple Primary Lung Cancer

Y. Liu[1], L. Wang[1], Q. Sun[1], R. Qi[1], B. Liu[1], X. Qian[1], Y. zhang[2], H. Niu[3], R. Li[4], [1]Nanjing Drum Tower Hospital, Nanjing/CN ,[2]West China Hospital, Chengdu/CN ,[3]Nanjing University of Chinese Medicine, Nanjing/CN ,[4]Nanjing Medical University, Nanjing /CN

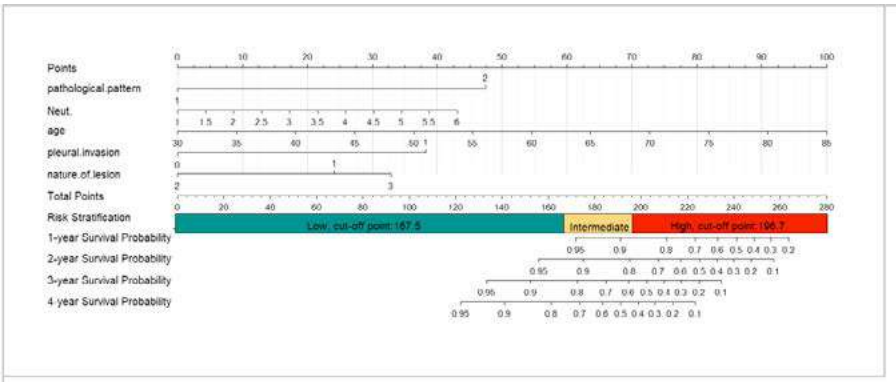
Introduction: Simultaneous multiple primary lung cancers (sMPLC) are detected increasingly nowadays, but there is no reliable tool for the assessment of long-term survival probability. This study aimed to develop a nomogram estimating the probability of the overall survival for patients with sMPLC undergoing resection.

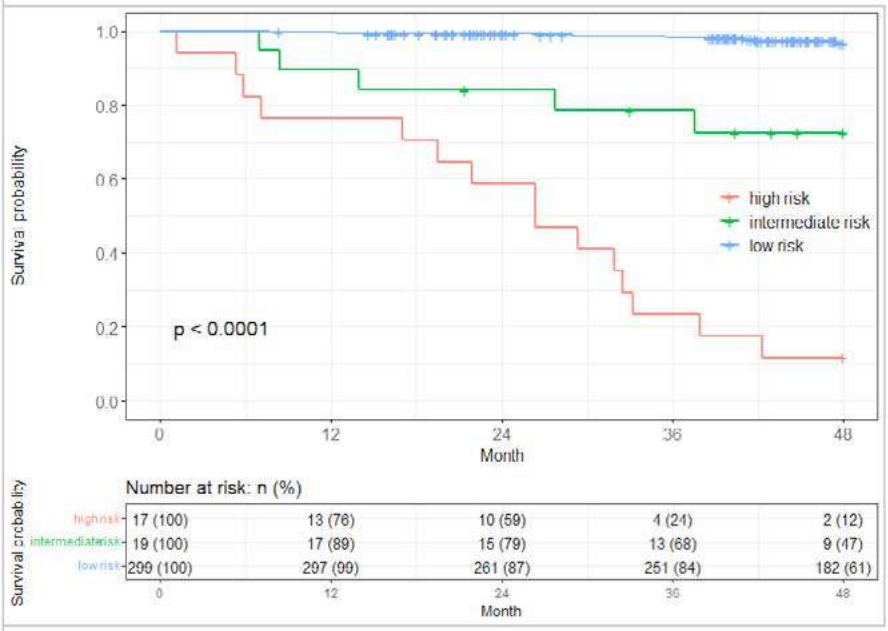
Methods: This retrospective study enrolled 447 patients with sMPLC from two centers between June 2010 and April 2023. All patients were randomly divided in a 3:1 ratio to generate training and validation cohorts. The least absolute shrinkage and selection operator regression analysis and Multivariable Cox regression analysis were utilized to identify risk factors for overall survival. Based on the factors, a nomogram for predicting overall survival was constructed. Areas under the receiver operating characteristic curves (AUC), calibration plots and decision curve analysis (DCA) were used to evaluate the efficiency of the nomogram in both the training and validation cohorts.

Results: The training cohort included 335 patients, and the validation cohort included 112 patients, with a total of 43 (9.6%) patients experiencing all-cause death. Age, pathological pattern, pleural invasion, neutrophile granulocyte, and nature of lesions were used to build the nomogram. The AUC values of the nomogram were 0.910, 0.902, 0.871 and 0.860 for the 1-, 2-, 3-, and 4-year overall survival in the training cohort, and 0.892, 0.894, 0.895 and 0.873 in the validation cohort, respectively. The calibration curves for probability of overall survival showed optimal agreement between the prediction by nomogram and the actual observation, and the DCA indicated that the constructed nomogram conferred high clinical net benefit.

Conclusions: This nomogram can accurately predict the probability of overall survival for patients with sMPLC.

Keywords: Simultaneous Multiple Primary Lung Cancer, nomogram, overall survival





P1.01B RISK FACTORS, RISK REDUCTION & TOBACCO CONTROL - DISEASE - PROFILE
SUNDAY, SEPTEMBER 8, 2024 - 12:00 - 14:00

P1.01B.02 The Genomic Landscape of Lung Cancer in Never-Smokers from the Women's Health Initiative

S. Moorthi[1], A. Paguirigan[1], P. Itagi[1], M. Ko[1], M. Pettinger[1], A.C.H. Hoge[1], A. Nag[2], N.A. Patel[2], F. Wu[1], C. Sather[1], K.M. Levine[1], M.P. Fitzgibbon[1], A.R. Thorner[2], G.L. Anderson[1], G. Ha[1], A.H. Berger[1], [1]Fred Hutchinson Cancer Center, Seattle/WA/USA ,[2]Dana-Farber Cancer Institute, Boston/MA/USA

Introduction: Therapies targeting driver oncogenes such as EGFR have transformed the clinical management of lung cancer, which has contributed to the decline in mortality rates. However, much of our understanding of lung cancer stems from studies involving individuals with a history of smoking. Despite smoking being the primary risk factor, a substantial proportion of lung cancer cases occur in never-smokers, particularly affecting women. The rising incidence of lung cancer in never-smokers mirrors both global shifts in smoking habits and an increase in never-smoker lung cancer cases. Lung cancer in never-smokers presents distinct clinical and genetic features compared to smoker-associated lung cancer. In this study, we explore the genetic landscape of lung cancer in never-smoker women enrolled in the Women's Health Initiative and explore the impact of smoking history, sex, and age.

Methods: We conducted whole exome and/or whole genome sequencing on tumor and/or matched normal DNA samples obtained from participants of the Women's Health Initiative who developed lung cancer. The analysis encompassed samples from 73 women, enabling the genomic profiling of never-smoker lung cancer cases. Bioinformatic analyses were performed to identify somatic mutations, mutational signatures, copy number alterations, and fusion events. Furthermore, we corroborate the novel genetic findings with data from the TCGA, MSK, and GENIE cohorts.

Results: Never-smokers exhibit a significant enrichment in EGFR indel mutations compared to heavy smokers. Intriguingly, among never-smokers, those diagnosed at a younger age (under 50 years) displayed a significant enrichment in EGFR indel mutations compared to their older counterparts (aged 50 years or more). In contrast, heavy smokers demonstrated a heightened prevalence of KRAS G12C mutations, whereas never-smokers showcased diverse occurrences of other G12 amino acid changes. Moreover, mutations in MGA were notably prevalent among smokers, particularly in individuals diagnosed at an older age. Conversely, MET mutations were found to be enriched in never-smokers, as well as in individuals diagnosed later in life. Analysis of somatic mutation signatures unveiled DNA repair defects in a subset of tumors, although no attributable germline predisposition variants were identified. Interestingly, the absence of ALK, RET, and ROS1 fusions in the WHI cohort can be partially attributed to the older age at diagnosis and the early tumor stage within this group. Lastly, it's worth noting that there was no discernible difference in aneuploidy based on smoking

Conclusions: Our analysis revealed a unique mutational spectrum of EGFR and KRAS variants in never-smoker lung cancer cases, with implications for both targeted and immunotherapeutic interventions. We found that chromosomal fusions involving ALK, RET, and ROS1 were absent, suggesting lower rates of fusion oncogenes in older female never-smokers. Contrary to expectations, distinct copy number subtypes previously associated with never-smoker lung cancer were observed across tumors from both smokers and never-smokers, indicating that aneuploidy and somatic copy number alterations are general features of lung cancer independent of smoking status.

Keywords: Never-smokers, Non-small cell lung cancer, Lung adenocarcinoma

P1.01B RISK FACTORS, RISK REDUCTION & TOBACCO CONTROL - DISEASE - PROFILE
SUNDAY, SEPTEMBER 8, 2024 - 12:00 - 14:00

P1.01B.03 Risk Factors Associated with Venous Thromboembolism in Advanced ALK Rearranged Non-Small Cell Lung Cancer

C. Kamali, S. Ekman, Karolinska Institutet, Stockholm/SE

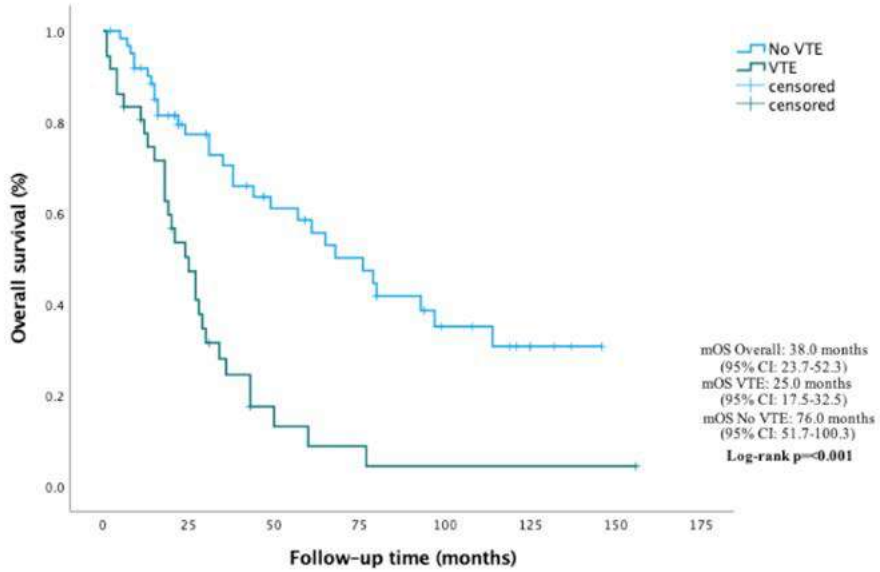
Introduction: Non-small cell lung cancer (NSCLC) patients are at an elevated risk of venous thromboembolism (VTE), which is associated with poor prognosis. The incidence of VTE in patients with anaplastic lymphoma kinase (ALK) rearrangements is reported to be three to five times higher, suggesting a potential benefit from prophylactic anticoagulant therapy. This study aimed to identify clinical and molecular factors associated with an increased risk of VTE in patients with advanced ALK-positive NSCLC.

Methods: A retrospective study was conducted involving patients with advanced ALK-positive NSCLC treated at Karolinska University Hospital between January 2009 and December 2021. ALK rearrangements were assessed using immunohistochemistry (IHC) or fluorescence in situ hybridization (FISH), while EML4-ALK fusion variants were detected by reverse-transcriptase-polymerase-chain-reaction (RT-PCR). Patients diagnosed after 2015 were analyzed by Next-generation sequencing (NGS). VTE events were recorded from 90 days before the histological cancer diagnosis until death or the end of follow-up.

Results: Ninety-eight advanced ALK-positive NSCLC patients were enrolled, among whom 36 developed VTE. The location of the VTE was pulmonary in 23 cases (63.9%) and 17 (47.2%) occurring beyond 6 months from treatment initiation. Re-thrombosis was observed in 6 patients (16.7%). The median time from diagnosis to the first clot was 170.0 days. Median overall survival (mOS) was 25.0 months (95% CI: 17.5, 32.5) for VTE-positive patients and 76.0 months (95% CI: 51.7, 100.3) for VTE-negative patients. Logistic multivariable regression analysis revealed that the presence of adrenal metastasis (OR, 3.35; 95% CI: 1.42, 7.91), BMI ≥35 kg/m2 (OR: 11.7; 95% CI: 2.42, 57.0), Leukocyte count >11x10^9/L (OR, 5.44; 95% CI: 2.40, 12.3) and Hemoglobin <10g/dL (OR, 6.38; 95% CI: 1.93, 21.1) significantly increased VTE risk, while Albumin ≥3.5 g/dL lowered the odds (OR, 0.36; 95% CI: 0.15-0.89).

Conclusions: Patients with ALK-positive NSCLC, particularly those with adrenal metastasis, BMI ≥35 kg/m^2, leukocyte count >11x10^9/L, or hemoglobin <10g/dL, face an elevated risk of VTE. Prophylactic anticoagulation may benefit these patients due to their increased susceptibility to cancer-related thrombosis. However, further studies are needed to validate these findings before considering clinical implementation.

Figure 1. Kaplan-Meier curve for overall survival for ALK-positive NSCLC patients with and without VTE.



Number at risk								
No VTE	62	36	24	18	9	5	0	0
VTE	36	16	4	6	2	1	1	0

P1.01B RISK FACTORS, RISK REDUCTION & TOBACCO CONTROL - DISEASE - PROFILE
SUNDAY, SEPTEMBER 8, 2024 - 12:00 - 14:00

P1.01B.04 A Highly Unmet Need: Patterns of Lung Cancer Screening in Head and Neck Cancer Survivors Preceding a Lung Cancer Diagnosis

C. Olazagasti[1], S. Malik[2], D.C. Qu[2], G. Stoel[2], J. Noy[2], E. Rodriguez[3], G. Lopes[4], [1]Sylvester: Sylvester Comprehensive Cancer Center, Miami/FL/USA ,[2]University of Miami Miller School of Medicine, Miami/FL/USA ,[3]Sylvester Comprehensive Cancer Center, Coral Gables/FL/USA ,[4]Sylvester Comprehensive Cancer Center, miami/FL/USA

Introduction: One fourth of head and neck cancer (HNC) survivors die from a second malignancy, and lung cancer (LC) is responsible for over half of the cases. HNC survivors with a smoking history have a 2.5 times higher incidence of LC than the average population. Contrary to most tumor types, there is no standard long-term image surveillance recommended for HNC survivors. However, NCCN does recommend annual low dose CT (LDCT) for LCS in HNC survivors with a ≥ 20-pack year (py) smoking history. Yet, the rates of LCS implementation in HNC survivors are unknown. We aimed to understand the patterns of LCS eligibility and implementation in HNC survivors preceding a LC diagnosis.

Methods: We performed a single institution study at the University of Miami including all subjects with a history of HNC and LC seen from 2018-2022. Demographic information including age, sex at birth, race/ethnicity was included. Smoking history, LC staging, LCS eligibility, and mortality status were collected. A descriptive analysis was performed.

Results: We reviewed the charts of 51 patients with HNC preceding a LC diagnosis, 16 were female and 35 men. 49 patients self-identified as White and 2 as Black race. 22 patients self-identified as Hispanic, 28 as non-Hispanic, and 1 as unknown or another ethnicity. As depicted in Table 1, most patients (61%) had a ≥ 30 py. history of smoking and up to 65% fulfilled LCS eligibility criteria. However, only 3.9% of patients underwent LCS following the HNC and preceding LC diagnosis. The majority of patients (29%) had stage IV at LC diagnosis. The average LC diagnosis following HNC was 4.04 years.

Conclusions: Despite the high incidence of second primary LC in HNC survivors, our study showed that LCS in eligible HNC survivors remains critically underutilized. Only 3.9% of the patients from our cohort underwent LCS following their HNC diagnosis despite most having a heavy tobacco history and fulfilling LCS criteria. The LCS rates for eligible Americans are suboptimal at 6%, however, our study shows that these rates could be disproportionately worse for HNC survivors. In our study, patients were diagnosed with LC an average of 4 years after HNC diagnosis. Enforcing and implementing LCS in HNC survivors could help overcome the high rates of late-stage diagnosis and potentially improve mortality rates in HNC survivors. Therefore, it is imperative to conduct prospective studies to better understand the barriers and promote LCS in this high-risk population.

Keywords: head and neck cancer, lung cancer screening, early detection

	N=51(%)
Gender	
Women	16 (31%)
Men	35 (69%)
Ethnicity	
Hispanic	22 (43%)
Non-Hispanic	28 (55%)
Other or unknown	1 (2%)
Race	
White	49 (96%)
Black	2 (4%)
AJCC 8 LC stage at diagnosis*	
1	9 (18%)
2	6 (12%)
3	4 (8%)
4	15 (29%)
Pack year history**	
0	5 (9.5%)
1-20	7 (13.5%)
21-29	4 (8%)
>30	31 (61%)
Met USPSTF21 LCS criteria**	
Yes	33 (65%)
No	14 (27%)
Underwent LCS	
Yes	2 (3.9%)
No	49 (96.1%)
Mortality status	
Dead	22 (43%)
Alive	29 (57%)
* Missing data for 17 patients	
**Missing data for 4 patients	

P1.01B RISK FACTORS, RISK REDUCTION & TOBACCO CONTROL - DISEASE - PROFILE
SUNDAY, SEPTEMBER 8, 2024 - 12:00 - 14:00

P1.01B.05 Real-World Data on 3-Year Survival in Non-Small Cell Lung Cancer (NSCLC): Results from 3 French Nationwide Cohorts from 2000 To 2020

D. Debieuvre[1], B. Delclaux[2], G. De Chabot[3], F. Al Freijat[4], J. Le Treut[5], J-Y. Tavernier[6], O. Leleu[7], P. Kuntz[8], S. Loutski[9], K. Fouet[10], J.M. Dot[11], M. Popa[12], A. Belle[13], C. Vincent[14], S. Julien[15], C. Perrin[16], N. Banciu[17], J. Virally[18], F. Lamotte[19], H. Morel[20], [1]GHRMSA, Mulhouse/FR ,[2]HOPITAL DES HAUTS CLOS, Troyes/FR ,[3]Centre Hospitalier Bretagne Atlantique, Vannes/FR ,[4]Hôpital Nord Franche-Comté, Belfort/FR ,[5]Hôpital Européen Marseille, Marseille/FR ,[6]Centre Hospitalier de Douai, Douai/FR ,[7]Abbeville Hospital Centre, Abbeville/FR ,[8]Groupe Hospitalier de la Haute Saone, Vesoul/FR ,[9]Centre Hospitalier Creil-GHPSO, Creil/FR ,[10]Centre Hospitalier La Rochelle, La Rochelle/FR ,[11]Medipole Lyon Villeurbanne, Villeurbanne/FR ,[12]Centre Hospitalier Chartres, Chartres/FR ,[13]Centre Hospitalier de Compiègne-Noyon, Compiègne/FR ,[14]Centre Hospitalier Intercommunal Elbeuf-Louviers-Val de Reuil, Elbeuf/FR ,[15]Centre Hospitalier de Rodez, Rodez/FR ,[16]Centre Hospitalier Princesse Grace, Monaco/FR ,[17]Centre Hospitalier de Bigorre, Tarbes/FR ,[18]Centre Hospitalier Intercommunal Robert Ballanger, Aulnay-Sous-Bois/FR ,[19]Centre Hospitalier de Chateauroux, Chateauroux/FR ,[20]Centre Hospitalier Régional D'orléans Hôpital de La Source, Orléans/FR

Introduction: KBP[i] is a Real-World French prospective study on Lung Cancer (LC) conducted in non-academic public hospitals (NPH) every ten years since 2000. Herein, we report the three-year survival (3-yS) rate in NSCLC among the 2020 cohort and the comparisons with the 2000 and 2010 cohorts.

[i] Debieuvre D et al. Two-year lung cancer survival between 2000 to 2020: Results from 3 French nationwide cohorts. JCO 41, 8542-8542(2023). DOI:10.1200/JCO.2023.41.16_suppl.8542

Methods: Collection of all consecutive diagnosed LC, all stage, and all histology, between 01/01 and 12/31 in NPH pulmonology or oncology units in 2000, 2010 and 2020 with the same methodology. A Scientific Committee controlled inclusion exhaustivity and quality in each center. The vital status was collected at different follow-up times. Survival rates were calculated using the Kaplan-Meier method.

Results: 8,999 patients were included in 82 centers in 2020, 7847 with NSCLC, including 7824 with vital status known. The 3-yS rate for patients with NSCLC was 34.6% [33.4 - 35.8], the median overall survival was 17.4 [16.5 - 18.3] months. Compared to 2000, survival improved significantly (+17.7%) (Table 1). Adenocarcinoma was the histological type whose prognosis has improved the most (+ 20.4%).

Factors associated with 3-yS were sex, age, ECOG Performans Status (PS), TNM stage. The 3-yS for women (F) was 41.4% [39.4 - 43.5] compared to men (M) 31.0% [29.6 - 32.4] in 2020, significantly increased over 20 years: + 22.5% for F and + 14.4% for M. In 2020, as expected, the 3-yS decreased with age from 40.1% [35.1 - 45.8] for patients <50 y-o to 16.4% [14.0 - 19.2] for patients > 80 y-o. PS was associated with the 3-yS rate of 43.0% [41.6 - 44.5] for patients with PS 0-1,11.2% [9.4 - 13.3] for PS 2 and 4.7% [3.2 - 6.9] for PS3-4. TNM stage was still determining for 3-yS, from 80.9% [78.2 - 83.6] for stage I to 18.3 [17.1-19.6] for stage IV.

Conclusions: These results showed the impressive improvement in the survival rate of NSCLC in real life conditions with new strategies and therapies. Expanding KBP 2020 follow-up provided us with longer-term overall survival data with a benefit that appears to be maintained.

Keywords: 3-year survival, non-small cell lung cancer

NSCLC survival	Months	2000 N=4669	2010 N=6083	2020 N=7824*
	1	90.7 [89.9 - 91.6]	90.9 [90.1 - 91.6]	92.7 [92.1 - 93.3]
	3	76.0 [74.7 - 77.2]	76.8 [75.8 - 77.9]	80.4 [79.5 - 81.3]
	12	41.1 [39.7 - 42.6]	44.3 [43.1 - 45.6]	57.6 [56.6 - 58.8]
	24	23.2 [22.0 - 24.5]	27.7 [26.6 - 28.9]	43.6 [42.5 - 44.7]
	36	16.9 [15.9 - 18.1]	21.0 [20.0 - 22.1]	34.6 [33.4 - 35.8]
	Median survival time (months)	9.0 [8.5 - 9.4]	10.0 [9.5 - 10.3]	17.4 [16.5 - 18.3]

**7824 patients with vital status captured at least once during the follow-up. Preliminary results with 1923 missing dataat Month 36 - Update will be available for the congress*

Conclusions: These results showed the impressive improvement in the survival rate of NSCLC in real life conditions with new strategies and therapies. Expanding KBP 2020 follow-up provided us with longer-term overall survival data with a benefit that appears to be maintained.

P1.01C RISK FACTORS, RISK REDUCTION & TOBACCO CONTROL - TOBACCO
SUNDAY, SEPTEMBER 8, 2024 - 12:00 - 14:00

P1.01C.01 Effectiveness of Health Education on Adolescent Tobacco Use Intention: Cluster RCT in Ibadan, Nigeria

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Introduction: Most adults who use tobacco start during adolescence. Curbing the initiation of tobacco use among adolescents has the potential to significantly diminish its prevalence. Notably, the intention to use tobacco serves as a proximal factor that reliably predicts actual tobacco uptake. Given the well-established addictive nature of tobacco and the associated challenges in cessation, directing prevention efforts toward non-tobacco users with an intention to use tobacco holds greater promise for successful intervention. Hence, this study aimed to assess the effect of a Health Belief Model (HBM) based health education program on school-going adolescents' intention to use tobacco in Ibadan, Nigeria.

Methods: In this cluster randomized controlled trial of in-school adolescents in Ibadan, Nigeria, we estimated a total sample size of 720 participants across eight schools. Using a two-stage cluster sampling, approximately 90 students were selected from each school, with schools randomized into either the intervention (4 schools) or control (4 schools) groups. The intervention comprised two sessions of expert-led tobacco-related lectures, the placement of classroom posters, and the distribution of customized notebooks containing key anti-tobacco messages. (Figure 1)In contrast, the control group received lectures focusing on oral hygiene practices. A modified and validated Global Youth Tobacco Survey questionnaire was used to collect sociodemographic information and intention to use tobacco (yes/no) at baseline and six months post-intervention (endline). Intention-to-treat analysis was employed. Binary logistic regression modeling was conducted to assess intervention effectiveness while controlling for potential confounding.

Results: The participants' mean (±SD) age was 14.7 (±1.2) years. About half of the participants were from private schools (50.1%) and males (50.6%). No differences in the baseline characteristics between the two groups (p>0.05). At baseline, the prevalence of intention to use tobacco was 13.6% in both groups. In the intervention group, this prevalence decreased to 8.9% at the endline, while it increased to 14.4% in the control group (p=0.020). After adjusting for age, gender, and school type (public vs private), the odds of improvement (no intention at endline) in the intervention group were 1.7 times higher than the control group (aOR: 1.71; 95%CI: 1.07-2.74).

Conclusions: The HBM-based behavioral change intervention notably reduced the participant's intention to use tobacco six months post-intervention, affirming the effectiveness of targeted health education grounded in the HBM. These findings emphasize the importance of sustained, contextually relevant health education in broader tobacco control initiatives for diverse populations.

Keywords: High school students, Cigarette smoking, Cancer prevention

P1.01C RISK FACTORS, RISK REDUCTION & TOBACCO CONTROL - TOBACCO
SUNDAY, SEPTEMBER 8, 2024 - 12:00 - 14:00

P1.01C.02 Tobacco Control and Smoking Cessation-related Content in Oncology Meetings: A Scoping Review

S. Choi[1], A. Alghabban[1], J. Do[1], W. Boateng[1], D. Chen[1], R.S. Huang[1], M. Khan[1], N.K. Quartey[1], S. Raman[1], M.E. Giuliani[1], W.K. Evans[2], L. Eng[1], [1]Princess Margaret Cancer Centre, Toronto/ON/CA ,[2]McMaster University, Hamilton/ON/CA

Introduction: Tobacco is a known risk factor for the development of cancer, and patients with cancer who continue to smoke have poorer outcomes. Despite the importance of tobacco control and smoking cessation in cancer care, it remains unclear how much tobacco control and smoking cessation content are included in major oncology meetings. The purpose of this project is to evaluate how much tobacco control and smoking cessation-related content is presented at major oncology meetings.

Methods: We performed a scoping review for tobacco control and smoking cessation-related content using online programmes, proceeding files, and abstract books from January 2018 to July 2023 for 12 major international oncology meetings representing different disciplines and disease sites. Eligible abstracts and education sessions included content evaluating the impact of tobacco on cancer risk, tobacco use on cancer outcomes, and/or smoking cessation in cancer care. Content was excluded if tobacco use was solely evaluated as a co-variate or if the content did not have a primary focus on tobacco control or smoking cessation. Descriptive statistics helped to characterize frequencies and trends over time.

Results: A total of 5168 tobacco control and smoking cessation-related content was identified using our search criteria; 389 abstracts and 114 educational sessions met the inclusion criteria. Between 2018 and 2023, meetings from the World Cancer Congress (mean: 1.66 ± 3.06%), the World Conference on Lung Cancer (mean: 1.52 ± 0.59%), and the Multidisciplinary Head and Neck Cancers Symposium (mean: 0.72 ± 1.03%) had the highest percentages of tobacco-related abstracts presented with a consistent trend over the 5-year period. The World Cancer Congress (mean: 4.08 ± 1.30%) and the World Conference on Lung Cancer (mean: 3.94 ± 1.63%) had the highest percentages of tobacco-related educational sessions and were the only meetings that primarily presented tobacco-related educational sessions throughout every meeting across the 5 years. Among the included abstracts, 37% focused on tobacco and cancer risk, 37% focused on smoking cessation, and 26% focused on the impact of tobacco on cancer outcomes. Slightly less than half (43%) of the abstracts were focused on clinical/epidemiological research, followed by quality improvement/health services research (35%), basic science/translational research (20%), and review studies (2%). Most first author abstract presenters were from North America (56%), Asia (20%) and Europe (17%).

Conclusions: Despite the importance of tobacco control in cancer, tobacco control or smoking cessation-focused abstracts and educational content are limited at major oncology meetings. The organizers of cancer meetings need to be encouraged to include educational sessions focused on tobacco control and smoking cessation, and to explore new strategies to attract submissions on these topics, particularly from underrepresented regions of the world.

Keywords: Tobacco Control, Smoking Cessation, Cancer Education

P1.01C RISK FACTORS, RISK REDUCTION & TOBACCO CONTROL - TOBACCO
SUNDAY, SEPTEMBER 8, 2024 - 12:00 - 14:00

P1.01C.03 The Influence of Smoking on Morbidity and Early Mortality after Anatomical Lung Resections for Stage I-IIIA NSCLC

K. Grapatsas[1], F. Doerr[2], F. Oezkan[2], N. Baldes[2], D. Theegarten[2], K. Darwiche[2], W. Eberhardt[2], T. Gauler[3], M. Stuschke[3], H. Hautzel[3], K. Herrmann[3], C. Taube[2], M. Forsting[3], M. Schuler[3], S. Bölükbas[1], [1]University Medical Center Essen-Ruhrlandklinik, Essen/DE ,[2]University Medical Center Essen, Ruhrlandklinik, Essen/DE ,[3]University Medical Center Essen, Essen/DE

Introduction: Smoking status before an operation is associated with increased postoperative morbidity and mortality. The aim of this study is to investigate the impact of smoking status on patients undergoing anatomical lung resection for NSCLC with stage I-IIIA.

Methods: This retrospective single-center study included patients who underwent anatomical resection for NSCLC in postoperative stages I-IIIA between 2016 and 2022 at the West German Cancer Center. Smoking status was divided into three categories: never smokers, past smokers (patients who had quit smoking at least twelve months before surgery), and current smokers (patients who smoked up to one week before surgery). Early mortality was defined as death from any cause within 30 days after the operation.

Results: The study included 1093 patients. Histology showed IA1 stage in 8.8% of patients, IA2 in 15.1%, IA3 in 8.2%, IB in 16.7%, IIA in 7.0%, IIB in 22.8%, and IIIA in 21.5%. Never smokers were mostly detected in stage I (50.4% vs 54.6% vs 46.5%, p=0.01). Bilobectomy was performed in 4.3% of cases, lobectomy in 83%, pneumonectomy in 6.2%, and segmentectomy in 6.5%. Neo-adjuvant therapy was performed in 22.8% of patients. Of the study patients, 36% were current smokers, 53.2% were past smokers, and 10.9% were never smokers. More male patients were past smokers (52.9% vs. 22.7% vs. 62.6%, $p < 0.01$). Past smokers had more cardiovascular comorbidities and ECOG status >1 ($p = 0.01$). Current smokers were more likely to have liver disease (8.1%, $p = 0.01$), previous malignancies (30.1%, $p < 0.01$), and COPD of any stage (36.6%, $p < 0.01$). There was no statistical significance between the three groups regarding obesity, arterial hypertension, chronic kidney disease, stomach comorbidities, or the extent of lung resection ($p > 0.05$). More VATS resections were performed in never smokers (56.3%, $p < 0.01$). Past smokers had more complications diagnosed (30.5% vs. 22.7% vs. 34.3%, $p = 0.04$). Current smokers showed a higher incidence of persistent air leak after the operation (13.0% vs. 1.7% vs. 12.0%, $p < 0.01$) and postoperative atelectasis requiring bronchoscopy intervention (2.8% vs. 0.0% vs. 0.7%, $p < 0.01$). There was no statistical significance between the groups concerning ARDS, pneumonia, postoperative empyema, cardiac failure, renal failure, postoperative re-intubation and ventilation, and unexpected admission to the ICU ($p > 0.05$). Current smokers did not show an increased early mortality compared to the other two groups (1.0% vs. 3.4% vs. 1.0%, p=0.20).

Conclusions: Despite advances in medical technology and surgical techniques, postoperative morbidity remains higher for smokers. Both past and current smokers exhibited significant differences in the frequency of postoperative complications compared to never smokers. However, smoking status did not appear to influence early postoperative mortality.

Keywords: smoking status, lung surgery, morbidity

P1.01C RISK FACTORS, RISK REDUCTION & TOBACCO CONTROL - TOBACCO
SUNDAY, SEPTEMBER 8, 2024 - 12:00 - 14:00

P1.01C.04 Key Stakeholder Priorities on Embedding Smoking Cessation Into Lung Cancer Screening: National Australian Consensus Workshop

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Introduction: International clinical practice guidelines recommend the integration of smoking cessation interventions in low-dose computed tomography lung cancer screening (LCS). In LCS programs, smoking cessation interventions have demonstrated cost-effectiveness, and have favourable outcomes for LCS participants who smoke, including high sustained quit rates. There is emerging evidence on the optimum strategies to integrate cessation interventions into LCS programs, but little data specific to the Australian setting, where a targeted National LCS Program (NLCSP) will commence in 2025. To inform policy and program development, we sought national expert stakeholders' views on factors that would enhance feasibility and acceptability of cessation interventions in NLCSP implementation.

Methods: In July 2023, a full-day, in-person consensus workshop was conducted. Varied recruitment strategies, including cancer advocacy/professional organisations, our existing networks, and snowball sampling, were used to invite stakeholders. The priority setting process was guided by modified Nominal Group Technique methodology. In small-group activities, stakeholders identified facilitators/barriers of smoking cessation interventions in assigned LCS delivery models (e.g., mobile screening, primary care-led), and potential cessation interventions for implementation throughout the LCS screening and assessment pathway. Each group generated priorities across defined categories (e.g., 'delivery', 'equity'), before individual online voting to shortlist priorities, and refinement of priorities through whole-group discussion. Workshop notes and audio recordings were interpreted through a deductive rapid qualitative analysis.

Results: Stakeholders (N=38) were from all Australian states and territories, and broad disciplines including tobacco control, respiratory medicine, cancer policy, and community advocacy. The 12 shortlisted priorities represented both short- and long-term considerations, aligned with policy-level to consumer-driven actions (Figure 1). Foremost was development of a strategy to design and deliver smoking cessation training packages with professional disciplines involved in NLCSP delivery (priority 1), reflecting concerns about existing workforce capacity. Stakeholders strongly endorsed smoking cessation interventions co-designed for priority population groups (2), an embedded cessation-specific evaluation framework (3), and cessation messaging featuring participant testimonials to avoid exacerbating stigma (4). An overarching 'equity' principle (c.f. standalone priority) was suggested to support "participant-centric" program design and delivery.

Conclusions: These priority-based, pre-implementation recommendations emphasise equity-focused approaches to embedding cessation and capitalising on existing resources, including authentic priority population engagement. Considering a broad range of implementation determinants, these findings provide foundational evidence to improve LCS program planning. Based on multidisciplinary expert consensus and a comprehensive methodological approach to elicit and determine priorities, this study provides a framework from which to detail short- and long-term LCS delivery approaches.

Keywords: smoking cessation interventions, low-dose computed tomography lung cancer screening, expert stakeholders

Figure 1. Overview of identified priorities, numbered 1-12 in order of endorsement by stakeholders, and plotted against relative timeframe of implementation (x-axis) and extent to which policy-level vs. consumer engagement are required for implementation (y-axis).
EMR = Electronic Medical Records. MBS = Medicare Benefits Scheme. NCSR = National Cancer Screening Register. NLCSCP = National Lung Cancer Screening Program. PROMs/PREMs = Patient-Reported Outcome/Experience Measures.

P1.01C RISK FACTORS, RISK REDUCTION & TOBACCO CONTROL - TOBACCO
SUNDAY, SEPTEMBER 8, 2024 - 12:00 - 14:00

P1.01C.05 Potential Impact of Tobacco Control Policies in Preventing Incident Lung Cancers in the Eastern Mediterranean Region

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Introduction: Lung cancer is the second leading cause of cancer deaths in the Eastern Mediterranean Region (EMR). While an estimated 85% of lung cancer deaths are attributable to tobacco smoking, tobacco control policies have still not been well-implemented in most EMR countries. To investigate the impact of the highest level of implementation of tobacco control policies on preventing incident lung cancer cases between 2025 to 2050 in the EMR countries.

Methods: We extracted information on the level of anti-tobacco policy implementation and calculated the cigarette affordability index (percentage of GDP per capita required to purchase 2000 cigarettes) for 16 EMR countries using publicly available data sources. Anti-tobacco policy implementation was measured by the World Health Organization (WHO) introduced the MPOWER measures score (range: 7-34) that constitutes monitoring tobacco use and prevention policies (4 score); protecting people from tobacco smoke (5 score); offering help to quit tobacco use (5 score); warning about the dangers of tobacco (5 score), Anti-tobacco mass media (5 score); enforcing bans on tobacco advertising, promotion, and sponsorship (5 score); and raising taxes on tobacco (5 score). First, we used Linear Fixed-effect regression models to investigate the associations between changes in MPOWER scores, cigarette affordability index, and alterations in tobacco prevalence over the past decade in each EMR country. Then, for each EMR country, we calculated the population attributable fraction (PAF) and number of incident lung cancer cases that would be attributable to tobacco smoking between 2025 and 2050 using their current tobacco smoking prevalence, WHO-estimated number of incident lung cancer cases in 2025, WHO-estimated annual percentage change in lung cancer incidence rates, population growth rate, and tobacco-related lung cancer risk estimate from the latest meta-analysis. Finally, for each country, we assessed the separate and combined effects of the highest level of MPOWER implementation, and a 10% increase in the affordability index, on their tobacco prevalence. To estimate the number of preventable lung cancer cases, the PAF of tobacco smoking under each scenario was calculated and subtracted from the PAF under the current prevalence scenario.

Results: Between 2025-2050, we estimate that 38,381,600 new lung cancer cases will occur among men, and 11,923,098 among women. We estimated that the highest implementation of the MPOWER measures could potentially prevent 574,828 lung cancer cases in men (1.5% of the total) and 366,761 in women (3.0%). Increasing the cigarette affordability index by 10% is estimated to prevent 475,995, and 342,004 new lung cancer cases in men (1.2%) and women (2.8%), respectively. A simultaneous application of both strategies could prevent a total of 886,949 cases in men and 549,361 in women in the EMR by 2050. The greatest impact is estimated for Iran (prevention of 518,494 new cases), Pakistan (prevention of 509,944), and Morocco (prevention of 140,606).

Conclusions: Our analysis shows that the implementation of robust tobacco control policies at the population level, encompassing the comprehensive enforcement of WHO-introduced MPOWER measures along with increasing the cigarette affordability index, may significantly decrease lung cancer incidence over the upcoming 25 years in the EMR countries.

Keywords: Tobacco control polices, Lung cancer prevention, Population attributable fraction

P1.02A TUMOR BIOLOGY - PRECLINICAL BIOLOGY - EARLY STAGE DISEASE/STEM CELLS
SUNDAY, SEPTEMBER 8, 2024 - 12:00 - 14:00

P1.02A.01 ADAR1 Regulates Tumorigenesis and Stem Cell Properties in Non-Small Cell Lung Carcinoma

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Introduction: RNA editing gene, ADAR1, has been implicated as an important regulatory node in many cancers including NSCLC. ADAR1 regulates gene expression by editing RNA post-transcriptionally but also inhibits type I interferon response. In melanoma and colorectal cancer, ADAR1 loss has been shown to enhance therapy with immune checkpoint inhibitors in murine syngeneic models in a process that is dependent on tumor-derived IFN-β. In NSCLC, ADAR1 loss has been shown to lead to marked cytotoxicity of exogenous IFNβ in some cells, however, the effect of ADAR1 loss in vivo has been less well documented. We previously showed that ADAR1 loss in murine LM2 NSCLC cells led to near complete loss of tumorigenicity in syngeneic immune competent cells as well as athymic mice suggesting that the mechanism was not dependent of the presence of T cells. Here, we add to our work by studying the effects of ADAR1 loss on tumorigenicity of human NSCLC cells. Based on our previous work, we hypothesized that the mechanism maybe related to lung cancer stemness.

Methods: ADAR1 was knocked out using CRISPR/Cas9 in human NSCLC cell lines, H2009 and A549. We previously confirmed that CRISPR/Cas9 gene editing resulted in loss of ADAR1 expression by Western Blot and PCR. Wild-type (WT) and ADAR1 knockout (ADAR-KO) cells were assayed for cell proliferation using CCK-8 assay. N=5 mice were injected with 1x106 cells on bilateral flanks (WT cells on left and ADAR-KO cells on right). Subsequent tumors were measured and mice were sacked when tumors reached 2000mm3 in volume. Also, the stem cell properties between WT and ADAR-KO (ALDH expression) were assessed by Western blot. Cells were treated with gemcitabine and cytotoxicity was compared between WT and KO cells in vitro.

Results: ADAR-KO cell lines grew in cell culture at the same rate as WT cells for H2009 and A549 cells over 72 hours. Morphologically, cells appeared similar under light microscopy. When grown in nude mice, WT cells formed tumors in 100% of the mice injected for both A549 and H2009. None of the ADAR1 KO cells formed tumors. In A549 cells, ALDH1A1 expression, a cancer stem cell marker, was completely lost in ADAR-1 KO cells compared to WT cells. H2009 cells do not express ALDH1A1 and will be evaluated by Aldefluor assay. A549 and H2009 KO cells were not more sensitive than WT cells to chemotherapy with gemcitabine in vitro.

Conclusions: ADAR1 loss in human NSCLC cells abrogates tumorigenicity. ADAR1 loss markedly decreases ALDH1A1 expression suggesting that ADAR1 is important in maintaining cancer stem cell phenotype. Further work will be done to evaluate the effect of ADAR-KO on cancer stemness (Aldefluor assay and tumor sphere formation). The mechanisms by which ADAR1 maintains the cancer stem cell phenotype will be further explored by evaluating the contributions on alteration of IFN signaling versus A to I RNA editing.

Keywords: NSCLC, ADAR1, cancer stem cell

P1.02B TUMOR BIOLOGY - PRECLINICAL BIOLOGY - GENOMICS
SUNDAY, SEPTEMBER 8, 2024 - 12:00 - 14:00

P1.02B.01 Mirnome Functional Profiling of Non-Small Cell Lung Cancer Identified New Mechanisms of PD-L1 Regulation

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Introduction: The use of immune checkpoint blockade (ICI), such as anti-PD-(L)-1 antibodies, has emerged as an effective treatment for both locally-advanced and advanced NSCLC. PD-L1 expression in cancer cells is regulated by a plethora of genetic and epigenetic mechanisms including genomic alterations, aberrant oncogenic and inflammatory pathways, post-transcriptional regulators (e.g., miRNA) and post-translational modification (e.g., ubiquitination, phosphorylation, glycosylation, palmitoylation). All these molecular processes contribute to dynamic and spatially heterogenous PD-L1 expression profile in lung cancer samples, which complicates PD-L1 pathological assessment thus limiting diagnostic accuracy. Interestingly, the 3' UTR of PD-L1 gene is disrupted in several tumor types, leading to a stabilized form of PD-L1 and high expression (i.e., with TPS≥ 50%). The 3' UTR of genes can be bound by microRNAs, small non-coding RNA that function as post- transcriptional regulators of gene expression, which induce mRNA degradation and translational repression.

Methods: By integrating miRNome and transcriptome profiling obtained from treatment-naïve (Stage IIIA) NSCLC mediastinal lymph node metastases and experimental lung cancer models, with high-throughput functional miRNA profiling using human miRNA lentiviral library (shMIMIC), we explored the role of miRNA in regulating PD-L1 expression and response to ICI treatment.

Results: Originally, we found that a signature of 16 miRNAs (aka LN-signature) can identify treatment naïve (Stage IIIA) NSCLC mediastinal lymphnodal metastases which develop resistance to induction chemotherapy (ICT). Importantly, LN-signature low-expressing tumors were characterized by a higher expression of PD-L1 as well as of enrichment of IFN stimulated genes (IFNG), which is a prerequisite to response to ICI treatment. Interestingly, LN-signature includes miR-455-5p, which we found to directly regulate PD-L1 expression and response to NACT. Next, we performed shMIMICs functional screening and identified the landscape of miRNAs enriched/depleted in PD-L1high vs. PD-L1low NSCLC. Since PD-L1 is mostly regulated by the IFNγ; signaling pathway, we identified also which miRNAs were modulated by IFNγ; signaling and involved in PD-L1 regulation. Such findings were then validated in cohorts of NSCLC patients (pre- and post-treatment by ICI) that we analyzed by combined miRNA-seq and RNA-seq profiling.

Conclusions: Our findings revealed a substantial role of miRNAs intertwined with other transcriptional signatures, in the regulation of PD-L1 expression and response to ICI therapy. Therefore, the heterogeneous tumor expression of PD-L1 can be explained, at least in part, by the modulation of the expression of such miRNAs functionally linked to PD-L1 and modulated by the IFNγ; signaling pathway. We anticipate that our findings will pave the way for the development of more accurate predictive biomarkers for ICI response.

Keywords: PD-L1, microRNA, functional screening

P1.02B TUMOR BIOLOGY - PRECLINICAL BIOLOGY - GENOMICS
SUNDAY, SEPTEMBER 8, 2024 - 12:00 - 14:00

P1.02B.02 Role of Chromosome 3 Aneuploidy in Basal Cell Differentiation and Lung Squamous Cell Carcinoma Initiation

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Introduction: Lung cancer remains the most commonly diagnosed cancer type and the leading cause of cancer-related death in the United States. In the lung squamous cell carcinoma (LUSC) subtype, basal cells are considered to be the cell of origin with few identified driver mutations to date. However, chromosome or chromosome arm imbalance (aneuploidy) is present since the early development of LUSC. Alterations affecting chromosome 3 are extremely common in LUSC, where in stage I 80% and 60% of the cases (TCGA data) show loss of chromosome arm 3p and gain of chromosome arm 3q, respectively. These findings suggest a possible role for aneuploidy in tumor initiation.

Methods: To study the relationship between aneuploidy and LUSC development, our lab genetically engineered immortalized human lung epithelial cells to harbor either chromosome 3p deletion (3pDel) or chromosome 3q gain (3qGain) using CRISPR. We then induced differentiation in wild type (WT) and aneuploid clones grown in organoids and characterized phenotypes at the histological, morphological and gene expression level.

Results: Using RNAseq and immunofluorescence, we validated the basal-like gene expression pattern in our cells, with the expression of the canonical basal cell markers TP63 and KRT5. Interestingly, aneuploid cells showed an increased proliferative gene expression signature. After differentiation induction in 3D culture using Pneumacult media, both WT and aneuploid organoids showed squamous morphologies with noticeable genotype-related differences. WT organoids showed well-structured basal layers populated with epithelial-shaped cells, whereas aneuploid organoids presented unorganized basal layers with stretched cells. Additionally, WT organoids developed inner structures with high cellularity and hollowing areas. In contrast, 3qGain organoids showed squamous carcinoma features such as the accumulation of keratin pearls. Then, we assessed the differentiation grade of the organoids. At the mRNA level, canonical differentiation markers SCGB1A1 and MUC5B expression was induced in all genotypes; however, these were only detectable in WT organoids at the protein level. While both WT and 3qGain organoids successfully upregulated KRT23 expression upon differentiation, 3pDel organoids did not. In both WT and 3qGain organoids, KRT14 expression was detectable at late differentiation time points. In WT organoids this expression was traceable to KRT14Low/KRT5High epithelial-shaped cells located in the basal layer of the organoids. In contrast, in 3qGain organoids, these cells showed to be KRT14High/KRT5Low with flattened morphologies located at the organoid's basal layer. Furthermore, gene expression analysis revealed increased expression of proliferation markers (AURKB, TOP2A, KI67) in 3qGain organoids, while 3pDel organoids showed increased expression of NOTCH and TGFB.

Conclusions: Our results show aneuploidy genotype-specific features upon basal cells differentiation in 3D. Furthermore, these results suggest that aneuploidy can impair the differentiation of basal cells in the lung, possibly contributing to the early steps of LUSC development. Future scRNAseq experiments will help to uncover the specific mechanisms disrupted by aneuploidy during these process.

Keywords: Aneuploidy, Squamous, Differentiation

P1.02C TUMOR BIOLOGY - PRECLINICAL BIOLOGY - IMMUNE MODULATION
SUNDAY, SEPTEMBER 8, 2024 - 12:00 - 14:00

P1.02C.01 Intrinsic STING of CD8+T Cells Regulates Self-Metabolic Reprogramming and Improves Anti-Tumor Effects

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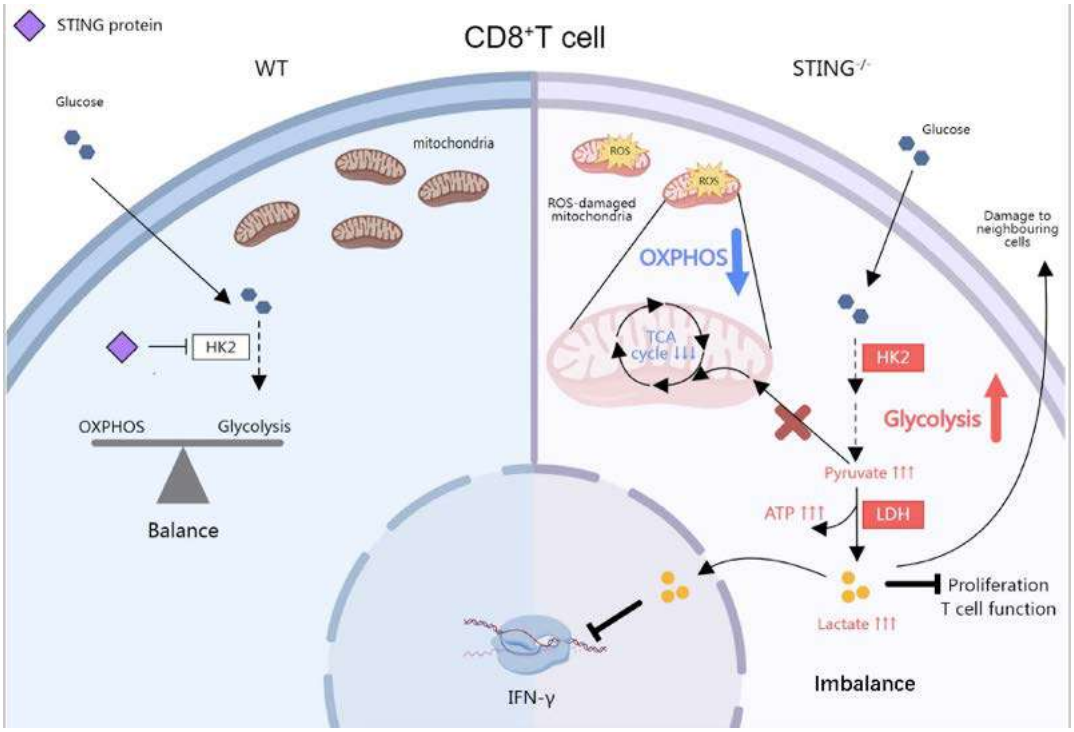
Introduction: Many preclinical studies have demonstrated that STING agonists have effective anti-tumor effects, but their adverse effects prevent practical use. Previous research by our team has demonstrated that STING has a more significant anti-tumor role in host immune cells than tumor cells, and the level of STING mRNA is associated with the outcome of immunotherapy in non-small cell lung cancer. Although STING is necessary for CD8+T cells to exert immunological activity, its effect on CD8+T cells is debatable. Therefore, we will concentrate on the particular roles of STING in CD8+T cells.

Methods: We used in vitro and in vivo models to confirm the influence of STING on CD8+T cell function. We examined the impact of STING on CD8+T cell metabolic function using RNA-seq, Seahorse, flow, electron microscopy, and other techniques. STING knockout mice were used to study the effect of competitive inhibition of glycolytic products during immunotherapy. In addition, we collected peripheral blood immune cells from 30 immunotherapy patients to examine the correlation between immune cell glycolysis levels and immunotherapy efficacy.

Results: RNA-seq showed significant changes in signaling pathways such as glycolysis/glycogen synthesis, oxidative phosphorylation, tricarboxylic acid cycle, and one carbon unit in STING-/- CD8+T cells. In vitro experiments revealed that the inactivation of the STING gene reduced the number of mitochondria, altered the choice of metabolic pathways, and impaired the anti-tumor ability. Flow results showed that the mean fluorescence intensity of mitochondria in STING-/- CD8+T decreased. Seahorse experiment showed that STING-/- CD8+T glycolysis was enhanced, and oxidative phosphorylation was decreased. Meanwhile, the content of lactic acid in the culture supernatant of STING-/- CD8+ T increased dramatically, the high level of lactic acid further inhibited the proliferation of CD8+ T and the secretion of IFN-γ. Competitive inhibition of the glycolysis process or lactic acid formation can save the function of STING-/- CD8+ T cells and the secretion of IFN-γ, save the immunotherapy effect of STING-/- mice. This provides a new therapeutic idea for patients with low STING expression and poor immunotherapy response. In the peripheral blood immune cells of immunotherapy patients, we observed a negative correlation between the mRNA levels of glycolysis-associated molecules and STING. Additionally, we found a correlation between the levels of glycolysis-associated molecules in immune cells and immunotherapy efficacy outcomes.

Conclusions: Our study is the first to explore the effect of STING on the metabolic process in CD8+ T cells. Intervening in the metabolic process of STING-deficient CD8+ T can save the efficacy of immunotherapy.

Keywords: Metabolic reprogramming, CD8+T, PD-1 therapy



P1.02C TUMOR BIOLOGY - PRECLINICAL BIOLOGY - IMMUNE MODULATION
SUNDAY, SEPTEMBER 8, 2024 - 12:00 - 14:00

P1.02C.02 NIR-II Mediates Cancer Nanocomposite Vaccines for Lymph Node Targeted Delivery and Enhanced Immunotherapy

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Introduction: Lung cancer, with its high morbidity and mortality rates, stands as a formidable challenge in the realm of oncology. While immunotherapy has shown initial promise, its efficiency leaves room for improvement, underscoring the pressing need for precise diagnostic and effective treatment strategies. Cancer vaccines, an emerging modality for solid tumors, hold great promise for future tumor treatments, but their systemic administration often results in adverse side effects. Nanovaccines, leveraging nanotechnology to effectively deliver tumor antigens and adjuvants, activate antigen-presenting cells, and induce specific anti-tumor immune responses, present a unique solution to these challenges. In this context, we propose a straightforward approach for in situ programming of lung cancer using a lymph node-targeting nanovaccine.

Methods: Initially, we synthesized non-toxic PSS-modified gold nanorods (Au-PSS), along with the amphiphilic polymer mPEG-PHEP and cationic liposome DOTAP nanoparticles, which encapsulate the immune adjuvant R848 (VNPR848). Following this, we conducted a comprehensive characterization of these nanoparticles, which revealed vaccine-like effects at the cellular level and lymph node targeting capabilities of the nanovaccine at the animal level. Furthermore, in animal models, we observed the nanovaccine's efficacy in distal models, lung metastasis, and postoperative recurrence. These findings collectively validated the potent therapeutic impact of this nanovaccine.

Results: Under near-infrared II light irradiation, antigens were released by orthotopic tumor cells via gold nanorods and captured by VNPR848, which has promoted the synergistic transport of antigen and R848 to lymph nodes and then had a significant therapeutic effect on distant tumors (Fig. 1a). This procedure resulted in a notable maturation rate of DCs at 46.9% within the Au(+)/VNPR848 group (Fig. 1b) and facilitated the activation of primary T cells, leading to the generation of tumor-specific CD8+ T cells. These combined effects not only completely inhibited the growth of distant tumors but also curtailed lung metastasis and postoperative recurrence, thereby inducing a long-term immune memory effect.

Conclusions: In our research, we have strategically designed two distinct nano-vaccine systems, each with unique functionalities. These systems effectively amalgamate the processes of in situ tumor antigen production, antigen capture by nanoparticles, and co-delivery of these antigens and immune adjuvants to lymph nodes. This approach engenders a potent anti-tumor response, stimulates systemic immunity, and fosters long-term immune memory. Our findings pave the way for a novel strategy in constructing in situ cancer vaccines.

Keywords: In Situ Cancer Vaccines, Lymph Nodes-targeted Delivery, Cancer Immunotherapy

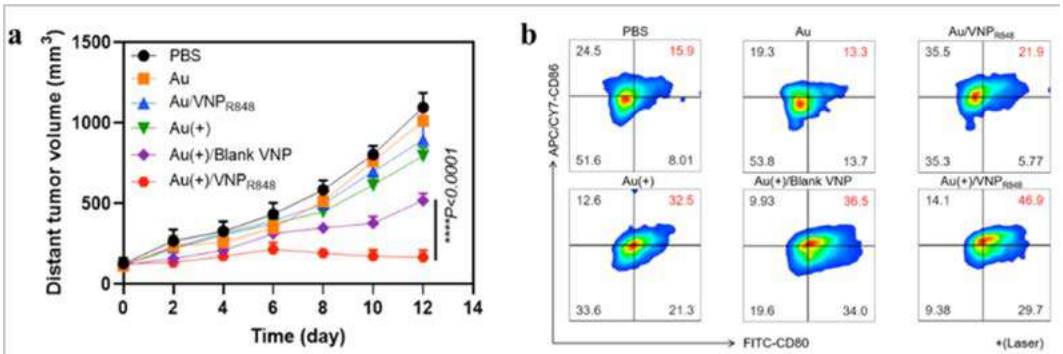

Figure 1: Antitumor effect and induced immune response of in situ nanovaccines programmed in vivo.
(a) Average distant tumor growth curves of LLC tumor-bearingmice receiving various treatments (n = 5).
(b) Representative flow cytometry plots of DCs separated from tumor-draining LNs of LLC tumor-bearing mice.

P1.02C TUMOR BIOLOGY - PRECLINICAL BIOLOGY - IMMUNE MODULATION
SUNDAY, SEPTEMBER 8, 2024 - 12:00 - 14:00

P1.02C.03 A Novel IL-15 Superagonist SHR-1501 Promotes Immune Response in Lung Cancer via Modulating Tumor Microenvironment

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Introduction: Interleukin-15 (IL-15) is a pleiotropic cytokine and identified as a promising agent to be used in caner immunotherapy. Now, we developed a novel IL-15 super-agonist, SHR-1501, a pharmacological grade IL-15/IL-15Rα complex fused to an IgG1 Fc, in which structure exhibits prolonged the half-life in vivo and increased biological activity of IL-15. In this study, we investigated the anti-tumor effects of the newly developed IL-15RA, SHR-1501, both alone and in combination with PD-1 monoclonal antibody (mAb), in two murine lung cancer models. And this is the first study conducted to examine the alteration of the TME and the immune response induced by SHR-1501.

Methods: We investigated its antitumor effects of SHR-1501 by intra-tumoral injection in two lung cell-delivered murine lung cancer models: Lewis lung cancer (LLC) and Kras G12D, p53-/- (KP) lung cancer cell models. We administered SHR-1501 through intratumoral injection (5/15μg) and collect tumor, spleen, and peripheral blood samples for analysis. We use flow cytometry analysis, single-cell sequencing and IHC staining to examine the alteration of tumor microenvironment (TME) and flow cytometry analysis for peripheral immune system.

Results: We found that the administration of SHR-1501 alone at the dose of 5 or 15μg can significantly inhibit tumor growth in both mice models. And the higher dose had shown more effective anti-tumor effects with no significant toxicities. We found an enhanced infiltration of CD8+ T cells, effector CD8+ T lymphocytes, and natural killer (NK) cells in the TME. Additionally, there was a significant increase in the proportion of CD8+ T cells and effector CD8+ T cells in the spleen and peripheral blood samples of mice, and the proportion of NK cells in the peripheral immune system showed a significant early elevation upon SHR-1501 administration (day 7). The results of single-cell sequencing also demonstrated that SHR-1501 can regulate cell populations such as macrophages within the TME, leading to a shift towards a more favorable anti-tumor immune response. We further explored the synergistic anti-tumor immune efficacy of SHR-1501 in combination with PD-1 mAb. Using a subcutaneous tumor model of mouse lung cancer, SHR-1501 was injected into the tumor (15μg, once) and PD-1 mAb was injected intraperitoneally (200μg/each, 6 times). We found that in the combination treatment group, the inhibition of tumor volume growth was most significant and the tumor volume was the smallest. Survival analysis also showed that the combination group had the longest survival period, and the mice did not exhibit obvious drug toxicity. These results indicate that SHR-1501 has a synergistic anti-tumor immune effect with PD-1 mAb. In addition, by establishing a bilateral tumor mouse model, we observed an obscopal effect induced by SHR-1501.

Conclusions: The novel IL-15 superagonist, SHR-1501, has a strong anti-tumor effects in lung cancer cell mouse models, and the combination of SHR-1501 with PD-1 mAb had shown a potent synergistic anti-tumor effect. The findings from this study can provide evidence and experimental basis to support further clinical trial.

Keywords: SHR-1501, IL-15 superagonist, Non-small cell lung cancer

P1.02D TUMOR BIOLOGY - PRECLINICAL BIOLOGY - NOVEL MODELS/NOVEL TECHNOLOGIES
SUNDAY, SEPTEMBER 8, 2024 - 12:00 - 14:00

P1.02D.01 Exosome PAICS Enhances Radioresistance in NSCLC by Mitigating Radiation-Induced DNA Damage and Facilitating Immune Evasion

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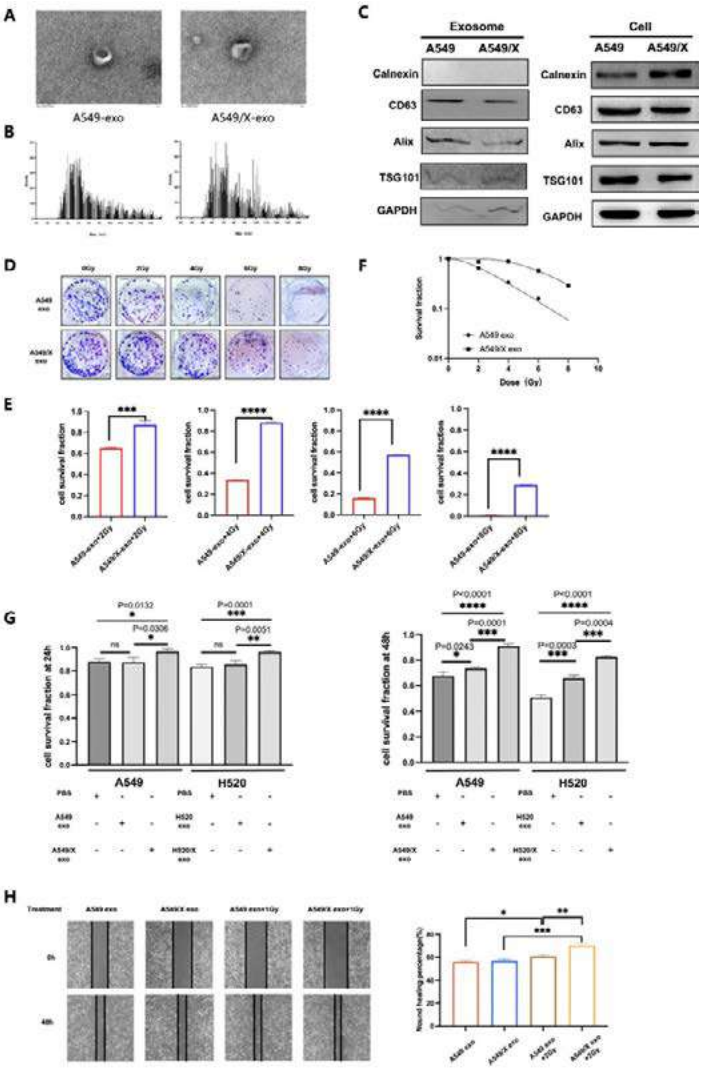
Introduction: Radioresistance in NSCLC is not solely a consequence of tumor cell adaptation but also involves significant alterations within the tumor microenvironment, including changes in immune cell dynamics. Tumor-derived exosomes play a critical role in this adaptive resistance, influencing not just the tumor cells but also the immune cells. Unraveling the molecular mechanisms of exosome-mediated radioresistance is crucial for identifying novel targets that can sensitize tumors to radiotherapy and serve as predictive markers for treatment response.

Methods: Colony formation assay, wound healing assay and immunofluorescence assay were utilized to assess how exosomes from radioresistant cells influence the radiosensitivity of NSCLC cells. RNA-seq sequencing was performed to identify the functional gene of radioresistant NSCLC cells. We conducted comprehensive in vitro and in vivo studies, including subcutaneous tumor models and flow cytometry, to explore the impact of exosome-delivered functional proteins on NSCLC and the underlying mechanisms.

Results: Our research found that exosomes from radioresistant A549/X cells reduce DNA damage and increase radioresistance in NSCLC cells(Figure1). Specifically, PAICS(Phosphoribosylaminoimidazole carboxylase, phosphoribosylaminoimidazole succinocarboxamide synthetase), significantly upregulated in A549/X and its exosomes, appears to contribute to NSCLC's radioresistance. Silencing PAICS in A549/X cells diminished these effects, suggesting PAICS's role in mitigating radiation damage and inhibiting NSCLC cell migration. This process involved alterations in DNA damage response and immune evasion mechanisms, including changes in H2AX phosphorylation, RAD51 expression, and STING pathway activation. Additionally, animal studies demonstrated that A549/X-derived exosomes decreased radiotherapy's tumor-reducing effects, which was counteracted by using exosomes from PAICS-silenced A549/X cells. Flow cytometry revealed that exosome PAICS promotes an immunosuppressive environment, aiding in tumor immune escape by inhibiting CD4+T cells, CD8+T cells, DC cells infiltration and promoting the polarization of M2-type macrophages.

Conclusions: Our results demonstrate that PAICS, a crucial enzyme in the purine biosynthesis pathway, can be conveyed to recipient NSCLC cells via exosomes. This mechanism may play a significant role in conferring radioresistance in NSCLC.

Keywords: exosome, radiotherapy resistance, tumor immune microenvironment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A549/X-exo
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cell survival fraction at 24h
cell survival fraction at 48h
A549
H520
H
0h
48h

P1.02D TUMOR BIOLOGY - PRECLINICAL BIOLOGY - NOVEL MODELS/NOVEL TECHNOLOGIES
SUNDAY, SEPTEMBER 8, 2024 - 12:00 - 14:00

P1.02D.02 Tumor-Derived Exosomal tsRNA 3' tiRNA-AlaCGC Promotes Immune Tolerance by Inducing Fibroblast Senescence in LUAD

Y. Zhang, G. Zhao, H. Zhang, D. Ge, Zhongshan Hospital, Fudan University, Shanghai/CN

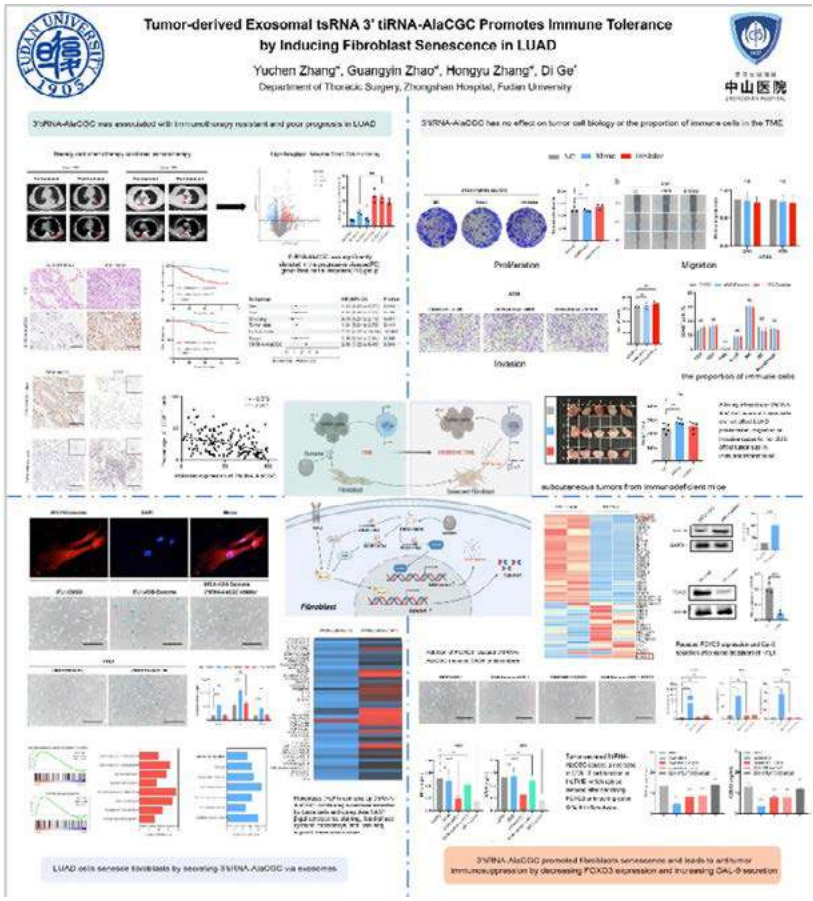
Introduction: The benefit of immunotherapy varies among lung adenocarcinoma(LUAD) patients due to the heterogeneity of the tumor microenvironment(TME). Transporter RNA-derived small RNAs(tsRNAs) are able to influence mRNA stabilization and thus the TME, but their role in immunotherapy resistance in LUAD has not been elucidated.

Methods: The correlation between tsRNA and immunotherapy resistance in the neoadjuvant chemotherapy combined immunotherapy cohort was investigated using high-throughput Arraystar Small RNA microarray. The expression, clinical relevance and biological functions of 3'tiRNA-AlaCGC in LUAD were investigated. By adding 3'tiRNA-AlaCGC mimics and inhibitors, extracting exosomes secreted by tumor cells, and using FISH, flow cytometry, senescence staining, liquid phase cytokine microarrays, and RNA-seq, the role of 3'tiRNA-AlaCGC on immune cells and fibroblasts and the mechanism leading to immune resistance were investigated. Meanwhile, at the animal level, it has been demonstrated that 3'tiRNA-AlaCGC leads to resistance to anti-tumor immunotherapy.

Results: 3'tiRNA-AlaCGC was significantly elevated in the progressive disease(PD) group than partial response(PR) group. It was associated with poor prognosis and decreased CD8+ T cells in multiple other cohorts. Altering intracellular 3'tiRNA-AlaCGC levels in tumor cells did not affect LUAD proliferation, migration or invasive capacity, nor did it affect tumor size in immunodeficient mice. LUAD cells can secrete tsRNA 3'tiRNA-AlaCGC via exosomes. Its overexpression in tumor exosomes did not affect immune cells in the TME, but inhibited the proliferation and migration abilities of fibroblasts and caused an increase in their senescence-associated secretory phenotype(SASP), which promoted their senescence. Mechanistically, 3'tiRNA-AlaCGC decreased the expression of FOXO3, which led to the enrichment of senescence-related pathways, promoted fibroblast senescence, and suppressed the function of CD8+ T cells in the TME. In addition, tsRNA 3'tiRNA-AlaCGC increased the secretion of the immunosuppressive ligand Gal-9 through the TGFβ-Smad pathway, which further suppressed anti-tumor immunity. Animal experiments confirmed that 3'tiRNA-AlaCGC overexpression decreased the level of FOXO3 and increased the expression of Gal-9 in cancer tissues, causing a decrease in CD8+T anti-tumor function and leading to anti-PD-L1 treatment resistance.

Conclusions: LUAD cells can secrete tsRNA 3'tiRNA-AlaCGC through the exosomal pathway to induce fibroblast senescence, which induces a decrease in the anti-tumor capacity of CD8+T cells, leading to anti-PD-L1 immunotherapy resistance and poor prognosis in LUAD. Targeting tsRNA 3'tiRNA-AlaCGC may be a novel strategy for synergistic immunotherapy in LUAD.

Keywords: tsRNAs, Immunotherapy, cell senescence



P1.03A TUMOR BIOLOGY - TRANSLATIONAL BIOLOGY - BIOMARKERS
SUNDAY, SEPTEMBER 8, 2024 - 12:00 - 14:00

P1.03A.01 Identification of Disulfidptosis in ESCC Based on Single-Cell and Bulk RNA-seq Data to Predict Prognosis and Treatment Response

X. Zhang, B. Zheng, M. Chen, Fujian Medical University Union Hospital, Fuzhou/CN

Introduction: Our study aims to identify the molecular subtypes of genes associated with disulfidptosis in ESCC, construct a scoring model to explore the differences in tumor growth behavior and find novel potential therapeutic targets.

Methods: Consensus cluster analysis was performed based on the GSE53625 dataset. The prognostic signature was constructed using univariate, multivariate, and Lasso-Cox regression analysis. The TCGA-ESCC dataset and single-cell RNA-seq data from the GSE160269 dataset was combined with trajectory analysis to analyze the prognostic signature. Additionally, the differences in tumor growth patterns, immune microenvironment, and cellular communication were explored, immunotherapy effects were predicted between high- and low-score groups, and potential therapeutic strategies were investigated to provide ideas for follow-up studies.

Results: We identified two distinct patterns of disulfidptosis expression with significant differences in overall survival. Then, we constructed the prognostic signature of disulfidptosis, and results showed patients with high score had worse prognosis. Univariate and multivariate Cox analysis demonstrated that the constructed prognostic signature was an independent prognostic factor and was validated in an independent validation set. The two subgroups differed in the proportion of immune cell infiltration and related signaling pathways in ESCC. The exploration of immunotherapy data confirmed our prognostic signature also had certain predictive power for immunotherapy. Regarding drug prediction, the results suggested the EGFR inhibitor had a stronger inhibitory effect on the low-score group.

Conclusions: This study provides a new prognostic signature for ESCC, explores new therapeutic targets, and provides new theoretical support for personalized treatment.

Keywords: Disulfidptosis, Esophageal squamous cell carcinoma, Prognostic analysis

P1.03A TUMOR BIOLOGY - TRANSLATIONAL BIOLOGY - BIOMARKERS
SUNDAY, SEPTEMBER 8, 2024 - 12:00 - 14:00

P1.03A.02 FBXO32 Promotes EMT and Regulates the Cell Cycle by Targeting PTEN for Proteasomal-Dependent Degradation in LUAD

J. Wu[1], T. Wen[2], A. Marzio[3], D. Song[1], S. Chen[4], C. Yang[1], F. Zhao[1], H. Ren[1], Q. Chen[2], Y. Yang[5], S. Qin[1], [1]The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an/CN ,[2]School of Basic Medical Sciences, Xi'an Jiaotong University, Xi'an/CN ,[3]Meyer Cancer Center, Weill Cornell Medical Center, New York/NY/USA ,[4]The Second Affiliated Hospital of Xi'an Jiaotong University, Xi'an/CN ,[5]Clinical Research Center for Shaanxi Provincial Radiotherapy, Shaanxi Provincial Cancer Hospital, Xi'an/CN

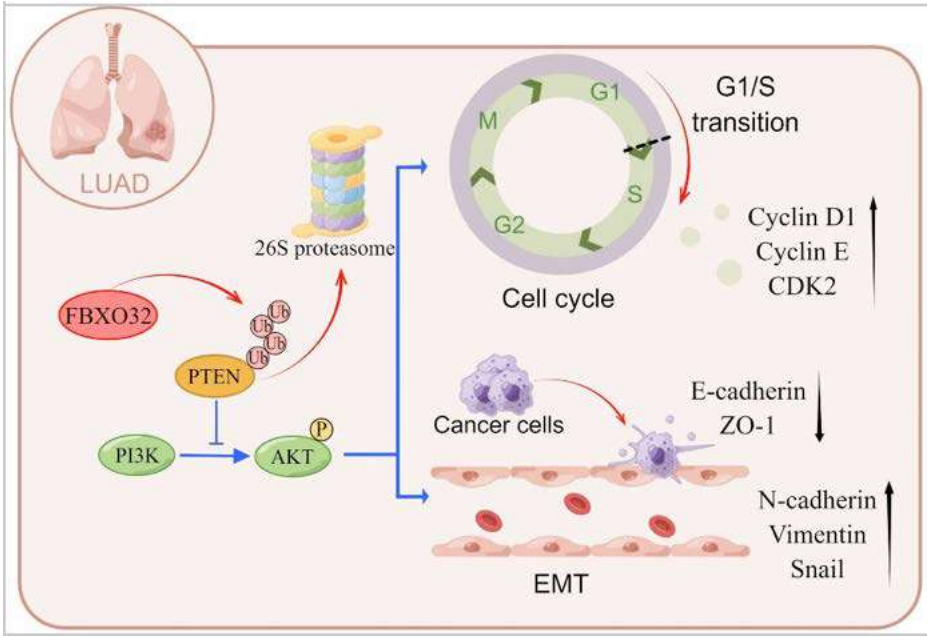
Introduction: FBXO32, a member of the F-box protein family, is known to play both oncogenic and tumor-suppressive roles in different cancers. However, the functions and the molecular mechanisms regulated by FBXO32 in lung adenocarcinoma (LUAD) remain unclear.

Methods: The expression of FBXO32 and PTEN in LUAD tissues and cells was measured by RT-qPCR, immunohistochemistry and Western blotting. The distribution of cells in the cell cycle was determined via flow cytometry. Transwell and wound-healing assays were performed to analyse the migration and invasion ability of LUAD cells. The expression of related molecular markers was measured by Western blot and immunofluorescence assays. A nude mouse model of tumour metastasis was established to evaluate the effect of FBXO32 on metastasis in vivo. The regulatory mechanisms were validated by coimmunoprecipitation and ubiquitination assays.

Results: FBXO32 is overexpressed in LUAD compared with normal lung tissues, and high expression of FBXO32 correlates with poor prognosis in LUAD patients. Firstly, we observed with a series of functional experiments that FBXO32 alters the cell cycle and promotes the invasion and metastasis of LUAD cells. We further corroborate our findings using in vivo mouse models of metastasis and confirmed that FBXO32 positively regulates LUAD tumor metastasis. Using a proteomic-based approach combined with computational analyses, we found a positive correlation between FBXO32 and the PI3K/AKT/mTOR pathway, and identified PTEN as a FBXO32 interactor. More important, FBXO32 binds PTEN via its C-terminal substrate binding domain and we also validated PTEN as a bona fide FBXO32 substrate. Finally, we demonstrated that FBXO32 promotes EMT and regulates the cell cycle by targeting PTEN for proteasomal-dependent degradation.

Conclusions: In summary, our study highlights the role of FBXO32 in promoting the PI3K/AKT/mTOR pathway via PTEN degradation, thereby fostering lung adenocarcinoma progression.

Keywords: LUAD, FBXO32, Ubiquitination



P1.03B TUMOR BIOLOGY - TRANSLATIONAL BIOLOGY - EARLY STAGE/STEM CELLS
SUNDAY, SEPTEMBER 8, 2024 - 12:00 - 14:00

P1.03B.01 Multi-Omics Profiling Reveals the Genomic Origin and Adeno-Squamous Transdifferentiation Mechanism in Adenosquamous Carcinoma

X. Zheng[1], G. Lin[1], Q. Miao[2], K. Jiang[1], X. Zheng[1], L. Zhang[1], [1]Clinical Oncology School of Fujian Medical University, Fujian Cancer Hospital, Fuzhou/CN ,[2]Clinical Oncology School of Fujian Medical University, Fujian Cancer Hospital, Fozhou/CN

Introduction: Adenosquamous carcinoma (ASC) represents a rare subtype (0.4-4%) of non-small-cell lung cancer (NSCLC), with its multi-omic landscape yet to be fully elucidated. This study aims to explore the genomic origins and molecular mechanisms of adeno-squamous transdifferentiation in lung ASC through comprehensive multi-omics.

Methods: We analyzed 69 samples from 31 lung ASC patients, including 16 FFPE samples with microdissected paired adenocarcinoma (AC) and squamous cell carcinoma (SCC) components, and additionally, incorporated pure Lung Adenocarcinoma (LUAD, n = 51) and pure Squamous Cell Carcinoma (LUSC, n = 28) for comparative analysis. Techniques included whole-exome sequencing, whole-genome methylation profiling, transcriptomics, single-cell RNA sequencing, and spatial transcriptomics.

Results: AC and SCC exhibited similar genomic mutation landscapes, indicating a common genomic origin for AD and SCC. The SCC component in ASC displayed higher homologous recombination repair deficiency (HRD) and a notable 16p13.3 deletion in 31% of ASC transformations. Differential methylation analysis highlighted TP63's lower methylation in SCC, correlating negatively with RNA expression ($P < 0.001$), indicative of methylation-driven regulation. DMR binding motif analysis revealed hypo-methylation in p63, p53, and AP-1 motifs, and hyper-methylation in MKX2-1, FOXA1/2 motifs ($P < 0.05$). The transition from AC to SCC in ASC was marked by upregulated MYC signaling, proliferation, and DNA repair, with EMT changes not methylation-driven. Metabolic pathways were upregulated, and EMT/KRAS pathways downregulated in SCC compared to LUSC. Immune infiltration in LUAD-AC-ASC transformation showed an initial increase and subsequent decrease, transitioning from immune-infiltrated and immune-excluded to immune-desert phenotypes. IL36G of the IL1 family was highly expressed in the SCC component and strongly correlated with the squamous marker P63 (Pearson $r = 0.72$, $P < 0.001$). Single-cell RNA-seq data demonstrated a significant increase in IL36G in squamous cells of lung ASC. In vivo models showed adeno-squamous differentiation in adenocarcinoma cells expressing IL36G.

Conclusions: This study provides a comprehensive multi-omic insight into the complex genomic and epigenomic landscape of ASC, highlighting a shared genomic origin and distinct molecular mechanisms in the adeno-squamous transdifferentiation process. The findings, particularly the role of TP63 methylation and IL36G expression in the SCC component, offer novel insights into the molecular heterogeneity of ASC.

Keywords: Adenosquamous carcinoma of lung, adeno-squamous transdifferentiation, Multi-Omics

P1.03C TUMOR BIOLOGY - TRANSLATIONAL BIOLOGY - GENOMICS
SUNDAY, SEPTEMBER 8, 2024 - 12:00 - 14:00

P1.03C.01 A Landscape of the Driver Alterations in 920 Brazilian Lung Cancer Patients.

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Introduction: The profile of driver alterations directly impacts the clinical management of lung cancer patients and can significantly change among ethnic groups. The molecular profile in admixed populations, as in Brazil, is poorly understood. We aimed to describe the molecular profile of Brazilian patients with non-small cell lung cancer (NSCLC) using real-world data from a single center in Brazil.

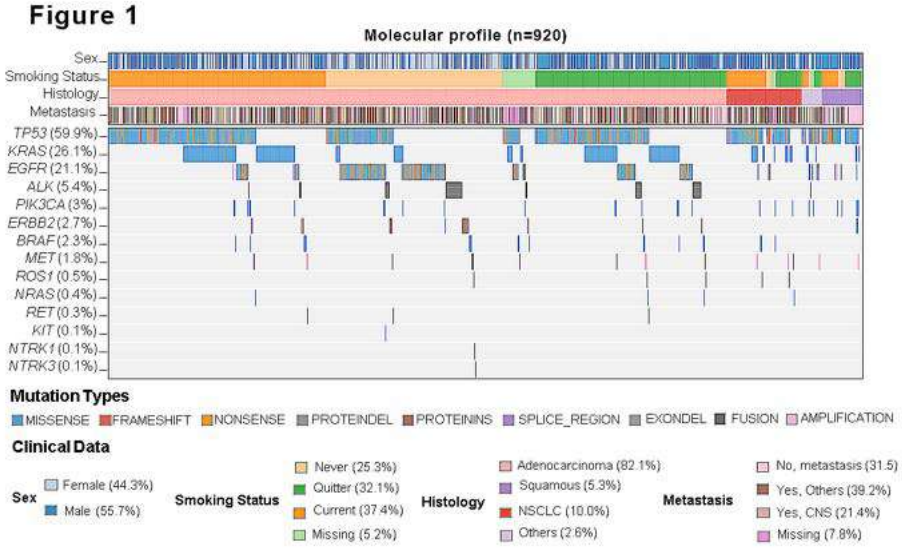
Methods: Driver mutations and fusions in 920 NSCLC patients were assessed by NGS (TruSight Tumor 15) and RNA-based nCounter approaches, respectively. The genetic ancestry was assessed using 46-ancestry-informative markers. Additionally, the molecular profile was associated with patients' clinicopathological and survival features.

Results: Most patients harbored at least one oncogenic alteration (88.4%; n=813/920)(Figure 1). EGFR mutations were associated with females, never-smokers, diagnosed with non-squamous histology, and the presence of metastasis in the nervous system. KRAS mutations were associated with ever-smoker, loss of weight (6-months prior to diagnosis), and adenocarcinoma histology. TP53 mutations were associated with males, ever-smoker, and squamous histology. ALKfusions were associated with younger patients, never-smokers, and adenocarcinoma subtype. Higher African ancestry was associated with TP53 mutations (p=0.002). Patients harboring EGFR mutations showed longer overall survival than wild-type patients (p<0.0001, 36.3 and 14.5 months, respectively). Of note, patients harboring concomitant EGFR and TP53 mutations showed shorter overall survival than patients with only EGFR mutations (p=0.019; 25.7 and 62.0 months, respectively). Similar trends were observed in patients who received TKI treatment, with EGFR-mutant patients harboring TP53 mutations presenting shorter overall survival than patients with only EGFR mutations (p=0.086; 23.4 and 33.1 months, respectively).

Conclusions: Most patients harbor at least one oncogenic alteration. The association of TP53 mutations and African ancestry suggests an influence of genetic ancestry in molecular profile in Brazilian patients. Co-occurrence of TP53 and EGFR mutations suggested an unfavorable prognosis for TKi-treated patients. Our results reinforce the importance of molecular characterization in ethnic admixed NSCLC patients.

Keywords: Molecular Profile, Brazil, Admixed

Figure 1



P1.03C TUMOR BIOLOGY - TRANSLATIONAL BIOLOGY - GENOMICS
SUNDAY, SEPTEMBER 8, 2024 - 12:00 - 14:00

P1.03C.02 Different STK11 Mutation Status Defines Various TIME in NSCLC

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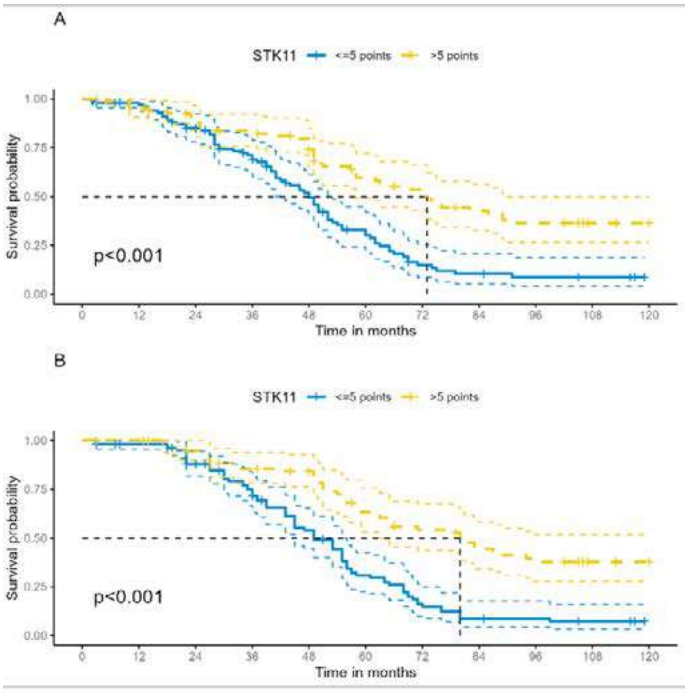
Introduction: To unveil whether overexpressed- and mutated-STK11 impact survival in NSCLC and to explore whether immune related genes (IRGs) are involved in STK11 mutations.

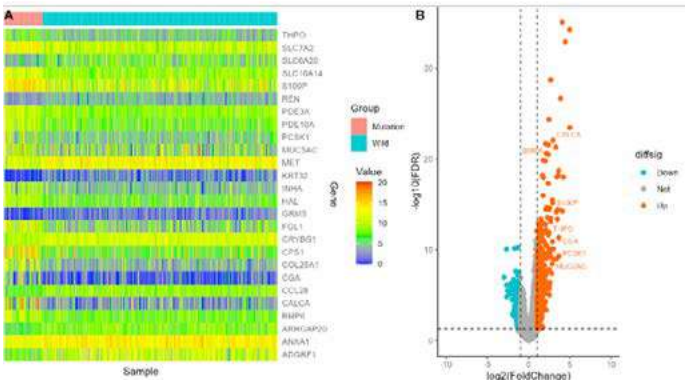
Methods: 188 NSCLC patients with intact FFPE tissue available for detecting STK11 protein expression were included. After IHC detection of STK11 protein, patients were divided into high STK11High and STK11Low, and survival analysis and COX proportional hazards model were used to compare survival. In addition, the mutation data from the TCGA database was used to categorize the NSCLC population, i.e., STK11Mut and STK11Wt subgroups. The difference in OS between STK11Mut and STK11Wt was compared. Finally, bioinformatics analysis was used to compare the differences in IRGs expression between STK11Mut and STK11Wt populations.

Results: The median follow-up time was 51.0 months (range 3.0 - 120.0 months) for real-life cohort. At the end of follow-up, 64.36% (121/188) of patients experienced recurrence or metastasis. 64.89% (122/188) of patients ended up in cancer-related death. High expression of STK11 was a significant protective factor for NSCLC patients, both in terms of PFS [HR=0.42, 95% CI= (0.29-0.61), P<0.001] and OS [HR=0.36, 95% CI= (0.25, 0.53), P<0.001], which was consistent with the finding in TCGA cohorts [HR=0.76, 95%CI= (0.65, 0.88), P<0.001 HR=0.76, 95%CI= (0.65, 0.88), P<0.001]. In TCGA cohort, STK11 mutation was a significant risk factor for NSCLC in both lung squamous cell carcinoma (LUSC) and lung adenocarcinoma (LUAD) histology in terms of OS [HR=6.81, 95%CI= (2.16, 21.53), P<0.001; HR=1.50, 95%CI= (1.00, 2.26), P=0.051, respectively]. Furthermore, 7 IRGs, namely CALCA, BMP6, S100P, THPO, CGA, PCSK1 and MUC5AC, were found significantly overexpressed in STK11-mutated NSCLC in both LUSC and LUAD histology.

Conclusions: Low STK11 expression at protein level and presence of STK11 mutation were associated with poor prognosis in NSCLC, and mutated STK11 might probably alter the expression IRGs profiling.

Keywords: STK11 gene, immune related genes, non-small cell lung cancer





P1.03D TUMOR BIOLOGY - TRANSLATIONAL BIOLOGY - IMMUNE MODULATION
SUNDAY, SEPTEMBER 8, 2024 - 12:00 - 14:00

P1.03D.01 Efficacy and Biomarker Analysis of Neoadjuvant Toripalimab Plus Chemotherapy in Resectable Stage IIB-IIIB Non-Small Cell Lung Cancer (NSCLC)

B. Liu[1], N. Wu[2], S. Yan[1], E. Zhang[3], L. Xu[3], X. Cheng[3], [1]Peking University Cancer Hospital & Institute, Beijing/CN ,[2]Peking University Cancer Hospital, Beijing/CN ,[3]Genecast Biotechnology Co., Ltd, Wuxi/CN

Introduction: Immune checkpoint inhibitors revolutionized cancer treatment, including NSCLC. Several studies have revealed preliminary efficacy and safety of neoadjuvant chemoimmunotherapy in NSCLC. However, further studies are still necessary to validate its efficacy and safety. Furthermore, while neoadjuvant chemoimmunotherapy exhibits superior efficacy over standard chemotherapy, it does not confer benefits to all patients, as evidenced by on-going trials.

Methods: This was a prospective single-arm, phase II clinical trial conducted at Peking University Cancer Hospital & Institute (NCT04606303). From December 18, 2020 to January 9, 2023, 100 patients with histologically confirmed clinical stage IIB to IIIB NSCLC (stage IIIB, T3-4N2M0 only) received the following drugs intravenously in each 21-day treatment cycle: toripalimab, cis-platinum, pemetrexed for lung adenocarcinoma (LUAD) and albumin-bound paclitaxel for lung squamous cell carcinoma (LUSC) or NSCLC-not identified subtype (NSCLC-other). We conducted targeted methylation panel sequencing and analyzed the methylation profiling for all plasma samples and calculated methylation fragment ratio scores (MFR) and performed whole methylation sequencing (WMS) and assessed chromosomal aneuploidy of featured fragments (CAFF) score.

Results: Among the 100 patients enrolled in this study, 83 (83.0%) patients successfully underwent surgical resection and included in the final efficacy analysis, and R0 resection was achieved in all these patients. Surgical complications occurred in 21 (25.3%) patients. According to postoperative pathological evaluation, 54 (65.1%) patients achieved major pathological response. For MPR patients, both the MFR score and CAFF score significantly reduced from C0 to C1 ($P < 0.001$) and remained low at BS ($P < 0.001$). In contrast, non-MPR patients exhibited a different dynamic pattern. The MFR score similarly reduced at C1 ($P < 0.05$), but it tended to increase at the end of neoadjuvant treatment (BS), showing no significant difference between BS and C0 time points ($P = 0.132$). A similar dynamic pattern was observed for the CAFF score in MPR group. Notably, the CAFF score showed no significant reduction at C1 compared to C0 for non-MPR patients ($P = 0.111$).

Conclusions: We demonstrated the efficacy of neoadjuvant toripalimab combined with chemotherapy and the predictive value of MFR and CAFF score in neoadjuvant chemoimmunotherapy.

Keywords: non small cell lung cancer, neoadjuvant chemoimmunotherapy, biomarker

P1.03D TUMOR BIOLOGY - TRANSLATIONAL BIOLOGY - IMMUNE MODULATION
SUNDAY, SEPTEMBER 8, 2024 - 12:00 - 14:00

P1.03D.02 An Enhanced Immunotherapeutic Strategie for NSCLC via in Situ Tumor Nanovaccines and Activation of STING and TLR7/8 Pathways

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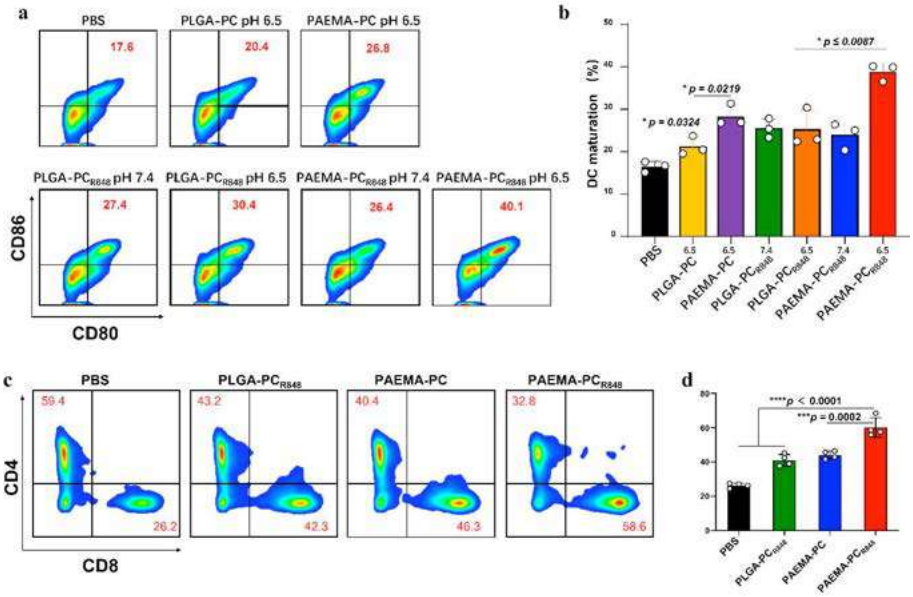
Introduction: Following surgical treatment, radiotherapy, and chemotherapy, immunotherapy has emerged as a novel and promising therapeutic approach for tumors. Among the various strategies, therapeutic tumor vaccines are gaining attention due to their potential in eradicating tumors and preventing recurrence and metastasis by inducing or amplifying T cell-mediated immune responses. However, the therapeutic efficacy of these vaccines is often limited by the heterogeneity observed both between and within tumors. In contrast, in situ tumor vaccines, which are prepared directly from tumor patients and thus produce whole autologous antigens, present another promising strategy that is gaining momentum in the field.

Methods: In our research, we engineered a multifunctional nanopolymer, termed as PAEMA-PCR848, which is a transformable nanoassembly. This assembly is composed of the photosensitizer PEG-Ce6 (Polyethylene glycol-chlorin-e6), a tumor pH-responsive polymer P-AEMA (Poly(2-azepane ethyl methacrylate)), and the immune adjuvant Resiquimod (R-848). We validated the activation of bone marrow-derived dendritic cells at a cellular level and subsequently investigated the inhibition of distal tumor growth mediated by PAEMA-PCR848 through photodynamic therapy (PDT).

Results: We have successfully prepared and characterized an acid-responsive nanovaccine loaded with agonists of the STING and TLR7/8 pathways. Enhanced Dendritic Cells (DCs) Maturation In vitro studies demonstrated a notable maturation rate of DCs at 38.8±2.0% within the PAEMA-PCR848 group which was significantly superior compared to other groups, indicating that PAEMA-PCR848 efficaciously fosters DC maturation and augments antigen presentation capabilities. In the C57BL/6 mouse model, the PAEMA-PCR848 group demonstrated a significantly higher infiltration ratio of 60.1±5.8% for CD8+ T cells in distant tumors, indicating an enhancement in immunogenicity and antigen presentation, thereby potentially augmenting the efficacy of immunotherapy.

Conclusions: In this research, we have devised a straightforward yet potent approach centered on in situ tumors. This strategy has demonstrated potential in curbing tumor growth, triggering immunogenic cell death, and eliciting a systemic anti-tumor immune response. Furthermore, we aim to extend our investigations to ascertain the therapeutic impact on metastatic and distal tumors.

Keywords: Drug delivery, Immunotherapy, In situ tumor vaccin



Fifure 1. The immunologic mechanism study triggered by in situ tumor nanovaccines in vivo. (a,b) Representative flow cytometry plots (a) and proportions (b) of CD8+ T cells in CD3+ T cells. DC maturation induced by in situ tumor nanovaccines under PDT in vitro. (c, d) Representative flow cytometry plots (c) and proportions (d) of mature DCs (CD11c+CD80+CD86+) induced by various treatments in vitro.

P1.03D TUMOR BIOLOGY - TRANSLATIONAL BIOLOGY - IMMUNE MODULATION
SUNDAY, SEPTEMBER 8, 2024 - 12:00 - 14:00

P1.03D.03 Artemisinin Enhances Anti-Tumor Immunity by Increasing FGL1 Ubiquitination Degradation via Activating TRIM21 In NSCLC

Y. Zhang[1], P. Zhou[1], D. Ge[1], J. Gu[1], C. Zhang[2], [1]Zhongshan Hospital, Fudan University, Shanghai/CN ,[2]Key Laboratory of Metabolism and Molecular Medicine, Ministry of Education, and Department of Biochemistry and Molecular Biology, School of Basic Medical Sciences, Fudan University, Shanghai/CN

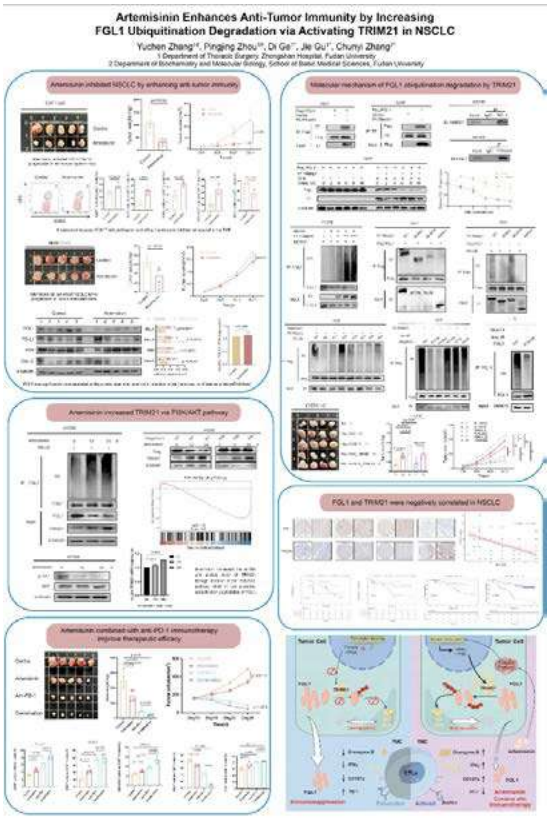
Introduction: In addition to malaria, artemisinin has recently been reported have antitumor effects, but the mechanism in non-small cell lung cancer(NSCLC) remains unclear. Fibrinogen-like protein-1 (FGL1) has been reported an inhibitory ligand for lymphocyte activation gene-3 (LAG3) on T cells.High expression of FGL1 in NSCLC was correlated with poor prognosis in immunotherapy. However, the pathway of endogenous degradation of FGL1 was unknown.

Methods: A subcutaneous tumor model of NSCLC with artemisinin therapy was established in immunodeficient and immunocompetent mice. Immune ligands in the tumor microenvironment(TME) were analyzed at protein and RNA levels to find targets of artemisinin. IP-MS and co-IP were used to search and validate potential ubiquitin ligases of FGL1. The mechanism of ubiquitination degradation of FGL1 by TRIM21 was clarified by constructing mutant proteins and whether it affects tumor progression was clarified using animal models. The molecular mechanism of FGL1 degradation by artemisinin was clarified by RNA-seq and animal experiments. The application prospect of artemisinin combined with immunotherapy was explored in vivo. Clinical cohorts were used to explore the correlation between FGL1 and TRIM21 and its impact on prognosis.

Results: Artemisinin inhibited tumor progression in immunocompetent mice, but not in immunodeficient mice. Artemisinin increased CD8+ T cell proliferation and killing function and inhibited exhausted in the TME. The immunosuppressive ligand FGL1 was significantly downregulated at the protein level, but not at the mRNA level. TRIM21 was identified as a ubiquitin ligase for FGL1. Overexpression of TRIM21 resulted in a shortened half-life and increased ubiquitination levels of FGL1 and vice versa. Clinical cohorts suggested FGL1 and TRIM21 were negatively correlated in NSCLC and their ratio correlated with prognosis. TRIM21 interacted with FGL1 through PRYSPRY domain and catalyzed K27 ubiquitination of FGL1 through RING domain. The ubiquitination sites of human FGL1 were lysine 159 and lysine 278, corresponding to lysine 161 in mouse. Tumors were enlarged after overexpression of FGL1 and could be shrunk after overexpression of TRIM21, but not after mutation of K161. Artemisinin increased the level of TRIM21 through inhibition of the PI3K/AKT pathway which in turn promotes ubiquitination degradation of FGL1. Artemisinin combined with anti-PD-1 immunotherapy in mouse models can better activate the anti-tumor function of CD8+ T cells and improve the efficacy of immunotherapy.

Conclusions: Artemisinin can increase TRIM21 expression, thereby enhancing FGL1 ubiquitination degradation and activating anti-tumor immunity. Artemisinin combined with immunotherapy may improve therapeutic efficacy and provide a new target for immunotherapy in NSCLC.

Keywords: Ubiquitination, Immunotherapy, FGL1



P1.03D TUMOR BIOLOGY - TRANSLATIONAL BIOLOGY - IMMUNE MODULATION
SUNDAY, SEPTEMBER 8, 2024 - 12:00 - 14:00

P1.03D.04 Circulating APOBEC Signature as a Non-Invasive Biomarker Delineating Potential Responder to Neoadjuvant Immunotherapy for IIIA-N2 NSCLC

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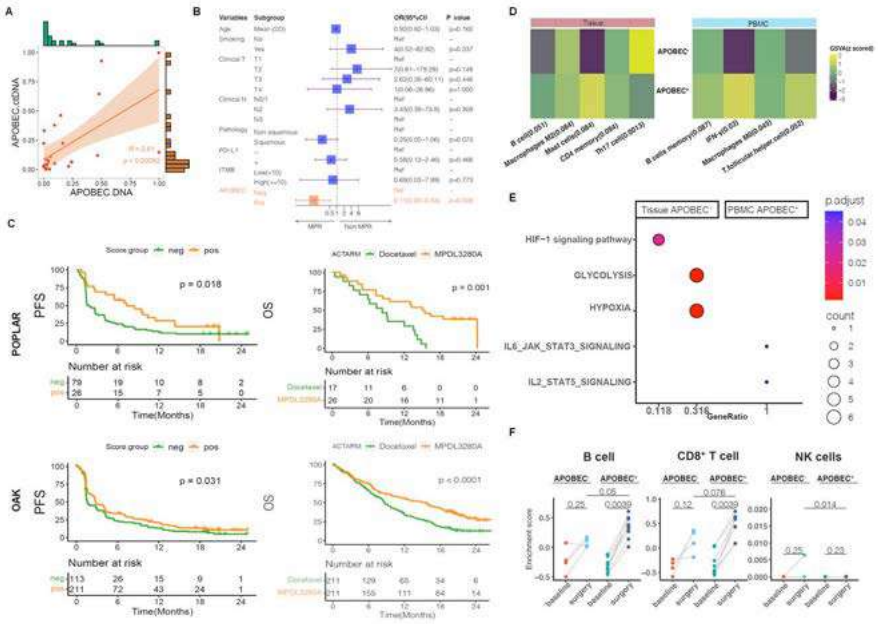
Introduction: Circulating tumor DNA offers a non-invasive method to assess tumor genomics. The impact of circulating tumor genomic signatures on the efficacy of neoadjuvant immunotherapy (NAI) for locally advanced NSCLC is largely unexplored. Leveraging a phase II trial of NAI in locally advanced NSCLC (NCT04422392), this study explores the relationship between pre-NAI circulating tumor DNA genomic signatures and NAI therapeutic efficacy.

Methods: A single-arm, phase II trial of Sintilimab with chemotherapy as neoadjuvant treatment for IIIA-N2 NSCLC (NCT04422392) was conducted. Plasma and peripheral blood mononuclear cell (PBMC) were prospectively collected. Genomic DNA from Pre-NAI FFPE biopsies and cell-free DNA were subjected to comprehensive genomic profiling. Signature Multivariate Analysis (SigMA) was used to evaluate mutation signatures (Gulhan DC, et al, Nat Genet. 2019). Tumor microenvironment of pre-and post-NAI tissues was analyzed by RNA-seq.

Results: A higher ctDNA APOBEC signature, closely matching tissue APOBEC (R = 0.61, P < 0.001) (Fig. A), strongly linked to major pathologic response (MPR) (OR = 0.11, P = 0.009) (Fig. B). ctDNA profiling from POPLAR (n=211) and OAK (n=642) showed APOBEC+ status improves progression-free survival (PFS) with immunotherapy (POPLAR HR=0.56, p=0.018; OAK HR=0.77, P=0.031) but not chemotherapy. Immunotherapy also enhanced overall survival (OS) in APOBEC+ patients compared to chemotherapy (POPLAR HR=0.32, p=0.001; OAK HR=0.59, P<0.0001) (Fig. C). APOBEC+ patients showed higher infiltration of B cell (P = 0.051), Mast cell (P = 0.084) and memory CD4+ cells (P = 0.094) in tumor microenvironment (Fig. D). In PBMC, enriched IL6-JAK-STAT3 (FDR = 0.02) and IL2-STAT5 pathways (FDR = 0.045) were revealed (Fig. E). These patients also displayed increased signatures of IFN-γ (P = 0.03), M0-macrphage (P = 0.045), memory B cells (P = 0.087), follicular T cells (P = 0.052) (Fig. D). Conversely, APOBEC- patients had a hypoxia microenvironment featured by elevated HIF-1 signaling (FDR = 0.022), glycolysis (FDR < 0.001) (Fig. E). And higher infiltration of Th17 cell (P = 0.0013), M2-macrophage (P = 0.084) (Fig. D) were also identified in those patients. Correspondingly, microenvironmental remodeling with vast infiltration of various types of pro-inflammatory cells were observed in post-NAI APOBEC+ tissues, especially for increased CD8+ T cells (P = 0.076), B cells (P = 0.05) and NK cells (P = 0.014) (Fig. F).

Conclusions: The circulating APOBEC signature is a novel, non-invasive biomarker for immunotherapy in locally advanced NSCLC patients, indicative of systemic and local immune response changes against tumors.

Keywords: Circulating APOBEC, Neoadjuvant immunotherapy, Microenvironmental remodeling



P1.03D TUMOR BIOLOGY - TRANSLATIONAL BIOLOGY - IMMUNE MODULATION
SUNDAY, SEPTEMBER 8, 2024 - 12:00 - 14:00

P1.03D.05 A Novel DNA Repair-Gene Model to Predict Responses to Immunotherapy and Prognosis in Patients with EGFR-Mutant Non-Small Cell Lung Cancer

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Introduction: The epidermal growth factor receptor mutant (EGFRm) non-small cell lung cancer (NSCLC) has a unique "cold" immune profile. DNA-damage repair (DDR) genes are closely related to tumorigenesis and the effectiveness of immunotherapy in many tumors. However, the role and mechanism of DDR in the genesis and progression of EGFRm NSCLC remain unclear.

Methods: This study included 101 EGFRm NSCLC samples from The Cancer Genome Atlas (TCGA) dataset and 246 samples from a GSE dataset (external set). Cluster analysis was used to classify DDR subtypes. LASSO regression analysis was used to develop a DDR-based predictive model. The prognostic significance of this model was assessed using Cox regression, Kaplan-Meier, and receiver operating characteristic (ROC) curve analyses. Bioinformatics analysis was performed to investigate the clinicopathological characteristics and immune profiles associated with this model.

Results: We identified two subtypes of EGFRm NSCLC: DDR-activated and DDR-suppressed. The DDR-activated subtype showed more aggressive clinical behavior and poorer prognosis and was more responsive to immunotherapy. A prognostic model for EGFRm NSCLC was constructed using four DDR genes: CAPS, FAM83A, IGLV8-61, and SLC7A5. The derived risk score could serve as an independent prognostic indicator. High- and low-risk patients exhibited distinct clinicopathological characteristics, immune profiles, and responses to immunotherapy. The T-cell inflammation and Tumor Immune Dysfunction and Exclusion (TIDE) scores differed between the high- and low-risk subgroups, with both showing enhanced effectiveness of immunotherapy in the low-risk subgroup. Targeted therapy such as BI.2536, an inhibitor of polo-like kinase 1, could be effective for patients with high-risk EGFRm NSCLC.

Conclusions: This study demonstrated a diversity of DDR genes in EGFRm NSCLC and developed a predictive model using these genes. This model could assist in identifying potential candidates for immunotherapy and in assessing personalized treatment and prognosis of patients with EGFRm NSCLC.

Keywords: non-small cell lung cancer, epidermal growth factor receptor, DNA-damage repair

P1.03D TUMOR BIOLOGY - TRANSLATIONAL BIOLOGY - IMMUNE MODULATION
SUNDAY, SEPTEMBER 8, 2024 - 12:00 - 14:00

P1.03D.06 Targeting IL-6 And Immune Checkpoint Interactions to Augment the Anti-Tumor Immune Response in Lung Carcinoma

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Introduction: The central role of the tumor microenvironment in non-small cell lung cancer (NSCLC) progression is well recognized, with tumor-stromal interactions impacting response to therapeutic intervention. Yet mechanisms to effectively inhibit immune suppression and promote tumor clearance are largely unknown. Interleukin-6 (IL-6) is a critical modulator of immune responses in cancer, mediating accumulation and activation of immune suppressive cells, including myeloid derived suppressor cells (MDSCs) which can hinder the efficiency of immune directed therapy. IL-6 has been shown to induce MDSC recruitment into the tumor microenvironment and upregulate arginase-1 expression and reactive oxygen species production by MDSCs, leading this suppressive cell population to be more efficient in inhibiting anti-tumor immunity. We hypothesize that targeting IL-6 signaling in combination with frontline immune checkpoint directed therapeutics may increase efficacy by altering recruitment and function of immune suppressive cell populations within the lung tumor microenvironment.

Methods: Using an ex vivo perfusion culture platform, remnant tumor tissue specimen from 12 patients were cultured. Matched autologous peripheral blood mononuclear cells (PBMCs) were pre-stained with CFSE, and placed into circulation to track recruitment and retention of immune cells into tumor tissues in a subset of samples (6 tissues). Starting on day 3 of culture, tissues were treated with an immune checkpoint inhibitor (ICI, 10 μg/ml anti-PD-1, Pembrolizumab biosimilar) and an IL-6 receptor inhibitor (5 μg/mL anti-IL6R, Tocilizumab biosimilar) or ICI alone (11 days treatment, 14 days ex vivo culture). Flow cytometry and histologic analyses were performed following intervention.

Results: Tissue specific increases in cell apoptosis are observed in 70% of tissues when combination therapy is compared to ICI alone (average percentage within tissue: 16.4% ± 3% (ICI + anti-IL6R) vs. 14% ± 3% (ICI)). When tumor cell (PanCytokeratin+EpCam+/-) death was assessed using a viability dye, an increase in tumor specific death was observed in 91% of tissues when combination therapy is compared to ICI alone (average percentage within tissue; 15.7% ± 6.3% (ICI + anti-IL6R) vs. 9.8 % ± 4% (ICI), p=0.03). Two populations of MDSCs were assessed, monocytic MDSCs (M-MDSC) constituted about 6% of the total CD45+ immune cell population and granulocytic (G-MDSC) comprised only about 0.4% of the total CD45+ immune cell population in the tissues evaluated. When recruitment of M-MDSC and G-MDSC was measured by evaluation of CFSE+ MDSC populations in the subset of tissues with circulating PBMCs, patient specific decreases in MDSC recruitment were observed with combination therapy. A reduction in recruited (CFSE+) M-MDSCs was seen in 67% of tissues with combination therapy (average percentage within tissue: 7.1% ± 3.1% (ICI + anti-IL6R) vs. 21% ± 6.2% (ICI), p=0.07) and a reduction in recruited (CFSE+) G-MDSCs was seen in 83% of tissues with combination therapy (average percentage within tissue: 49.1% ± 13.2% (ICI + anti-IL6R) vs. 76.3% ± 11.2% (ICI), p=0.03).

Conclusions: This combination strategy may increase long-term therapeutic benefit by reducing immune suppression within the tumor microenvironment. Further understanding of how cell-cell interactions are modulated by this combination strategy and additional characterization of the tumor microenvironment following intervention is critical.

Keywords: Immunotherapy, Non-Small Cell Lung Cancer, Ex Vivo Tissue Culture

P1.03D TUMOR BIOLOGY - TRANSLATIONAL BIOLOGY - IMMUNE MODULATION
SUNDAY, SEPTEMBER 8, 2024 - 12:00 - 14:00

P1.03D.07 Overcoming Immunotherapy Resistance in Non-Small Cell Lung Cancer With a Triple Combination Therapy: Efficacy and Mechanisms

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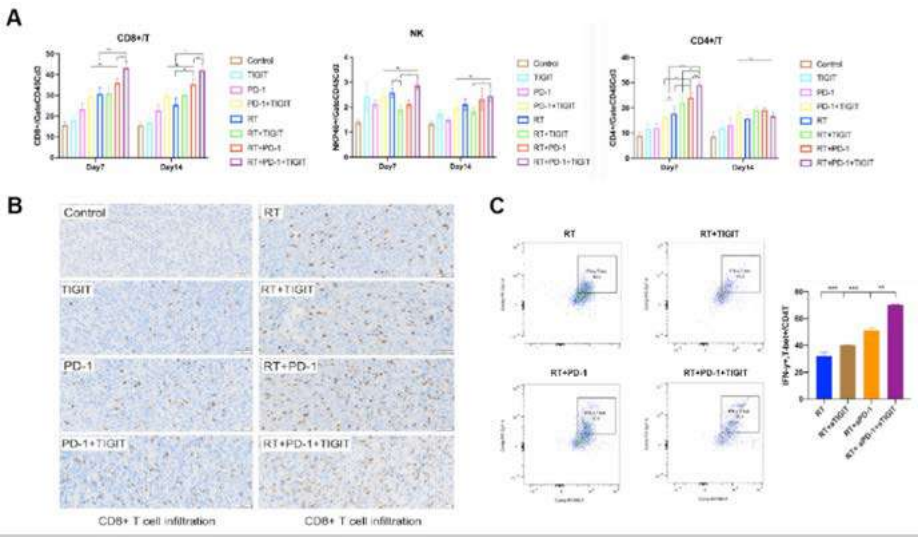
Introduction: Immunotherapy including anti-programmed death receptor-1 (PD-1) antibody is one of the most effective treatments for cancers, but the efficacy of anti-PD-1 antibody in monotherapy for advanced non-small cell lung cancer (NSCLC) patients is only 20%. Hypofractionated radiotherapy and anti- T cell immunoreceptor with immunoglobulin and ITIM domain (TIGIT) antibody are potential therapies in combination with PD-1 therapy for advanced NSCLC patients. Therefore, this study investigated the efficacy and mechanism of hypofractionated radiotherapy in lung combined with anti-PD-1 antibody and anti-TIGIT antibody in the treatment of advanced NSCLC.

Methods: Here, 51 out of 142 NSCLC patients with immunotherapy resistance received hypofractionated radiotherapy for progressive lesions in the lungs. Besides, we investigated the efficacy and safety of 5 patients with locally-advanced NSCLC recieved radiotherapy combined with anti-PD-1 antibody and anti-TIGIT antibody. Primary and distant lung cancer models were established by subcutaneous injection of mouse lung cancer line KP cells into C57BL/6 mice followed by radiation and immunization treatment using anti-PD-1 and anti-TIGIT antibodies. Immune cell infiltration status of mouse tumors was measured by flow cytometry and immunohistochemistry (IHC). RNA sequencing was utilized to explore targeted genes and pathways of the combination treatment of hypofractionated radiation, anti-PD-1 antibody, and anti-TIGIT antibody.

Results: Hypofractionated radiotherapy ameliorates immunotherapy resistance to improve abscopal effects in advanced NSCLC. All patients (5/5, 100%) who received radiotherapy combined with anti-PD-1 antibody and anti-TIGIT antibody achieved partial response. Besides, anti-TIGIT antibody enhances the efficacy of hypofractionated radiotherapy combined with anti-PD-1 antibody in vivo, while hypofractionated radiotherapy facilitates antitumor immune effects activated by anti-PD-1 antibody and anti-TIGIT antibody and promotes tumor-associated macrophage (TAM) infiltration and M1-like polarization as well as promotes abscopal effects. Additionally, the combination treatment of hypofractionated radiation, anti-PD-1 antibody, and anti-TIGIT antibody might exert effects by various of immune-related signaling pathways including leukocyte transendothelial migration and complement and coagulation cascades in NSCLC.

Conclusions: The combination treatment of lung hypofractionated radiation, anti-PD-1 antibody, and anti-TIGIT antibody ameliorates immunotherapy resistance and induces obvious abscopal effects by enhancing antitumor immune effects in advanced NSCLC. These findings provide a novel strategy for treating advanced NSCLC.

Keywords: Non-small cell lung cancer, Hypofractionated radiotherapy, Abscopal effect



P1.03D TUMOR BIOLOGY - TRANSLATIONAL BIOLOGY - IMMUNE MODULATION
SUNDAY, SEPTEMBER 8, 2024 - 12:00 - 14:00

P1.03D.08 Padeliporphin VTP Reverts NSCLC Orthotopic Tumors in Animal Models Into Highly Responsive to aPD1 Therapy

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Introduction: The recent administration of immune checkpoint inhibitors (ICI) (aPD-1, aCTLA-4, aPD-L1) as first line treatments, appeared promising. Although patient' survival is lower than expected, it indicates the significance of attenuating the cancer induced antitumor immunity for treatment's success. We hypothesized that complementary activation of the antitumor immunity by vascular targeted photodynamic therapy (VTP) with Padeliporfin (WST11, TOOKAD®) would prolong animal survival. Padeliporfin-VTP is a non-thermal ablation approach approved by the EMA for grade 1 localized prostate cancer and is being evaluated in Phase 3 trial for treatment of upper tract urinary cancer. In multiple animal tumor models Padeliporfin-VTP triggers innate and adoptive antitumor immunities. Concomitantly, in the tumor microenvironment (TME), a significant increase in immune suppressive signals is observed including PD-1, PD-L1 and CTLA-4. We therefore hypothesized that synchronized combination of VTP and clinically approved ICI may markedly increase the therapeutic success. Here we show the results of testing this concept on mice orthotopic model of NSCLC.

Methods: C57BL/6 mice bearing orthotopic LLC-Luc-mCherry were divided into eight treatment groups: Controls, Padeliporfin-VTP, aPD-1, aCTLA-4, aPD-1+aCTLA-4, Padeliporfin-VTP+aPD-1, Padeliporfin-VTP+aCTLA-4 and Padeliporfin-VTP+aPD-1+aCTLA-4. Padeliporfin-VTP using relatively low light dose (60mW/cm2) was performed when the bio-luminescence measured by IVIS, reached 107. Tumor morphology, immune markers, and pathological changes were assessed at different time intervals post VTP. Multiplex immunohistochemistry and Micro CT were performed before, and at different time intervals post treatment. Tumor progression was followed up to 90 days using IVIS and complementary H&E staining

Results: Non-treated tumor bearing mice survived for up to 40 days. Low light dose induced up to 50% tumor necrosis at 3 days post treatment with only 5% animal survival at day 90. No survival was observed in animals treated by aPD1 or aCTLA4. Animals treated with aPD1+ aCTLA4 reached 14% survival at day 90. Thirty-three and 70% of the animals treated by VTP+aPD1 and VTP+aCTLA-4+aPD1, respectively were tumor free at day 90. Micro CT analyses enabled prediction of treatment success already at day 20 post VTP application.

Conclusions: Based on the immune landscape of the LLC tumors, timely synchronization of VTP and clinically used ICI was designed and found effective and safe for treatment of orthotopic NSCLC in mice. Similar exploration in the upcoming Phase 1 clinical trial of Padeliporfin-VTP in patients with peripheral lung cancer is expected to provide guidelines for new treatment protocols combining ICI and VTP.

Keywords: immune checkpoint inhibitors (ICI), vascular targeted photodynamic therapy (VTP), mice orthotopic model

P1.03D TUMOR BIOLOGY - TRANSLATIONAL BIOLOGY - IMMUNE MODULATION
SUNDAY, SEPTEMBER 8, 2024 - 12:00 - 14:00

P1.03D.09 Single Cell RNA Sequencing and Functional Monocyte Stimulation Reveals Phenotypic Predispositions to Developing Lung Cancer in Never Smokers

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Introduction: There is little research into how never-smoking patients develop lung cancer. 20% of men and >50% of women with lung cancer are never smokers. Recent studies have revealed interleukin1-beta (IL1B) secretion by macrophages in response to exposure to pollution is a key step in the development of lung cancer in never smokers (LCINS). Single nucleotide polymorphisms (SNPs) can alter gene expression in a cell-specific manner. Expression quantitative trait loci (eQTL) analysis measures the effect of SNPs on gene expression. We have developed methods to measure eQTLs at a cellular level which can be applied to inflammatory response genes. We hypothesised that genetic variation in inflammatory response to pollution could contribute to risk of LCINS. Comparing healthy people with patients with LCINS, we aimed to assess eQTLs in inflammatory response genes in immune cells to identify genetic predispositions to LCINS.

Methods: Peripheral circulating immune cells (PBMC) from 17 patients with LCINS were processed for single cell RNA sequencing (cells, n = 50,000). These were compared with 265 age matched, healthy, never-smoking controls (cells, n = 330,000). Cell sub-typing was undertaken using automated methods. PBMCs were analysed using our single cell eQTL methods in inflammatory response genes. Confirmatory tests in circulating monocytes were done in vitro using lipopolysaccharide (LPS) stimulation to measure IL1B and TNFa levels.

Results: 85% of patients had a driver mutation. 23 distinct immune cell subtypes were characterised. Comparing the LCINS and healthy cohort, 294 eQTLs in 77 inflammatory genes from 20 immune cell types were identified. Figure 1 shows eQTLs found in inflammatory genes by cell types. The heatmap shows the effect size (beta) of gene expression seen in the eQTL. The monocyte population had the highest incidence of eQTLs including in IL1B. Functional assays demonstrate varied IL1B responses by monocytes to LPS by genotype.

Conclusions: Individual variation in the IL1B genotype may affect monocyte responses to external stimuli and could be used to identify at-risk individuals for developing LCINS.

Keywords: Never-smoking, Single cell, single nucleotide polymorphism

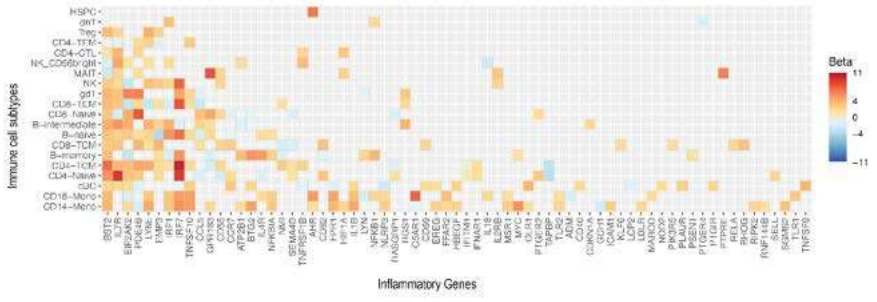

Figure 1. Heatmap demonstrating the genes in cell-types where eQTLs were identified. The colour shows the effect size of gene expression represented by the calculated beta

P1.03D TUMOR BIOLOGY - TRANSLATIONAL BIOLOGY - IMMUNE MODULATION
SUNDAY, SEPTEMBER 8, 2024 - 12:00 - 14:00

P1.03D.10 Uncovering the Molecular Pathways Associated with Immunotherapy-Induced Pneumonitis in Non-Small Cell Lung Cancer Patients

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Introduction: Immune checkpoint inhibitor-related pneumonitis (CIP) is a concerning complication of cancer immunotherapy, especially in non-small cell lung cancer (NSCLC) patients, and can lead to immune-related mortality. Despite the effectiveness of corticosteroids in most cases, 15%-20% of patients exhibit poor responsiveness, and the systemic immunosuppressive effects of corticosteroids may hinder the effectiveness of antitumor therapies. Elucidating the cellular and molecular characterization of the tissues during the occurrence of CIP is crucial for understanding the specific pathogenesis and developing new therapeutic strategies. There is no study of single-cell sequencing of CIP based on tissue samples. In this study, we selected a population of NSCLC patients with the highest number of CIP occurring after treatment with ICI, with the aim of revealing the immune landscape of CIP, and to provide a theoretical basis for future disease diagnosis and targeted interventions.

Methods: We employed a cross-sectional approach to investigate this issue, wherein the experimental group comprised pneumonitis tissues from NSCLC patients who developed CIP after immunotherapy, while the paired non-cancerous adjacent tissues from NSCLC(NSCLC) patients following neoadjuvant therapy. We applied several research tools, single-cell transcriptome sequencing(scRNA-seq)/TCR/BCR was performed to analyze 10 patients/controls and validated our findings with IHC, multiplex immunohistochemistry, and previously published bulk RNA-seq data.

Results: We observed an increase in the proportion of CD8+ T cells and a decrease in the proportion of DC cells in CIP, indicating dysregulation of immune homeostasis during CIP. Furthermore, we confirmed that CD8+ tissue-resident memory T (TRM) cells were the predominant activated subset of T cells in CIP, accompanied by upregulation of the transcription factor STAT1 and substantial release of IFNγ. This phenomenon has also been documented in autoimmune-related skin diseases and Immune Checkpoint inhibitor-colitis. Meanwhile CIP patients expressed macrophage M1 phenotypes, the expression of pro-inflammatory chemokines CCL3 and CCL4 in macrophages was observed to be elevated. as well as high expression of pyroptosis-related genes in macrophages, especially increased expression levels of the pyroptosis-related protein GSDME, which was verified by immunofluorescence and bulk-RNA sequencing data, we guess that nuclear release of pro-inflammatory cytokines and chemokines from macrophages, thereby establishing a positive feedback loop during the process of macrophage pyroptosis may be one of the core links in the development of CIP.

Conclusions: Our findings provide more insights into the immune microenvironment at the single-cell level during the occurrence of CIP in NSCLC patients. Based on these results, we suggest that a significant increase in IFNγ-producing CD8+ TRM cells may be a common pathway for a number of immune-related adverse events. Macrophage pyroptosis may be a key factor contributing to the development of CIP, intervening in the process of CIP by specifically inhibiting key proteins and signals for pyroptosis development is expected to achieve precise prevention and treatment of CIP patients.

Keywords: checkpoint inhibitor-related pneumonitis, single-cell RNA sequencing, immune microenvironment

P1.03D TUMOR BIOLOGY - TRANSLATIONAL BIOLOGY - IMMUNE MODULATION
SUNDAY, SEPTEMBER 8, 2024 - 12:00 - 14:00

P1.03D.11 Association Between Plasminogen Activator Inhibitor-1 & Tolerance Against Anti-PD-1 Antibody in Non-Small Cell Lung Cancer

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Introduction: Immune checkpoint inhibitors (ICIs) have improved the prognosis of patients with advanced non-small-cell lung cancer (NSCLC). Despite ICI treatment, most of patients with advanced NSCLS cannot be cured due to ICI-tolerant cells (ICI-TCs), survived cancer cells within a tumor after ICI treatment. Eliminating these ICI-TCs would potentially lead to the cure of advanced NSCLC. Our previous research has shown the involvement of plasminogen activator inhibitor-1 (PAI-1) in the tolerance of EGFR-mutated NSCLC cells to osimertinib.

Methods: To examine the role of PAI-1 in tolerance of lung cancer to ICI treatment, and if PAI-1 could serve as a viable therapeutic target to overcome the ICI-tolerance.

Results: In a mouse subcutaneous tumor model using mouse lung adenocarcinoma or squamous cell carcinoma cell line, surviving cancer cells within the tumor seven days after anti-programmed death-1 (PD-1) antibody treatment, were defined as ICI-TCs. PAI-1 and epithelial-mesenchymal transition (EMT)-related gene expression levels were significantly higher in ICI-TCs than those in control cells. Subsequently, to examine the tumor microenvironment seven days after PD-1 antibody treatment, immunohistochemical staining of tumor sections was performed. Immunohistochemical analyses showed higher PD-L1 expression of cancer cells and increased M2 macrophages in the tumor seven days after anti-PD-1 antibody treatment compared to control tumors, alongside a reduction in CD8-positive lymphocytes. Continuous administration of anti-PD-1 antibody led to tumor regrowth after 28 days. In contrast, a combination of anti-PD-1 antibody and a PAI-1 inhibitor, TM5614, resulted in decreased expression of EMT-related genes, PD-L1 expression of cancer cells, and M2 macrophages, alongside increased CD8-positive lymphocytes in tumors. Furthermore, this combination treatment exhibited prolonged inhibition of tumor growth.

Conclusions: This study underscores the involvement of PAI-1 in tolerance of NSCLC to ICI via its association with EMT of cancer cells and alteration of tumor immune-microenvironment. Additionally, PAI-1 may be a potential therapeutic target to overcome tolerance to ICI in NSCLC.

Keywords: PAI-1, Hiroshima, Respiratory

P1.03E TUMOR BIOLOGY - TRANSLATIONAL BIOLOGY - MICROBIOME
SUNDAY, SEPTEMBER 8, 2024 - 12:00 - 14:00

P1.03E.01 Effect of Gut Microbiota and Metabolites on the Efficacy of Immunotherapy Combined with Chemotherapy in Lung Squamous Cell Carcinoma Patients

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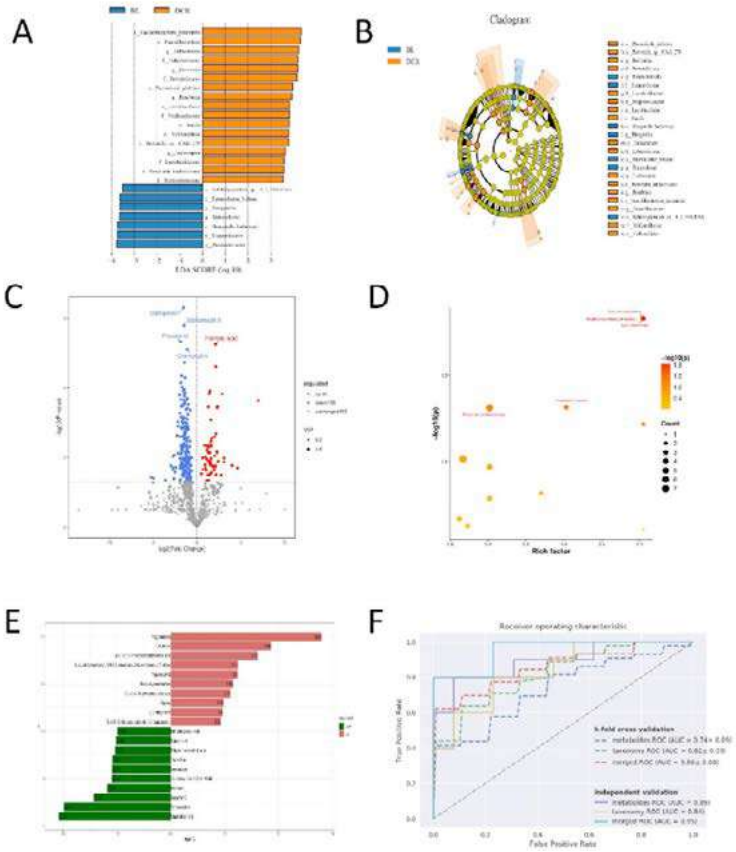
Introduction: The first-line application of immunotherapy combined with chemotherapy in lung squamous cell carcinoma (LUSC) patients has achieved an effective rate of 50-60%. Currently, evidence from preclinical to clinical studies has gradually established that the gut microbiota can regulate anti-tumor immunity and affect the efficacy of cancer immunotherapy. It is worth noting that one of the primary mechanisms by which the gut microbiota regulates anti-tumor immunity is through metabolites, which can diffuse from their initial gut location and influence both local and systemic anti-tumor immune responses.

Methods: We collected 112 fecal samples from patients with LUSC who underwent immunotherapy combined with chemotherapy. The samples were divided into a baseline group comprising samples from patients who had not received any treatment, and a disease control rate (DCR) group consisting of samples from patients who are complete response, partial response or stable disease after immunotherapy combined with chemotherapy. We performed metagenomic and metabolomic sequencing to compare the differences in gut microbiota and metabolites between the two groups of samples.

Results: Among all samples, there were 58 samples in the baseline group and 52 samples in the DCR group. Our analysis revealed significant differences in gut microbiota and metabolites between the two groups of samples. In the metagenomic analysis, it was found that the relative abundance of gut microbiota such as s_Faecalibacterium_prausnitzii (P<0.05), g_Faecalibacterium (P<0.05), g_Eubacterium (P<0.05), f_Eubacteriace (P<0.05), and g_Prevotella (P<0.05) was higher in the DCR group. Metabolomic analysis revealed that metabolites such as Pregnenolone (P<0.05), Cellobiose (P<0.05), Ggstop (P<0.05) and palmitic acid (P<0.05) had higher relative abundances. KEGG metabolic pathway analysis of the differential genes in both groups revealed significant differences in fatty acid biosynthesis and aldosterone synthesis and secretion pathways. Subsequently, we conducted a joint analysis of metagenomics and metabolomics. Random forest analysis showed an AUC > 0.8, indicating a high reliability of the selected gut microbiota and metabolites.

Conclusions: Our findings indicates the abundance of gut microbiota and their metabolites is associated with the efficacy of immunotherapy combined with chemotherapy in patients with LUSC. Gut microbiota and their metabolites may serve as effective targets for predicting the efficacy of immunotherapy combined with chemotherapy for LUSC.

Keywords: gut microbiota, immunotherapy, lung squamous cell carcinoma



P1.03F TUMOR BIOLOGY - TRANSLATIONAL BIOLOGY - NOVEL MODELS/NOVEL TECHNOLOGIES
SUNDAY, SEPTEMBER 8, 2024 - 12:00 - 14:00

P1.03F.01 Imaging the Nucleolus Using Two-Photon Microscopy to Distinguish Between Tumor Cells and Normal Cells

J. Gao, D. Xie, Shanghai Pulmonary Hospital, Shanghai/CN

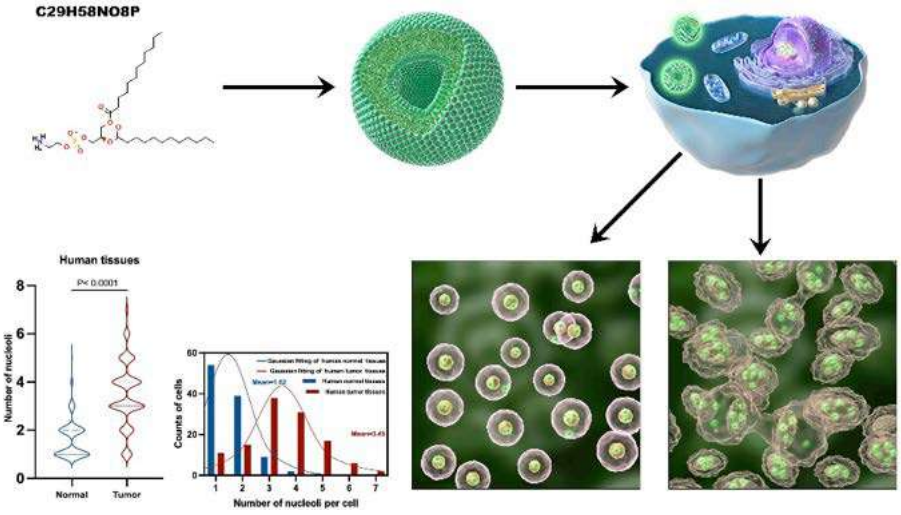
Introduction: Nucleoli can be used as diagnostic biomarkers, such as their number, which has received considerable attention in pathological testing. Fluorescent molecular probes are important for research and clinical applications to detect the precise location of lesions.

Methods: Here, we used fluorescent nanomaterials (NTFNPs) prepared from phospholipid materials to study the difference in the number of nucleoli between normal and tumor cells labeled by fluorescent probes and used NTFNPs as an example to study the difference in the number of nucleoli between tumor cells and normal cells labeled by two-photon effect in 3D tumor cell models, mouse tissue sections and lung adenocarcinoma patient samples. The staining differences of several nucleolar probes were compared, and the fluorescence recovery ability of NTFNPs in tissues was compared.

Results: Researchers used NTFNPs to label nucleoli to differentiate between normal and tumor cells fluorescently. Tumor cells exhibited irregular, featureless nucleoli compared to the uniform, rounded nucleoli in normal cells. Average nucleolar counts per cell were higher in tumor cells (2.36 for A549 and 2.11 for BEL7402) than in normal cells (1.49 for MRC5 and 1.71 for L02), with significant differences confirmed statistically. TEM also showed more nucleoli in tumor cells, corroborating fluorescence microscopy results. NTFNPs demonstrated two-photon fluorescence properties, enabling deeper tissue penetration and clearer detection. In 3D-printed and mouse models, NTFNPs effectively labeled nucleoli, distinguishing tumors from normal cells. Human patient samples showed an average of 3.45 nucleoli per tumor cell versus 1.62 for normal cells.

Conclusions: In this study, lung cancer cells A549, lung normal cells MRC5, liver cancer cell BEL7402, and liver normal cell L02 were used as examples to distinguish tumor cells from normal cells by fluorescently labeling nucleoli with NTFNPs, and the significant differences in the number of nucleoli between tumor cells and normal cells were counted. NTFNPs have a two-photon/three-photon effect with an optimal excitation wavelength of 900 nm, and NTFNPs labeling could distinguish tumor cells from normal cells in the 3D printed cell model. Significant differences in the number of nucleoli between tumor cells and normal cells were observed in mouse and patient tissues. NTFNPs have excellent fluorescence recovery ability and can be used for long-term observation of labeled cells in animal lung cancer tissue sections. This study focused on the feasibility of applying nucleolar-targeted fluorescent nanoparticles (NTFNPs) in tumor diagnosis and diagnosis and provided a new and rapid diagnostic method for tumor diagnosis.

Keywords: Nucleolus imaging, Fluorescent probe, Tumor diagnosis



P1.03F TUMOR BIOLOGY - TRANSLATIONAL BIOLOGY - NOVEL MODELS/NOVEL TECHNOLOGIES
SUNDAY, SEPTEMBER 8, 2024 - 12:00 - 14:00

P1.03F.02 Establishment of EBUS-TBNA Sample Derived Lung Cancer Organoid and Xenograft and Utility for Development of Targeted Therapy

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Introduction: Lung cancer patient-derived organoids (PDO) and patient-derived xenograft (PDX) have been reported as novel preclinical models for translational research. However, many of them were established from resected tumor of early-stage lung cancer, which do not require systemic therapy. Here, we explored the establishment of lung cancer organoids from patients with advanced lung cancer using EBUS-TBNA, which is a method routinely used in to biopsy tumors.

Methods: A total of 81 and 106 lung cancer samples were used to establish PDO and PDX, respectively. We also established xenograft derived organoids (XDOs) using PDX tumors. In organoid establishment, EBUS samples or PDX tumors were digested to single cells using collagenase II. Tumor cells were embedded in matrigel and cultured in M27 organoid culture medium developed at our institute. For PDX establishment, EBUS samples were engrafted subcutaneously in nonobese severe combined immune deficient gamma (NSG) mice. The models passaged more than ten times in organoid and twice in PDX were validated histologically to exclude non-cancer cells contamination. Whole exome sequencing, transcriptome sequencing and pathological assessment were performed on organoid and PDX models. We evaluated the drug sensitivity of PDX and organoids, and compared them with clinical treatment in the matched patients. The drug screening assay was performed using stable organoids to detect the potent drug for each model.

Results: In 71 lung cancer samples, we successfully established six stable lung cancer organoids (8.5%) including three lung adenocarcinoma and three small cell lung cancer. Twenty Stable EBUS-PDXs were generated with a 18.9% (20/106) success rate. Fourteen (70%) stable EBUS-XDOs including five adenocarcinoma, two squamous cell carcinoma, six small cell lung cancer, and one large cell neuroendocrine carcinoma were established from the PDX tumors. We detected a total of four non-cancer cell outgrowths during establishment process: two lymphomas in PDX, one normal airway cell outgrowth in PDO, one mouse cell outgrowth in XDO. Pathological and genetic characteristics were well recapitulated in organoid models. We treated the three matched PDX and XDO models with chemotherapy and observed consistent responses with matching models from individual patient. In the drug sensitivity assay, response heterogeneity was observed in HER2-altered models; an HER2 amplified PDO showed a potent response to HER2 targeted therapies, whereas PDO with HER2exon 20 insertion was resistat. Both PDO and XDO models were feasible for drug screening assay, and response to MEK inhibitor was observed in a XDO model harboring a rare MAP2K point mutation.

Conclusions: We were able to establish lung cancer organoids and PDX models with EBUS samples. These models recapitulated the characteristics of the source tumor samples. Since most EBUS samples are obtained from advanced lung cancers, these preclinical models may be useful for understanding the tumor biology and preclinical drug testing.

Keywords: Lung Cancer organoid, Patient derived xenograft, EBUS-TBNA

P1.03F TUMOR BIOLOGY - TRANSLATIONAL BIOLOGY - NOVEL MODELS/NOVEL TECHNOLOGIES
SUNDAY, SEPTEMBER 8, 2024 - 12:00 - 14:00

P1.03F.03 Utility of Patient-Derived Xenograft and Xenograft-Derived Organoid Models with EGFR Mutation to Study EGFR-TKI Resistance.

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Introduction: EGFR driver mutations are the most common druggable alterations in lung adenocarcinoma, however, there are still many outstanding issues including mechanisms of drug tolerance and acquired resistance to osimertinib. Preclinical models that reproduce tumor complexity are needed to understand and develop strategies for overcoming these issues. We have established patient-derived xenografts (PDXs) and their matched xenograft-derived organoids (XDOs) using both treatment naïve and post TKI-resistant lung adenocarcinomas.

Methods: Samples from surgical resection or core needle biopsy were engrafted into non-obese severe combined immune deficient gamma mice, and serially passaged for two or more times to stably establish PDX models. Stable XDO models were generated when they successfully passed for more than 10 times. Whole exome and transcriptome sequencing, and pathological assessment were performed on stable models. Models were evaluated for sensitivity towards EGFR tyrosine kinase inhibitors (TKIs), matched to their patient therapy lines. We performed drug screening on stable XDO models to identify novel therapy for overcoming TKI resistance.

Results: Twenty-two PDX models were established from patients with different EGFR mutation types and therapies, 7(32%) from treatment naïve and 15 (68%) from post EGFR-TKI. These include twelve with exon 19 deletion (55%), nine with exon 21 L858R (41%) and one with exon 19 insertion (4%). Among 15 PDX models derived from post EGFR-TKI tumors, two were after 1st line osimertinib, eight were after 2nd or later line osimertinib, five were treated only with 1G or 2G EGFR-TKIs. In nine PDXs of osimertinib resistant samples, MET amplification was identified in three models, and secondary G719, G724, G796, and C797 EGFR co-mutations were identified in one model each, concurrent with other gene alterations. Thirteen PDX models were evaluated for their sensitivity to one or more EGFR-TKIs in mice, and were categorized to sensitive, stable disease, delay resistant or resistant based on the response patterns. Of the 10 PDX models that could be compared to the treatment response in patients, eight showed consistent response to the same EGFR-TKIs. We successfully established 12 XDO models out of 18 PDXs and screening with 14 drugs has been completed. XDOs were categorized to two sensitive, seven intermediate, and three resistant models to osimertinib. High throughput screening is in progress in osimertinib resistant XDO models to identify potential drug combinations that can overcome EGFR-TKI resistance.

Conclusions: We have successfully established large cohort of EGFR mutant PDX and XDO models that show various sensitivity to EGFR-TKIs. Responses to EGFR-TKIs were generally consistent with the clinical responses in the patients. Models derived from osimertinib resistant tumor replicated the gene alteration that may represent resistant mechanisms. We are investigating the strategy to overcome the osimertinib resistance, taking advantage of the characteristics of models that reproduce the tumor complexity.

Keywords: patient-derived xenograft, xenograft-derived organoid, EGFR

P1.03G TUMOR BIOLOGY - TRANSLATIONAL BIOLOGY - SCLC
SUNDAY, SEPTEMBER 8, 2024 - 12:00 - 14:00

P1.03G.01 Lurbinectedin Synergizes with Selinexor by Inhibiting DNA Damage Repair and Enhancing Immune Cell Infiltration in Neuroendocrine Lung Tumors

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Introduction: Large cell neuroendocrine carcinomas (LCNECs) and small cell lung cancer (SCLC) tumors, are particularly aggressive lung neuroendocrine carcinomas (lung NECs) with limited clinical therapeutic options. Patients with lung NECs are treated with platinum-based chemotherapy as the first line of treatment, but they promptly develop resistance. Lurbinectedin has been approved by the FDA as a second-line treatment for SCLC due to its efficacy in metastatic chemorelapsed SCLC patients. However, there are still SCLC patients who do not respond to lurbinectedin and those who benefit from it show an ORR of 35.2% with a median duration of response of 5.3 months and a median OS of 9.3 months. Previous work from our group had shown that exportin-1 (XPO1) was a driver of chemoresistance in SCLC and its inhibition with selinexor resentitized to first- and second-line chemotherapies in naïve and chemorelapsed SCLC patients derived xenografts (PDXs), respectively. Importantly, selinexor is an FDA-approved drug for the treatment of relapsed multiple myeloma and is currently undergoing clinical testing in multiple solid tumors.

Methods: We performed synergy assays in vitro and characterized DNA damage/repair pathways by western blotting. Cell cycle and apoptosis were analyzed by flow cytometry. RNAseq was performed in cells treated in vitro. Drug efficacy was studied in SCLC and LCNEC PDXs, and in a SCLC syngeneic mouse model. Tumor microenvironment was characterized by single cell RNAseq.

Results: Selinexor strongly synergized with lurbinectedin in both SCLC and LCNEC cell lines. Mechanistically, this combination altered DNA damage and DNA repair mechanisms by inducing γH2A and decreasing CHK1 and CHK2 protein levels, suggestive of the impairment of DNA response. Additionally, selinexor reduced the expression of MLH, a key regulator of DNA mismatch repair in monotherapy and in combination with lurbinectedin. Consistent with these results, selinexor in combination with lurbinectedin also induced a significant increase in apoptotic cells and promoted cell cycle arrest. Interestingly, dual treatment activated STING and autophagy pathways via mTOR and LC3B-I/II. Pathway analysis of the genes differentially expressed in double treated cells versus untreated SCLC cells, analyzed by RNAseq, revealed very strong enrichment of DNA damage, inflammatory and IFNγ related pathways, suggesting an immunomodulatory role for this therapeutic combination. Accordingly, combination of selinexor with lurbinectedin strongly synergized not only in chemorelapsed SCLC and LCNEC PDXs, but also in a Rb1/Tp53/Rbl2 (RPR) mutant mouse model that was refractory to either lurbinectedin or selinexor alone. Transcriptomic characterization of the RPR model by scRNAseq revealed higher infiltration of immune cells along with increased antigen presentation in tumors treated with lurbinectedin and the combination. Lurbinectedin alone or in combination also enhanced the infiltration of T-cells but most notably promoted a very significant increase in monocyte and macrophage infiltration. These data suggest that lurbinectedin in combination with selinexor exerts a potent antitumor an immunomodulatory effect in lung NECs.

Conclusions: These findings suggest that selinexor combined with lurbinectedin is a promising therapeutic combination in both SCLC and LCNEC. Our study offers a strong preclinical rational for investigating this strategy in patients with lung NECs who fail chemotherapy regimens.

Keywords: Lung neuroendocrine tumors, SCLC LCNEC, Novel therapies

P1.03G TUMOR BIOLOGY - TRANSLATIONAL BIOLOGY - SCLC
SUNDAY, SEPTEMBER 8, 2024 - 12:00 - 14:00

P1.03G.02 Genotyping of RB1 Status Identifies Two Distinct Subtypes in EGFR-Mutant Lung Cancers with SCLC Transformation

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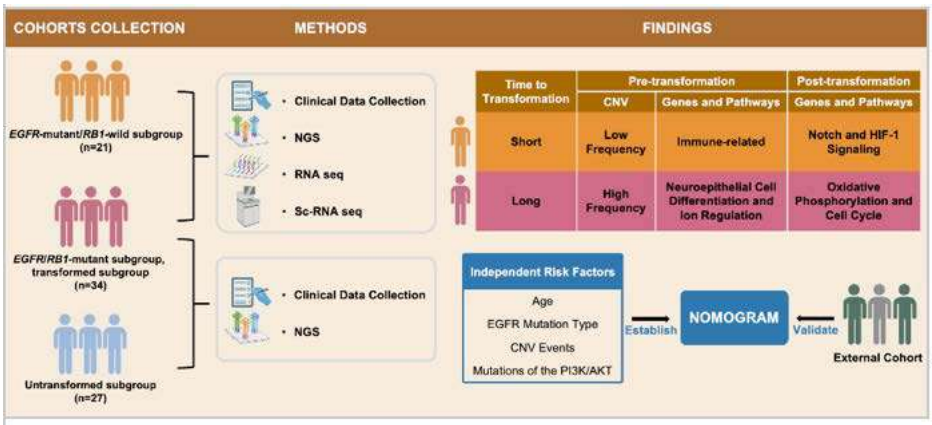
Introduction: Small cell lung cancer (SCLC) transformed from EGFR-mutant non-small cell lung cancers (NSCLC) exhibits significant clinical heterogeneity. However, whether the heterogeneity is attributable to the distinct molecular biology of transformation remains unclear. While patients with lung cancers harboring EGFR/RB1/TP53 mutations are at a high risk for SCLC transformation, precisely identifying individuals who will transform remains a formidable challenge.

Methods: From January 2017 to December 2021, we identified 63 SCLC patients transformed from EGFR-mutant NSCLC and 97 NSCLC patients with concurrent EGFR/RB1/TP53 alterations. The transformed SCLC patients were divided into two subgroups: the EGFR-mutant/RB1-wild subgroup and the EGFR/RB1-mutant subgroup. The EGFR/RB1/TP53-mutant NSCLC patients were categorized based on whether they underwent SCLC transformation. We comprehensively compared clinical profiles, genomic, and transcriptomic signatures across these subgroups.

Results: Time to transformation was significantly extended in the EGFR/RB1-mutant subgroup compared with the EGFR-mutant/RB1-wild subgroup, and RB1 alteration was an independent prognostic factor for SCLC transformation. Pre-transformation analyses revealed that neuroendocrine-related pathways were enriched in the EGFR/RB1-mutant subgroup, while immune-related pathways were upregulated in the EGFR-mutant/RB1-wild subgroup. A substantial increase in PI3K/AKT pathway mutation frequency was observed in the transformed subgroup compared with the untransformed subgroup, whereas this signaling appeared to be suppressed post-transformation in the EGFR-mutant/RB1-wild subgroup. Single-cell RNA sequencing of post-transformation samples further revealed significant differences in cellular cluster distribution and expression patterns of key transcriptional regulators between the EGFR/RB1-mutant subgroup and the EGFR-mutant/RB1-wild subgroup. Additionally, we developed and validated a nomogram model for predicting the risk of transformation in EGFR/RB1/TP53-mutant lung cancers.

Conclusions: The study introduces a novel classification of transformed SCLC from EGFR-mutant NSCLC based on RB1 status, suggesting potentially distinct therapeutic vulnerabilities of the subgroups. The established nomogram model offers a precise predictive tool for assessing the risk of SCLC transformation in patients with concurrent EGFR/RB1/TP53 alterations.

Keywords: SCLC transformation, Subtypes, RB1



P1.03G TUMOR BIOLOGY - TRANSLATIONAL BIOLOGY - SCLC
SUNDAY, SEPTEMBER 8, 2024 - 12:00 - 14:00

P1.03G.03 Role of SMARCA4, Core SWI/SNF Complex Component, in Small Cell Lung Cancer Development

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Introduction: : Small cell lung cancer (SCLC) is a lethal disease that is estimated to result in approximately 30,000 patient deaths annually in the United States. This high mortality is attributed to invariable resistance to current radiation and chemotherapies. SCLC is driven by a large number of loss of function mutations in tumor suppressor genes, including near-universal inactivation of both P53 and RB. The nature of these mutations makes it challenging to target and complicate the development of personalized therapies. Thus, understanding the molecular changes driven by these frequent alterations may help identify actionable targets for intervention strategies. Our research is focused on recurrent mutations in components of the SWI/SNF chromatin modifying complex, which regulates transcription through nucleosome sliding at enhancers and promoters of target genes. Particularly, SMARCA4, the encoding the catalytic component, harbors inactivating mutations in SCLC patient tumors. These observations led us to hypothesize that SMARCA4 acts as a tumor suppressor and its functional loss promotes SCLC development.

Methods: To determine the role of SMARCA4 in SCLC tumorigenesis, we used a combination of in vitro and in vivo models, including genetically engineered mouse models (GEMMs) of SCLC that contained floxed alleles for Smarca4. We employed two separate SCLC GEMMs: mice with an RPR2 (RbΔ/Δ; p53Δ/Δ; Rbl2Δ/Δ) or RPM background (RbΔ/Δ; p53Δ/Δ; MYCT58A). Tumor burden and histology were assessed through H&E staining. Neuroendocrine (NE) differentiation of tumor or lesion was determined using immunohistochemistry. Primary tumor cells were isolated from tumors and examined for proliferative capacity.

Results: Deletion of Smarca4 resulted in decreased tumor development in the lungs of SCLC GEMMs. Cells isolated from SMARCA4-deficient tumors formed significantly fewer colonies in soft agar that those from SMARCA4-wild type tumors. Despite being smaller in size, the SMARCA4-deficient tumors had numerous necrotic areas and lacked expression of NE markers. The SMARCA4-deficient tumor cells also had reduced expression of ASCL1, a well-known NE lineage survival factor. This phenotype of losing NE differentiation, which is typical of late-stage disease, was observed in numerous lines of mouse and human SCLC cells and coincided with loss of various SWI/SNF components. Moreover, lower SMARCA4 expression correlated with lower overall survival in patients.

Conclusions: Our study demonstrated that SMARCA4 is required for SCLC development, suggesting a previously unsuspected role of SMARCA4 in early-stage SCLC tumorigenesis. The mechanism by which SMARCA4 loss results in tumor suppression is not known, but the loss of ASCL1 in the SMARCA4-deficient tumor cells may be an important cause. The recurrent mutations in patient tumors and the spontaneous loss of SMARCA4 expression in SCLC cells suggest that its functional loss is a late-stage event. Given the role of SMARCA4 in NE differentiation, we are testing whether the loss of the chromatin modifier drives tumor heterogeneity in late stages. Integrating both in vitro and in vivo models resulted in unexpected findings that led us to raise previously unrecognized questions about the temporal role of recurrent mutations. Our findings provide novel insight into how we approach current intervention strategies.

Keywords: SCLC, Chromatin Modifiers

P1.03G TUMOR BIOLOGY - TRANSLATIONAL BIOLOGY - SCLC
SUNDAY, SEPTEMBER 8, 2024 - 12:00 - 14:00

P1.03G.04 A Model of Human Small Cell Lung Cancer Metastasis Utilizing Orthotopic Transplantation of Patient-Derived Xenografts

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Introduction: Small Cell Lung Cancer (SCLC) is a deadly and highly metastatic disease. Approximately 70% of patients are found with distant metastasis at diagnosis. Current in vivo models of SCLC include genetically-engineered mouse models and transplant models of human SCLC. The development of patient-derived xenografts (PDXs) has significantly advanced the study of human SCLC. The PDXs are genetically and functionally faithful to their original tumors including their responses to therapy. Most of PDXs are generated and grown in the subcutaneous flank of immunocompromised mice, which do not accurately reflect the microenvironment of SCLC. To date, metastasis of SCLC PDXs has yet to be reported - despite the fact that most of the PDXs are generated from biopsies of metastatic sites or circulating tumor cells. Here, we report on a model of an orthotopic transplantation of SCLC PDXs that metastasize to distant organs in a pattern consistent with human SCLC patients.

Methods: We adapted an orthotopic transplantation method that injects lung cancer cells directly into the lung parenchyma (Jacoby et al., J. Thoracic Oncol, 2010, Wilson et al., Methods Mol Biol, 2022) for our studies. After an incision of the skin was made to reveal the left chest wall of immunocompromised NSG mice, dissociated SCLC PDX cells suspended in 25% growth factor reduced Matrigel were injected through the chest wall and directly into the left lung, with visualization of the injection of tumor cells. Three PDX lines were been tested - one treatment naïve, and two drug-resistant lines - in at least 10 mice per PDX line. Lung tumor growth was followed by magnetic resonance imaging.

Results: All three PDX lines generated a primary left lung tumor and metastases to distant organs including the mediastinal lymph nodes, contralateral right lung, liver, adrenal glands, brain and ovaries. Rates of metastases ranged from 55 - 92% of mice injected with SCLC cells, depending on the PDX line. Mice bearing one particular drug-resistant SCLC PDX line consistently developed hydrocephalus and brain metastases. The primary left lung tumor and metastases expressed the neuroendocrine markers, synaptophysin and NCAM-1. Brain metastases were verified through their expression of TTF-1, a marker of SCLC and lung adenocarcinoma.

Conclusions: We have developed an orthotopic transplantation model of human SCLC that consistently generates metastases and faithfully mirrors the pattern of human SCLC, except for ovarian metastasis. To our knowledge, this is the first lung cancer PDX model that spontaneously metastasizes to distant organs and the first in vivo model of lung cancer that spontaneously metastasizes to the brain. Our model can be utilized to elucidate the biology of metastatic SCLC and as a platform to test therapeutic strategies against metastatic SCLC.

Keywords: SCLC metastasis, Orthotopic Transplantation, Mouse model

P1.06A PATHOLOGY AND BIOMARKERS - AI
SUNDAY, SEPTEMBER 8, 2024 - 12:00 - 14:00

P1.06A.01 Machine Learning Models Discriminate Independent Primaries with Metastatic in Non-Small-Cell Lung Cancer

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Introduction: The determination of multiple lung cancers (MLCs) as multiple primary lung cancers (MPLCs) or intrapulmonary metastases (IPMs) is the basic for staging and adjuvant treatment decision. Although there are large characteristic differences between MPLCs and IPMs with regards to their development and clinical outcome, the discrimination between MPLCs and IPMs remains challenging. This study sought to identify four indices based whole-exome sequencing (WES), and then employ machine learning algorithms to develop a novel approach to differentiate multiple primaries from metastasis.

Methods: We performed WES on DNA extracted from 152 lung nodules and 5 pleural metastatic nodules from 72 MLCs patients which were obtained from two cancer centers. Based on the somatic mutations, we characterized inter-tumor heterogeneity within MLCs by four indices including entropy, shared mutation number, spearman correlation and trunk mutation number. Patients with known MPLCs (n=36) and IPMs (n=10) were used as training cohort. Three distinct machine learning methods: decision trees (DT), random forests (RF), and gradient boosting decision trees (GBDT) were utilized for generation of differentiation models, which were then applied to undetermined MLCs (n=26).

Results: In training cohort, MPLCs exhibited lower shared mutation number (median, 0 vs. 22, $P < 0.0001$), spearman correlation (median, -0.52 vs. 0.65, $P < 0.0001$) and trunk mutation number (median, 0 vs. 22.5, $P < 0.0001$), and higher entropy (median, 0.67 vs. 0.39, $P < 0.0001$) than IPMs. DT model, RF model and GBDT model employed the four factors and each has a sensitivity of 1, specificity of 1 and accuracy of 1, with the area under curve (AUC) value of 1. Machine learning models discriminated the undetermined MLCs as MPLCs (n=15) and IPMs (n=11). MPLC identified by machine learning models demonstrated fewer shared mutations (median, 1 vs. 26; $P < 0.0001$), a lower Spearman correlation coefficient (median, -0.44 vs. 0.57; $P < 0.0001$), and fewer trunk mutations (median, 0 vs. 35; $P < 0.0001$), but higher entropy (median, 0.68 vs. 0.35; $P < 0.0001$), compared to IPMs. MPLCs also had significantly prolonged DFS comparing to IPMs (Hazard Ratio, 0.25; 95% CI, 0.04 to 1.18; $P = 0.04$).

Conclusions: Machine learning models based on WES enable precise differentiation between independent multiple primary lung cancers and intrapulmonary metastases in NSCLC.

Keywords: machine learning model, multiple primary lung cancers, intrapulmonary matastases

P1.06A PATHOLOGY AND BIOMARKERS - AI
SUNDAY, SEPTEMBER 8, 2024 - 12:00 - 14:00

P1.06A.02 Discovery of Morphomolecular Neighbourhoods in Lung Adenocarcinoma Using Self-supervised Learning

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Introduction: Lung adenocarcinoma (LuAd) is a morphologically heterogenous disease, and this variation in growth pattern underpins the current clinical grading system. Routinely collected diagnostic haematoxylin and eosin (H&E) sections are remarkably information-dense and contain a wealth of data we do not yet fully understand how to utilise. Are there further morphological clues that can help us risk stratify patients with LuAd in the adjuvant setting? How can we quantitatively and reproducibly encode the histological features of a patient's tumour in a scalable fashion? Can we link subsequently identified patterns to targetable biological signatures with therapeutic targets?

Methods: We trained a self-supervised artificial intelligence workflow, histomorphological phenotype learning (HPL), on 4456 whole slide images (WSIs) from 1025 patients from a single centre. Each WSI is broken down into tiles of approximately 400 microns in diameter. The model learns to recognise key morphologies on each tile with no prior annotation required. Tiles with similar appearances are grouped into histomorphological phenotype clusters (HPCs). Each cluster is a recognisable morphological entity, which can be reviewed and interpreted by a pathologist. This allows us to quantitatively express the spectrum of histological variance per patient as a compositional vector, which can be interrogated by statistical models such as logistic regression and Cox proportional hazards. Subsequent to this, we ran our trained model on 23 tissue microarray slides consisting of >2500 cores. We applied a basic immuno-oncology multiplex immunofluorescence Polaris panel to all sections, and a more detailed, high-plex immuno-oncology and fibroblast phenotyping PhenoCycler to a sub-selection.

Results: We discovered 64 HPCs. These accounted for the spectrum of appearances expected, such as classical growth patterns and normal parenchymal elements. Furthermore, we discovered HPCs defined by variant appearances, primary stromal patterns rich in fibroblasts, collagen or with varying quantities of immune cell populations. We constructed survival models using overall survival and recurrence-free survival and end-points and found that the highest risk morphologies were those characterised by morphoeic and discohesive epithelial morphology with dense eosinophilic stroma and abundant fibroblasts. In contrast, those with elastotic stroma and more abundant lymphocytes were associated with more favourable prognosis. For each cluster we obtained fractions of cell lineages and metrics of their spatial distribution to develop HPCs as integrated morpholomolecular neighbourhoods.

Conclusions: We demonstrate methodology which allows us to encode recurrent morphological features as HPCs in LuAd without prior annotations. HPCs serve as immediately hypothesis-generating entities which allow us to pursue clinical and biological questions. We observe that the tumour microenvironment is influential for prognosis and that HPC-led prognostication exceeds the clinical gold-standard. Furthermore, we characterise the cellular composition of our HPCs using spatially resolved proteomic data.

Keywords: lung adenocarcinoma, digital pathology, artificial intelligence

P1.06A PATHOLOGY AND BIOMARKERS - AI
SUNDAY, SEPTEMBER 8, 2024 - 12:00 - 14:00

P1.06A.03 Use of Biosimulation to Predict Concomitant Chemotherapy Benefit in NSCLC Patients with EGFR Mutations Being Treated with Osimertinib

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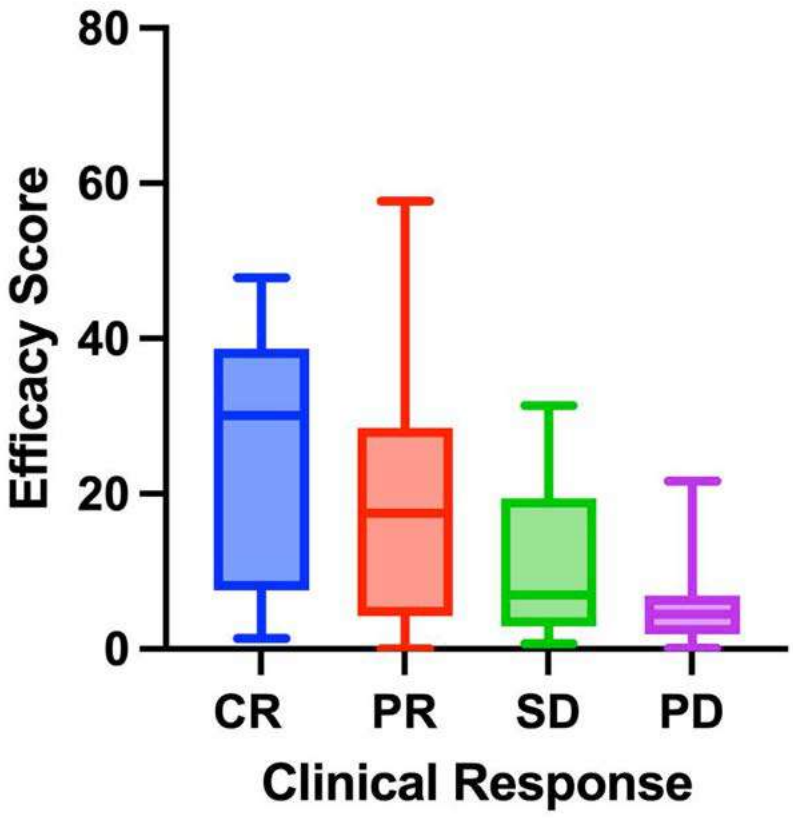
Introduction: Targeted therapy has become a standard treatment option in patients with non-small cell lung cancer (NSCLC) carrying EGFR mutations. Although targeted therapy is largely effective, it is imperfect and the addition of chemotherapy may be beneficial, although the additive value of chemotherapy may not be the same in all patients. A mechanistic computational biology model was developed by Cellworks that integrates a patient's tumor-based genomic profile as determined via next-generation sequencing, revealing signaling pathway dysregulation and patient-specific drug response. Model output was used to identify patients who may or may not respond to the addition of chemotherapy to targeted treatment for EGFR mutations.

Methods: Computational biosimulation was performed using a real-world retrospective cohort of 116 advanced NSCLC front-line patients with EGFR mutations receiving osimertinib, obtained from the nationwide (US-based) de-identified Flatiron Health-Foundation Medicine NSCLC clinico-genomic database (FH-FMI CGDB). The de-identified data originated from approximately 280 US cancer clinics (~800 sites of care). Efficacy scores (ES), based on biosimulated composite cell growth in response to disease and therapy, were generated on all patients for both osimertinib and osimertinib + carboplatin + pemetrexed. Chemotherapy-driven improvements in predicted clinical response was assessed, using the upper 95% CI of osimertinib ES as a threshold.

Results: Overall survival (OS) was associated with clinical response (median OS CR > 60, PR=34.1, SD=26.7,PD=15.7 months) as well as ORR (p = 0.017). Efficacy scores for osimertinib were significantly associated with clinical response (mean ES for CR=25.8, PR=19.3, SD=11.3, PD=6.7; ANOVA, p=0.011) and ORR (ttest, p=0.002). The biosimulated addition of chemotherapy to osimertinib led to a higher ES (median increase = 26.8) resulting in an increase in ORR from 75% to a predicted 79%, confirming previous clinical trial results. Although all patients showed response to chemotherapy addition, the benefit was variable. Patients predicted to have greater chemotherapy benefit tended to have deficiencies in DNA repair (DDR) genes such as ATM and SMARCA4, whereas patients predicted to have less benefit tended to have TP53 mutations and copy number gains in EGFR.

Conclusions: In this study, a therapy efficacy score produced through biosimulation was predictive of incremental chemotherapy benefit in a real-world cohort of patients with NSCLC being treated with osimertinib. Future studies will be performed to confirm the hypothesis that biosimulation has utility in deciding which patients receiving osimertinib may benefit from concomitant chemotherapy.

Keywords: osimertinib, chemothrerapy, biosimulation



P1.06A PATHOLOGY AND BIOMARKERS - AI
SUNDAY, SEPTEMBER 8, 2024 - 12:00 - 14:00

P1.06A.04 Deep Learning-based Whole Slide Image Analysis Predicts PD-L1 Status from H&E-Stained Histopathology Images in Lung Cancer

Y-F. Qi[1], W-Y. Huang[2], J-C. Liang[3], Z-X. Zhou[2], Z-B. Qiu[1,4], C. Zhang[1,4], Y-L. Wu[1,4], W-Z. Zhong[1,4], [1]Guangdong Lung Cancer Institute, Guangdong Provincial People's Hospital (Guangdong Academy of Medical Sciences), Southern Medical University, Guangzhou/CN ,[2]Department of Pathology, Guangdong Provincial People's Hospital (Guangdong Academy of Medical Sciences), Southern Medical University, Guangzhou/CN ,[3]School of Software, South China Normal University, Guangzhou/CN ,[4]School of Medicine, South China University of Technology, Guangzhou/CN

Introduction: Immune checkpoint inhibitors (ICIs) have greatly improved the survival of lung cancer patients. Programmed death ligand-1 (PD-L1) status is related to the ICIs benefit. Artificial assessment of PD-L1 scores may lack uniformity between different pathologists. Here, the H&E-stained images were used to predict the PD-L1 status of lung cancer using deep learning techniques.

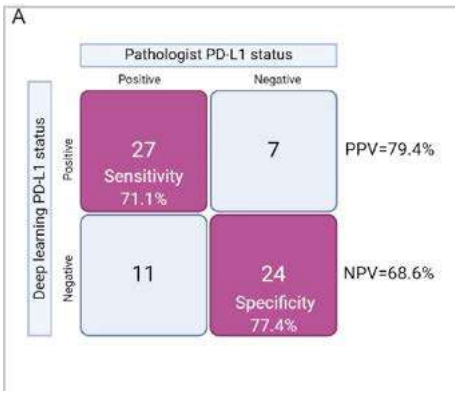
Methods: A total of 348 H&E-stained whole slide images (WSI) were tiled into 3480 non-overlapping patches of 380x380 pixels. Using the convolutional neural network (CNN) based on the ResNet50 to extract features about the PD-L1 status of each patch. Then we employ the attention mechanism to summarize the scores of 10 patches to train the PD-L1 status prediction model. The model has an output score between 0 and 1. A score ≥ 0.5 predicts a positive PD-L1 status (TPS ≥1%), and a score < 0.5 predicts a negative PD-L1 status for this HE-stained WSI (TPS <1%).

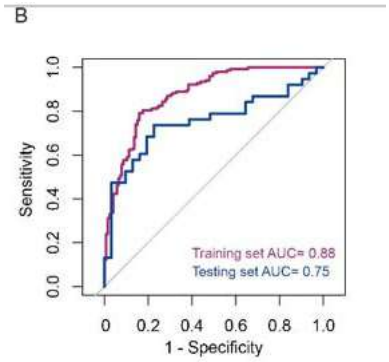
Results: The 348 patients were randomly split into the training set (N = 279) and the testing set (N = 69) (8:2). 94.83% of lung cancers were stained by the 22C3 clone. 12.93% of patients had high PD-L1 expression, and 44.83% had negative PD-L1. And the study included lung cancer at stages I to IV. Among them, stage III (48.55%) accounted for the largest proportion. Adenocarcinoma was the most common pathological type (83.48%). The AUC of the training set was 0.88 (0.84-0.92). In the testing set, the AUC was 0.75 (0.63-0.87), the sensitivity was 71.05% (27/38), and the positive predictive value (PPV) was 79.41% (27/34).

Conclusions: This study highlights the potential of utilizing deep learning techniques on H&E-stained WSIs to identify lung cancer patients who could benefit from ICIs.

Keywords: Lung Cancer, PD-L1, Whole Slide Image

	Characteristic	Overall	Training Set	Testing Set
N		348	279	69
sex (%)	female	165 (47.69)	125 (45.13)	40 (57.97)
	male	181 (52.31)	152 (54.87	29 (42.03)
age (%)	old	188 (54.34)	158 (57.04)	30 (43.48)
	young	158 (45.66)	119 (42.96)	39 (56.52)
Smoking (%)	no	220 (86.96)	174 (86.57)	46 (88.46)
	yes	33 (13.04)	27 (13.43)	6 (11.54)
Stage (%)	I	71 (20.52)	48 (17.33)	23 (33.33)
	II	95 (27.46)	80 (28.88)	15 (21.74)
	III	168 (48.55)	139 (50.18)	29 (42.03)
	IV	12 (3.47)	10 (3.61)	2 (2.90)
PD-L1_score (%)	≥ 50%	45 (12.93)	37 (13.26)	8 (11.59)
	<1%	156 (44.83)	125 (44.80)	31 (44.93)
	1-49%	147 (42.24)	117 (41.94)	30 (43.48)
PD-L1_clone (%)	22C3	330 (94.83)	264 (94.62)	66 (95.65)
	SP142	17 (4.89)	14 (5.02)	3 (4.35)
	ZR3	1 (0.29)	1 (0.36)	0 (0.00)
Pathology (%)	LUAD	288 (83.48)	231 (83.70)	57 (82.61)
	LELC	9 (2.61)	4 (1.45)	5 (7.25)
	other	12 (3.48)	9 (3.26)	3 (4.35)
	LUSC	36 (10.43)	32 (11.59)	4 (5.80)





P1.06A PATHOLOGY AND BIOMARKERS - AI
SUNDAY, SEPTEMBER 8, 2024 - 12:00 - 14:00

P1.06A.05 Assessing Pathologic Response to Neoadjuvant Chemoimmunotherapy for NSCLC: Aligning Current Protocols with Artificial Intelligence

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Introduction: Complete pathologic response (CPR) (i.e., 0% viable tumor cells) and major pathologic response (MPR) (i.e., less than or equal to 10% viable tumor cells) have emerged as indicators of survival after neoadjuvant chemotherapy and immune checkpoint inhibition (ICI) in patients with non-small cell lung carcinoma (NSCLC). Artificial intelligence (AI) algorithms have been developed to identify such a role, but their implementation in real-world practice has not been achieved yet.

Methods: Lung resection specimens from 24 patients with NSCLC who had been treated with neoadjuvant chemoimmunotherapy were prospectively included in this study. The residual primary tumor bed was entirely submitted for histopathological evaluation using a standardized grossing protocol. All hematoxylin-eosin (H&E)-stained tumor sections were reviewed by a thoracic pathologist using the IASLC response criteria and a calculator tool. In addition, the slides were scanned, and several tumor parameters (i.e., percent of tumor cells, total number of tumor cells and number of tumor cells per mm2) were extrapolated with the use of an AI algorithm (PathAI, Boston, MA). At the MPR cutoff, discrepancies between the digital and visual percentages were resolved using a second pathologist-in-the-loop approach. Treatment response in lymph nodes was excluded from assessment. A checklist-based standard operating procedure was drafted, integrating grossing with visual and digital assessments.

Results: The patients included 20 men and four women (mean age of 64.7 years and age range of 50-74 years). Fourteen tumors were squamous cell carcinomas, and the remaining 10 were adenocarcinomas. All patients received combined ICI therapy (single agent=22 or dual agent=2) and chemotherapy. The residual tumor bed ranged from 1 cm to 6.1 cm in greatest diameter (mean, 3.5 cm). A total of 313 H&E-stained slides were scored (median, 13 per patient; range, 4-29). Visual and digital MPR (less than or equal to 10% tumor cells, including CPR) were achieved in 79.2% (19/24; 95% CI: 57.8, 92.9) and 70.8% (17/24; 95% CI: 48.9, 87.4) of patients, respectively. On the basis of this cutoff, there was at least moderate agreement between the visual and digital assessments [kappa (95% CI): 0.78 (0.49, 1)]. In two discordant cases that were close to the 10% threshold, the digital percentage of tumor cells was greater than the visual result for both readouts. Interestingly, there was a significant association between the visual MPR and the AI-assisted estimation of both the total number of tumor cells and the number of tumor cells per mm2 (p=0.00012 and p=0.00057, respectively). Despite the short follow-up [median (95% CI): 14 months (12.6, 18.3)], there was a nonsignificant trend toward better outcomes in patients with visual or digital pathologic response.

Conclusions: It is feasible to apply AI algorithms to assist pathologists in predicting the effect of neoadjuvant chemoimmunotherapy in patients with NSCLC. Checklists were particularly helpful for resolving discrepancies. There was at least moderate agreement between the AI algorithm and the visual assessment of the pathologic response. The AI approach has the potential to refine the prognosis of NSCLC patients who do not achieve CPR or MPR after neoadjuvant therapy.

Keywords: neoadjuvant therapy, artificial intelligence, pathologic response

P1.06A PATHOLOGY AND BIOMARKERS - AI
SUNDAY, SEPTEMBER 8, 2024 - 12:00 - 14:00

P1.06A.06 Post-COVID-19 Tumor Microenvironment Features and AI-Based Evaluation in KRAS-Mutant NSCLC

Z. Huang[1,2], L. Li[1], S. Wang[3], Z. Peng[4], Y. Jia[4], J. Zhang[5], Q. He[5], S. Zeng[5,6,7], B. Yang[5], Y. He[5], T. Guan[5], Y. Li[1], [1]Fudan University Shanghai Cancer Center, Shanghai/CN ,[2]Shanghai Medical College of Fudan University, Shanghai/CN ,[3]Fudan University, Shanghai/CN ,[4]Alpha X Biotech (Beijing) Co., Beijing/CN ,[5]Shenzhen International Graduate School, Tsinghua University, Shenzhen/CN ,[6]Greater Bay Area National Center of Technology Innovation, Guangzhou/CN ,[7]Shenzhen Shengqiang Technology Co, Ltd., Shenzhen/CN

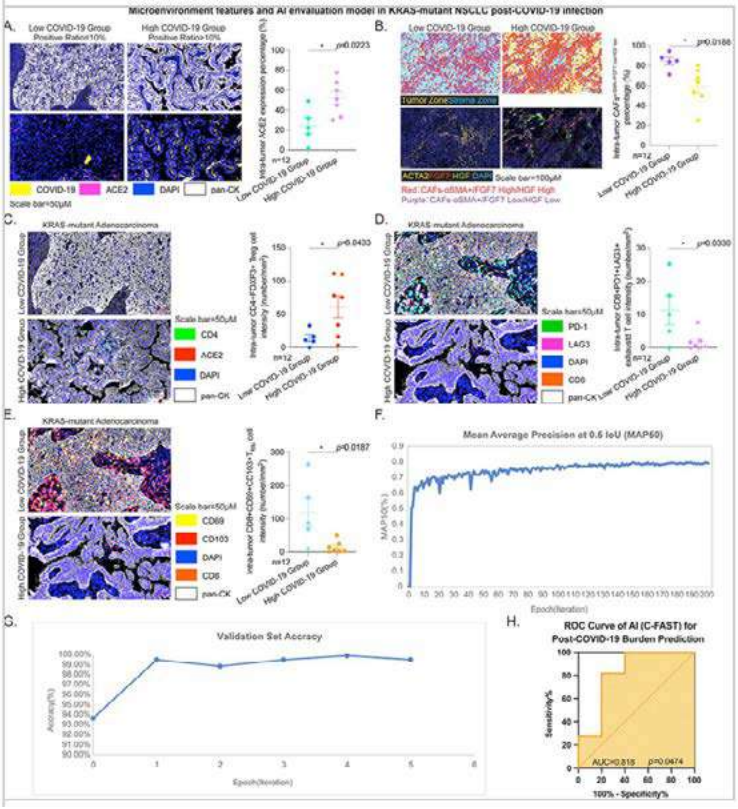
Introduction: Coronavirus Disease 2019 (COVID-19) is an acute respiratory syndrome, spreading all over the world and threatening human healthy. Its impact of tumor microenvironment (TME) in non-small cell lung cancer (NSCLC) is not well illustrated. KRAS mutation accounts for about 12% of NSCLC in China, which is reported highly related to smoking. Smoking is believed to be a potential risk factor of COVID-19 by upregulating its' receptor angiotensin-converting enzyme-2 receptor (ACE2). However, little is known about the post-COVID-19 TME in smoking-related cancer, especially KRAS-mutate NSCLC.

Methods: We collect 75 KRAS-mutant cases between 2023/3/1 to 2023/6/30 for COVID-19 infection evaluation. Then twelve infected adenocarcinoma cases are enrolled for microenvironment analysis by RNA in situ hybridization (RNA-ISH) and multiplex immunofluorescence (mIHC) staining, as they provide negative evidence for more than 12 weeks before surgery. Finally, 75 cases' TME features are evaluated to predict COVID-19 burden by a new optimized YOLOv8 AI model. The evaluation model is called "C-FAST" short for COVID-19 burden fast prediction.

Results: First, around 86.67% (65/75) KRAS-mutant cases suffer from COVID-19 infection before operation. Most are adenocarcinoma (81.33%, 61/75) rather than other subtypes (18.67%, 14/75). Among the 65 cases who have clear infection history, 12 can provide negative evidence for more than 12 weeks before operation. Further, for the microenvironment analysis, the receptor ACE2 dramatically express a lot in high COVID-19 burden group (Figure A). A reported CAFs subtype (α-SMA+/FGF7low/HGFlow), which can recruit T cell infiltration, is remarkably low in high COVID-19 group tumor area (Figure B). The inflammatory microenvironment is characterized by more TregCD4+FOXP3+ cells (Figure C), less exhausted TCD8+PD-1+LAG3+ cells (Figure D) and less TRMCD8+CD69+CD103+cells in tumor zone of high COVID-19 cases compared to low ones (Figure E). Finally, an optimized AI evaluation model is created based on microenvironment features. The model achieves an mAP50 accuracy of 80% in TME detection and around 99% accuracy rate in TME classification (Figure F-G). The prediction score model (C-FAST) shows a moderate area under the curve (AUC) score (AUC=0.818,p=0.474, Figure H).

Conclusions: Overall, COVID-19 recovered KRAS-mutant patients with high virus burden recruit an immunosuppressive microenvironment, indicating a poor response from immunotherapy. The AI based evaluation could help predict virus burden status depending on detail TME features. To our best knowledge, this is the first report to describe the TME features post-COVID-19 pandemic and propose a novel AI evaluation model on virus burden prediction in KRAS-mutant NSCLC.

Keywords: COVID-19, Immunosuppression microenvironment, Novel AI evaluation model



P1.06A PATHOLOGY AND BIOMARKERS - AI
SUNDAY, SEPTEMBER 8, 2024 - 12:00 - 14:00

P1.06A.07 Prognostic Gene Expression Profiling in Lung Adenocarcinoma Using Deep Learning Applied to Whole-Slide Images

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Introduction: Recent advances in computational pathology have shown potential in predicting biomarkers from haematoxylin and eosin (H&E) whole-slide images (WSI). However, predicting outcome directly from WSIs remains a substantial challenge. In this study, we aimed to investigate how gene expression, predicted from WSIs using deep learning, could be used to evaluate overall survival (OS) in patients with lung adenocarcinoma (LUAD).

Methods: Differentially expressed genes (DEGs) between tumour and normal samples were identified from The Cancer Genome Atlas (TCGA)-LUAD cohort. Cox regression analysis was performed on DEGs to identify genes prognostic of OS. Attention-based multiple instance learning (AMIL) models were trained to predict the expression of identified prognostic genes from WSIs using the TCGA-LUAD dataset using site-stratified cross-validation. Gene expression-based prognostic models were compared with survival-based prognostic models in which OS was evaluated directly from the WSIs. Models were externally validated in the Clinical Proteomic Tumour Analysis Consortium (CPTAC)-LUAD dataset. The prognostic value of predicted gene expression was then compared to the true gene expression measurements. Histological correlates of identified genes were evaluated using WSI heatmaps.

Results: The expression of 239 prognostic genes could be predicted in TCGA-LUAD with cross-validated Pearson's R > 0.4. Predicted gene expression demonstrated prognostic performance, attaining a cross-validated concordance index of up to 0.615 in TCGA-LUAD through Cox regression. For comparison, the survival-based AMIL model achieved a cross-validated concordance index of 0.562. In total, 36 genes had predicted expression in the external validation cohort that was prognostic of OS. Predicted high expression regions of a number of upregulated genes in patients with low OS exhibited tumour necrosis.

Conclusions: Gene expression predicted from WSIs is an effective method of evaluating OS in patients with LUAD. We show that using predicted gene expression from WSIs to evaluate OS in LUAD patients performed better than predicting OS directly from the WSIs. AMIL models trained to predict prognostic gene expression in LUAD tended to learn tumour necrosis as an indicator of poor OS. This explainable predictive capability could be particularly useful in settings where comprehensive molecular profiling of LUAD is not feasible on a clinically relevant timescale.

Keywords: Computational Pathology, Overall Survival, Deep Learning

P1.06B PATHOLOGY AND BIOMARKERS - BIOMARKER
SUNDAY, SEPTEMBER 8, 2024 - 12:00 - 14:00

P1.06B.01 NSCLC in Patients with CTD-ILD: Apobec-Related Mutagenesis, Frequent TP53 Mutations and Paucity of Targetable Alterations

I. Odintsov[1], M.M. Hammer[1], M.M. Awad[2], P.F. Dellaripa[1], L.M. Sholl[1], [1]Brigham and Women's Hospital, Boston/MA/USA ,[2]Dana-Farber Cancer Institute, Boston/MA/USA

Introduction: Patients with connective tissue diseases (CTD) have a higher risk of malignancies including lung cancer. Connective tissue disease-associated interstitial lung disease (CTD-ILD) is a proposed risk factor of lung cancer in this population, but the pathogenesis of lung cancer in CTD-ILD is poorly understood. Here, we investigate the cancer genomic changes in patients with CTD-ILD.

Methods: An institutional database of 5,181 non-small cell lung cancer (NSCLC) patients sequenced by our next generation tumor sequencing panel (OncoPanel) was reviewed to identify patients with clinical history of CTD or interstitial pneumonia with autoimmune features (IPAF). Additionally, an institutional pathology database was searched for cases of NSCLC with CTD-ILD. Candidate cases were reviewed for radiologic and/or pathologic pulmonary manifestations of CTD-ILD or IPAF. The final cohort included 20 patients with available genomic data (Figure 1A). Smoking history was categorized into never/light (< 20 pack years [PY], n=9) and moderate/heavy (≥ 20 PY, n=11).

Results: The findings are summarized the Figure 1B-D. Patients with never/light smoking history displayed universal alterations in TP53, that were significantly more frequent when compared to the general LUAD population (9/9, 100% vs 1861/3799, 49%, p = 0.0022). No conventional targetable alterations in EGFR, KRAS, ALK, ROS1, RET, MET, ERBB2, BRAF, NTRK1/2/3 or NRG1 were observed (Figure 1C). Pooled single base substitution (SBS) mutational signature analysis demonstrated predominance of COSMIC SBS 2 and 13 signatures, attributed to the APOBEC family of cytidine deaminases (Figure 1D). Patients with CTD-ILD and moderate/heavy smoking, on the other hand, had mitogenic drivers in 7/11 cases, including KRAS (3/11), BRAF (2/11), MAP2K1 (1/11) and EGFR (1/11) (Figure 1C). Only 5/11 of these patients had TP53 alterations, an incidence that was comparable to the general LUAD population (5/11 vs 1861/3799, p = 0.8). Mutational signature analysis demonstrated both smoking-related COSMIC SBS 4 signature, and APOBEC-related COSMIC SBS 2 and 13 signatures (Figure 1D).

Conclusions: Lung cancer in patients with CTD-ILD and history of never or light smoking demonstrates unique genomic features with frequent TP53 mutations and absence of targetable alterations. The predominance of the APOBEC mutational signature suggests the role of inflammation in the pathogenesis of LUAD in patients with CTD-ILD. Given the contraindication of immunotherapy and a paucity of targetable alterations in patients with CTD-ILD, this population has limited systemic therapeutic options. Further research is necessary to develop optimal preventive and therapeutic strategies for lung cancer in patients with CTD.

Keywords: Non-small cell lung cancer, Biomarkers, Interstitial lung disease

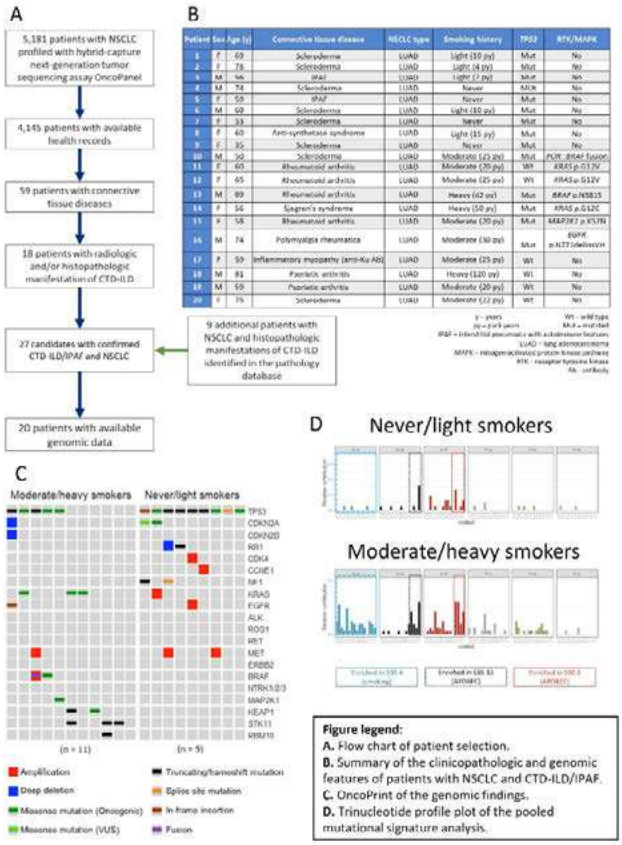


Figure legend:
A. Flow chart of patient selection.
B. Summary of the clinicopathologic and genomic features of patients with NSCLC and CTD-ILD/IPAF.
C. OncoPrint of the genomic findings.
D. Trinucleotide profile plot of the pooled mutational signature analysis.

P1.06B PATHOLOGY AND BIOMARKERS - BIOMARKER
SUNDAY, SEPTEMBER 8, 2024 - 12:00 - 14:00

P1.06B.02 A Comprehensive Analysis of FGF/FGFR Signaling Alteration in NSCLC

Z. Huang[1,2], L. Li[1,2], Z. Peng[3], Y. Jia[3], Y. Li[1,2], [1]Fudan University Shanghai Cancer Center, Shanghai/CN ,[2]Shanghai Medical College of Fudan University, Shanghai/CN ,[3]Alpha X Biotech (Beijing) Co., Beijing/CN

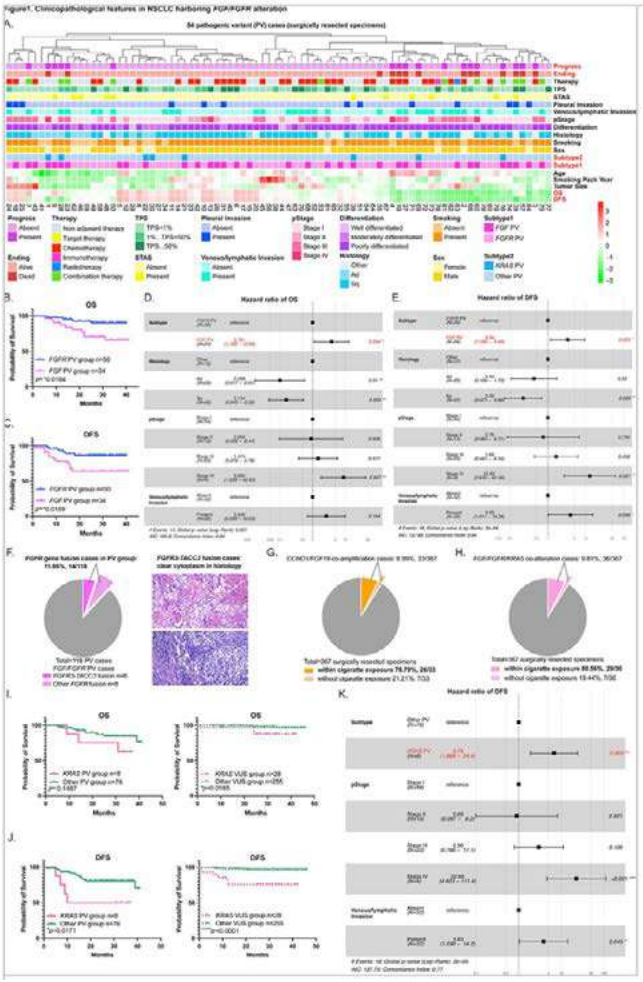
Introduction: Fibroblast Growth Factor (FGF) ligands and their receptor alteration have been identified as the potent target in non-small cell lung cancer (NSCLC). However, the clinicopathological and microenvironmental characteristics of FGF/FGFR in NSCLC remain poorly understood.

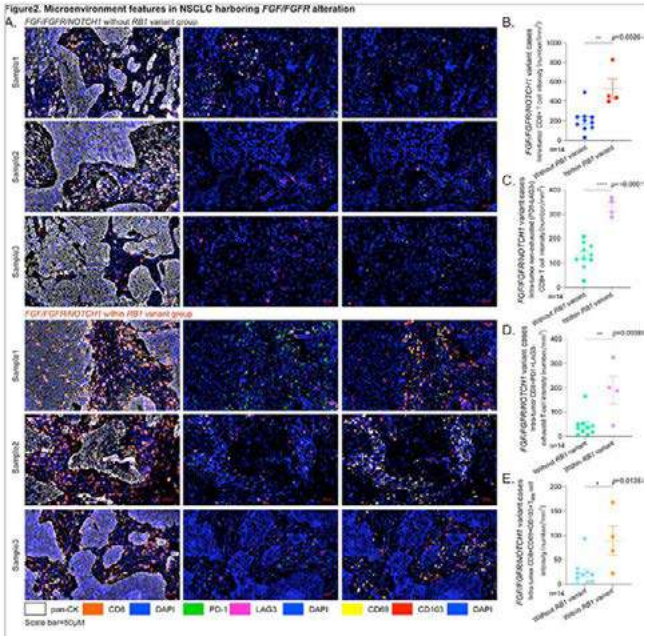
Methods: We investigate 4656 NSCLC cases examined by next-generation sequencing and summarize 478 cases harboring FGF/FGFR alteration, analyzing the clinicopathological features. Fourteen cases carrying NOTCH1 co-mutation are further stained by multiplex immunofluorescence to describe the microenvironment.

Results: First, around 10.27% (478/4656) NSCLC harbor FGF/FGFR alteration. Squamous cell carcinoma (99/236, 41.95%) is much more than adenocarcinoma (331/3978, 8.32%). In 118 cases harboring pathogenic variant (PV), the most frequent variant is FGF/FGFR copy number increase (98/118, 83.05%), and the second is FGFR gene fusion (14/118, 11.86%). Surprisingly, CCND1 always co-amplifies with FGF19 (100.00%). PV group is more invasive and predicts poor survival. Furthermore, FGF PV is proved as an independent risk factor for poor prognosis (overall survival, OS: HR=3.781, p<0.05, disease-free survival, DFS: HR=3.34, p<0.05, Figure 1A-E). One-third of FGFR3-TACC3 fusion cases show clear cytoplasm in histology (Figure 1F). Either CCND1/FGF19 co-amplification or KRAS co-mutation is closely related to cigarette exposure (Figure 1G-H), and KRAS co-mutation acts as an independent factor of poor DFS (HR=6.79, p<0.05, Figure 1A, I-K). Finally, the FGF/FGFR1/NOTCH1 within RB1 variant group has a remarkably high ratio of inner-tumor CD8+ T cell infiltration (Figure 2A, B), non-exhausted T cells (Figure 2A, C), exhausted TCD8+PD-1+LAG3- cells (Figure 2A, D) and TRMCD8+CD69+CD103+cells (Figure 2A, E).

Conclusions: The FGF/FGFR alteration mainly arises in squamous cell carcinoma. Both FGF PV and KRAS co-mutation are the independent factors for poor prognosis. To our best knowledge, this is the first report to describe an inflamed microenvironment recruited by the NOTCH1/RB1 co-mutation, which indicates potential benefit from immunotherapy. Overall, our study provides a comprehensive about FGF/FGFR alteration in NSCLC.

Keywords: FGF/FGFR, NSCLC prognosis, microenvironmental characteristics





P1.06B PATHOLOGY AND BIOMARKERS - BIOMARKER
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P1.06B.03 Genetic Profiles and Evolutionary Trajectory of Early-Stage Lung Adenocarcinoma (AAH,AIS,MIA and IA) revealed by Multiplex Sequencing

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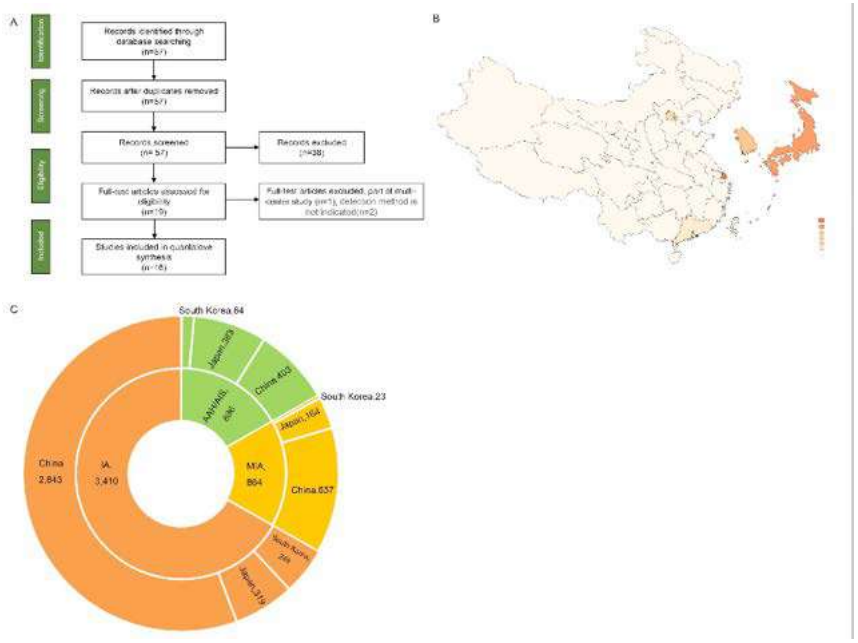
Introduction: The advent of early lung cancer screening has facilitated the detection of lung cancer at its nascent stages. The transition from AAH to IA involves a series of pivotal events, and currently needs more substantial data from large sample populations.

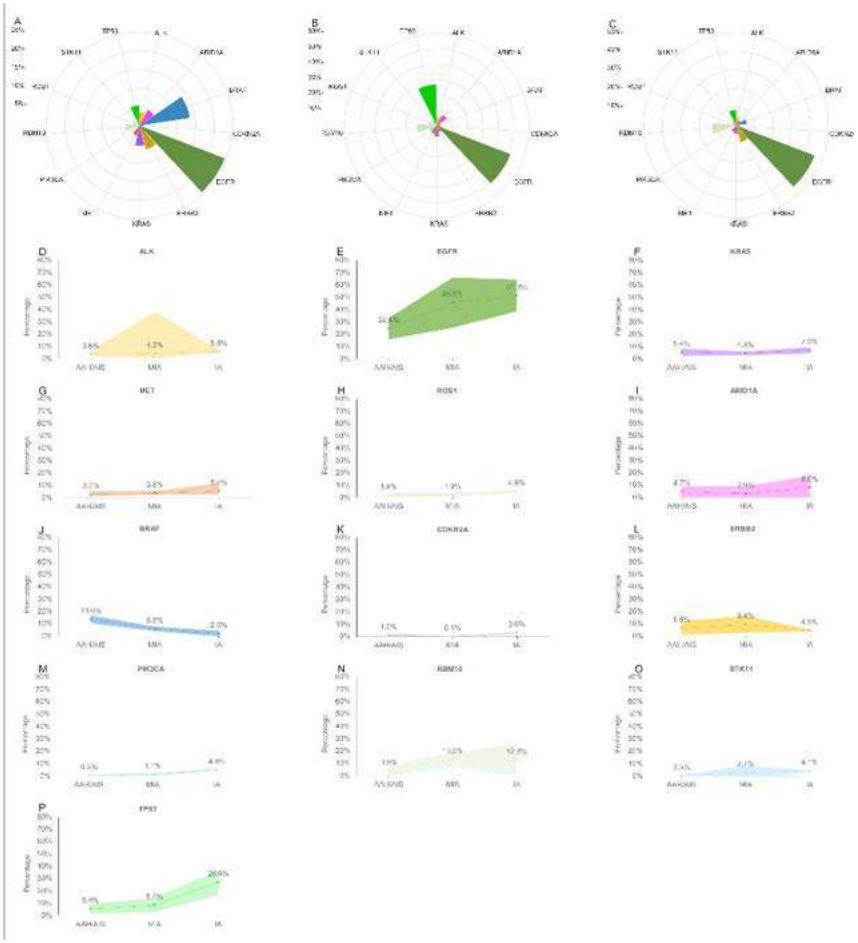
Methods: Adhering to the PRISMA guidelines, we conducted a systematic search up to August 1, 2023. PubMed and Web of Science databases were utilized for literature retrieval. Subsequently, we employed OpenMeta-analyst and direct superposition analyses to scrutinize the gene mutation spectrum.

Results: Our study incorporated 5315 samples from 16 articles. We observed a gradual increase in mutation rates of EGFR and TP53 throughout the evolution of lung adenocarcinoma (LUAD): AAH/AIS (24.4%, 5.4%), MIA (45.5%, 8.4%), and IA (51.3%, 26.9%). The mutation ratio of EGFR demonstrated a consistent change, whether assessed through NGS or PCR (NGS: AAH/AIS (20.9%), MIA (35.2%), and IA (63.0%); PCR: AAH/AIS (22.1%), MIA (44.6%), and IA (44.6%)). Conversely, the mutation rate of BRAF exhibited a progressive decrease (AAH/AIS (13.6%), MIA (5.8%), and IA (2.0%)). Additionally, subgroup analysis of samples from China revealed a consistent mutation trend, with EGFR and TP53 mutation rates gradually increasing (AAH/AIS (22.9%, 4.7%), MIA (41.0%, 4.3%), and IA (55.5%, 31.3%)), while BRAF mutation rates decreased (AAH/AIS (13.4%), MIA (5.8%), and IA (1.8%)). Our research shows the escalation of sensitive EGFR mutations, including EGFR-L858R and EGFR-19Del, during the progression of LUAD (AAH/AIS (11.4%, 13.9%), MIA (28.0%, 26.4%), and IA (25.2%, 27.7%)).

Conclusions: This study showed that gene mutations present different adaptations during the progression of LUAD. The low detection rates of EGFR and TP53 mutations among AAH/AIS and increasing trend along progression indicate some of them are not initiation events but serve as a driver for invasiveness. However, BRAF mutations represented an inverse effect, and other mutations showed no difference between different stages.

Keywords: gene mutation, early-stage lung adenocarcinoma, Genetic profiles





P1.06B PATHOLOGY AND BIOMARKERS - BIOMARKER
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P1.06B.04 Exploring Circulating Tumor Antigens as a Faster and Lower Cost Alternative to Circulating Tumor DNA in IMpower150

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Introduction: Molecular assays for the detection of circulating tumor DNA (ctDNA) or circulating tumor antigens (ctA) can enable the development of accelerated endpoints and provide higher resolution for patient risk stratification compared to standard radiographic imaging. Both ctDNA and ctA testing were deployed in IMpower150, a randomized phase 3 study comparing chemotherapy against combinations of atezolizumab ± bevacizumab + chemotherapy. Previous work showed that a machine learning (ML) model of ctDNA features1 or an optimized cutoff analysis using two ctA2 is able to effectively stratify stable disease (SD) patients in IMpower150 for survival risk. Given the significantly reduced testing time and sample testing cost for ctA, we applied a similar ML model for ctA and asked whether ctA could provide similar or improved predictive ability as ctDNA.

Methods: ctDNA testing was performed as previously described1. ctA testing was performed using electrochemiluminescence immunoassays (ECLIA) for CA 125, CA 15-3, CA19-9, CEA, CYFRA 21-1, HE4, NSE, SCC and ProGRP. Data imputation, normalization and training and testing of the ML model (EM) were done as previously described (1).

Results: Similar to ctDNA analysis using EM, we found that multiple ctA features at C3D1 best predicted risk for OS. Model performance using ctDNA and ctA were found to be similar (C-index of 0.66 and 0.72 for the training cohort, respectively, and 0.67 and 0.68 in the test cohort). OS HR between ctDNA and ctA models were also similar (OS HR: 3.3 [95% CI: 2.2-4.9] and OS HR: 2.82 [95% CI: 1.96-4.06], respectively). The EM, like the optimized cutoff model (2), showed that CYFRA 21-1 and CA 125 levels at C3D1 were among the top features for predicting OS.

Conclusions: ctA testing had similar agreement to ctDNA testing in a ML model for overall survival risk in patients with SD in IMpower150. ctA offers significant advantages over ctDNA as it can be performed for a fraction of the cost and is more accessible in standard clinical settings. Further comparison of the predictive performance of ctA against ctDNA is needed in additional studies and will support the development of this assay for risk assessment, for use as an early endpoint for treatment response, and for informing treatment decisions.

Keywords: NSCLC, circulating tumor antigen biomarker, overall survival surrogate

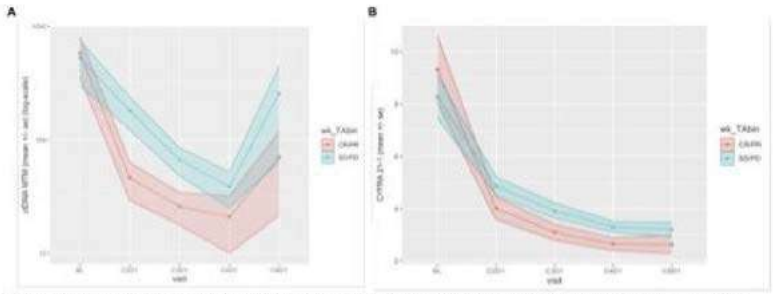

Figure 1. ctDNA and ctA levels over time can stratify patients by objective response. **A**, Mean ctDNA or **B,** mean CYFRA 21-1 levels are shown for responders (CR/PR) or non-responders (SD/PD) over time. BL: baseline.

P1.06B PATHOLOGY AND BIOMARKERS - BIOMARKER
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P1.06B.05 Utility of Molecular Tumor Board Driven by Precision Medicine Service and Cloud-Based Datamart for Therapy and Trial Matching

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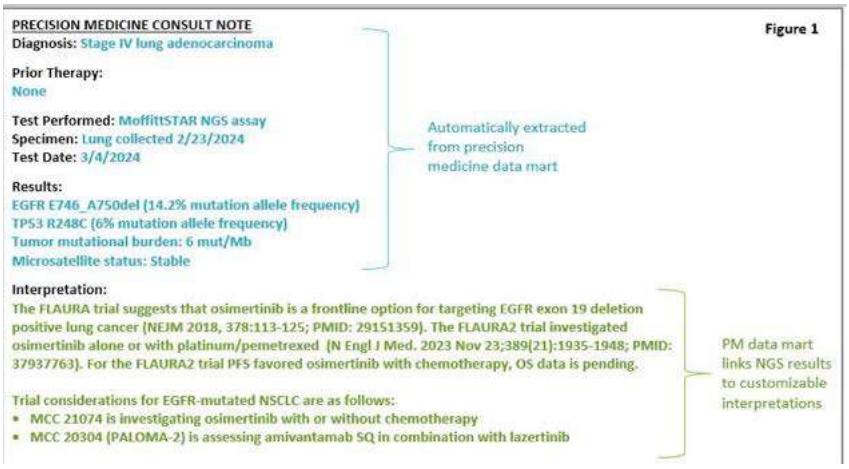
Introduction: Real-world implementation of precision oncology has several challenges including interpretation and clinical application of complex molecular profiling results. These challenges can result in patients not fully benefiting from precision oncology and may potentiate disparities. To mitigate clinical practice gaps, we established a multidisciplinary thoracic molecular tumor board (MTB) driven by a precision medicine (PM) clinical service and cloud-based data mart that provides real-time interpretation of next generation sequencing (NGS) results to facilitate trial matching and targeted therapy. We evaluated the clinical impact of this novel molecular tumor board approach on patient care.

Methods: A secure PM data mart was created by developing pipelines to ingest discrete genomic data and patient information stored in a cloud-based data warehouse. Within 24 hours of receiving NGS results, genomic and patient information are pulled into the PM data mart that links the information to customizable interpretations that are entered into the electronic health record (EHR) by PM clinical service (Figure 1). The PM data mart also generates a patient list to guide discussion at the weekly thoracic MTB. Recommendations made by the MTB are documented in the EHR and shared with primary oncologist and trial coordinators. We evaluated our novel clinical workflows from July 1, 2023 - December 31, 2023. Patient demographics and treatment history were extracted from either the PM data mart or EHR.

Results: A total of 364 cases (323 unique patients) had a precision medicine consult performed and discussed at the weekly thoracic MTB. Among all cases, 73% had Stage IV disease and 75% adenocarcinoma histology. EGFR mutations (17.9% of cases) and KRASG12C (8.5% of cases) were the most commonly observed targetable alterations. Targeted therapy opportunities were identified for 112 patients (34.7%), with 18.9% being frontline and 15.8% being later line options. For frontline therapy, 91.8% of patients received the matched targeted therapy. Two patients (3.3%) were lost to follow-up, 2 (3.3%) had not yet received systemic therapy, and 1 (1.6%, METexon 14 positive) received chemoimmunotherapy. Clinical trial opportunities were identified for 188 patients (58.2%). During the evaluation period, 60 patients were enrolled onto an interventional clinical trial with 45 (75%) discussed at the weekly thoracic MTB contributing to trial enrollment.

Conclusions: A PM service with subsequent expert review by a thoracic MTB is feasible, allows for real-time review of NGS results, and facilitates targeted therapy and trial matching. The cloud-based PM data mart enabled scalability for large patient volume.

Keywords: precision medicine, precision oncology, next generation sequencing



P1.06B PATHOLOGY AND BIOMARKERS - BIOMARKER
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P1.06B.06 Analysis of Antibody-Drug Conjugate Target Expression Across Genomic Subsets of Non-Small Cell Lung Cancer

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Introduction: Antibody-drug conjugates (ADCs) represent an expanding therapeutic modality in non-small cell lung cancer (NSCLC). While the ADC efficacy has variably correlated with corresponding target expression in tumors, limited knowledge exists regarding the landscape of ADC target expression across genomic subsets of NSCLC and whether the expression level differs pre- vs post-targeted therapy.

Methods: Patients with advanced NSCLC harboring EGFR mutations, ALK, ROS1, or RET fusions, or KRAS mutations were retrospectively identified. Pre- or post-targeted therapy formalin-fixed, paraffin-embedded (FFPE) archival tumor samples were retrieved. Expression of MET, HER2, TROP2, CEACAM5, and HER3 was assessed by immunohistochemistry (IHC) using commercial antibodies. The percentages of tumor cells with membrane +/- cytoplasmic staining by IHC at differential intensities (0=absent, 1=weak, 2=moderate, 3=strong) were determined to calculate H-scores (weighted summed scores). Comparisons were made using the Wilcoxon rank-sum, Friedman, and signed-rank tests.

Results: We assessed 106 tumor samples (EGFR, n=29; ALK, n=33; ROS1, n=21; RET, n=9; KRAS, n=14) from 78 patients with NSCLC [median age, 59 (range 22-84); female, 67%; nonsmoking history, 59%]. Among 50 pre-treatment samples, MET, HER2, TROP2, CEACAM5, and HER3 expression per oncogene driver was as summarized in Table; there were no significant differences among genotypes as compared in Table. Across the entire NSCLC cohort, MET, CEACAM5, TROP2 were more heavily expressed compared to HER2 and HER3 (p<0.001). We evaluated the ADC target expression in 9 paired pre- and post-osimertinib samples with EGFR mutations (exon 19 deletion, L858R, G719S/S768I, L861Q), finding no significant difference in the H-scores for MET [250 (100-291) vs 250 (0-300)], HER2 [0 (0-190) vs 3 (0-75)], TROP2 [130 (90-215) vs 115 (30-200)], CEACAM5 [40 (0-240) vs 60 (0-280)], and HER3 [0 (0-10) vs 0 (0-0)]. Similarly, among 15 paired pre- and post-TKI tumors with ALK/ROS1/RET fusions, there was no significant difference in the H-scores for MET [220 (160-300) vs 250 (56-295)], TROP2 [185 (120-265) vs 190 (10-300)], CEACAM5 [50 (0-295) vs 31 (0-290)], and HER3 [0 (0-110) vs 0 (0-131)] whereas HER2 expression decreased post-TKI [90 (0-160) vs 5 (0-130); p=0.010].

Conclusions: Distinct ADC targets demonstrated variable levels of expression across genomic subsets of NSCLC, with MET, TROP2, and CEACAM5 more heavily expressed than HER2 and HER3. In small cohorts of EGFR- and fusion-driven NSCLC, majority of the expression did not differ significantly pre- vs post-TKI. Further systematic assessment of differential expression of ADC targets is warranted and may inform the clinical development of ADCs in NSCLC.

Keywords: Antibody-drug conjugate, Protein expression, Resistance

H-score, Median (range)	MET	HER2	TROP2	CEACAM5	HER3
ALL (n=50)	220 (3-300)	15 (0-220)	152.5 (2-265)	137.5 (0-300)	0 (0-285)
EGFR (n=16)	237.5 (100-295)	8.5 (0-220)	125 (5-230)	75 (0-295)	0 (0-285)
ALK (n=10)	225 (160-300)	110 (15-160)	180 (137-220)	108 (0-295)	0 (0-8)
ROS1 (n=9)	195 (59-290)	0 (0-170)	120 (15-210)	115 (0-210)	0 (0-0)
RET (n=4)	242 (200-270)	52.5 (0-90)	90.5 (2-265)	126.5 (2-290)	3 (0-110)
KRAS (n=11)	190 (2-300)	6 (0-150)	182.5 (30-205)	200 (0-300)	0 (0-10)
Comparisons by oncogene driver					
EGFR vs KRAS	p=0.183	p=0.421	p=0.635	p=0.288	p=0.305
EGFR vs fusion	p=0.476	p=0.962	p=0.650	p=0.950	p=0.361
Fusion vs KRAS	p=0.265	p=0.223	p=0.540	p=0.216	p=0.608
EGFR+fusion vs KRAS	p=0.181	p=0.241	p=0.418	p=0.191	p=0.393

P1.06B PATHOLOGY AND BIOMARKERS - BIOMARKER
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P1.06B.07 Association of NEDD9 Expression and Survival of Patients with KRAS Mutant and STK11 Mutant Non-Small Cell Lung Cancer (KRASMUT/STK11MUT-NSCLC)

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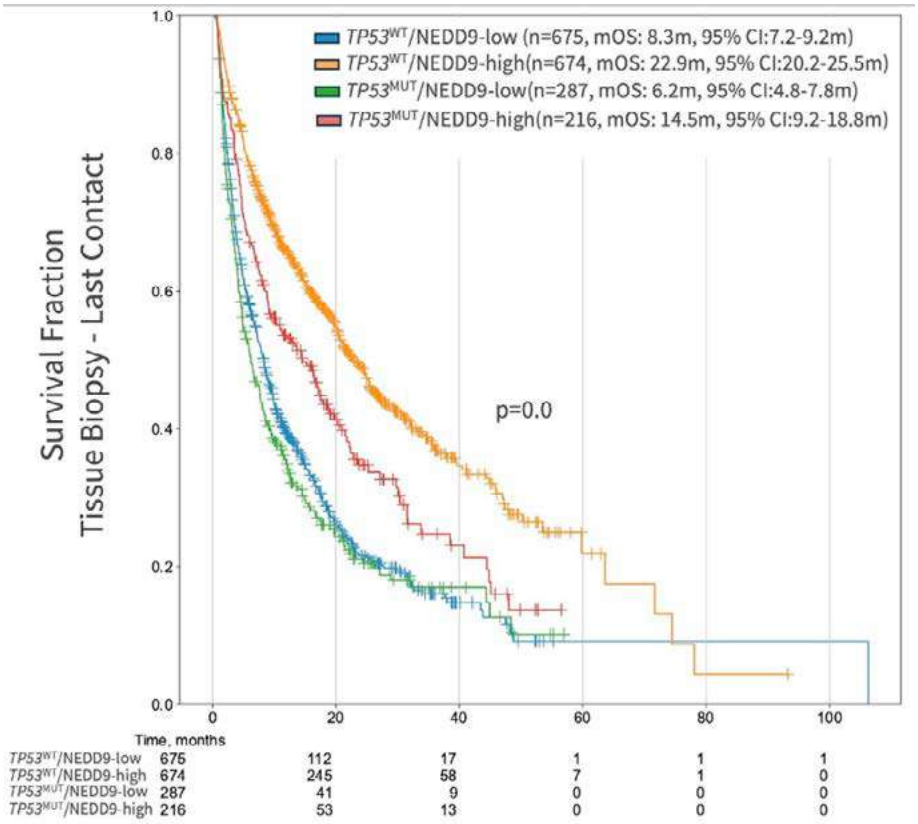
Introduction: STK11MUT are associated with an aggressive phenotype and worse prognosis in NSCLC. Co-mutations with TP53/KRAS may further influence survival in STK11MUT tumors. There is hence a need to contextualize STK11MUT while identifying biomarkers associated with survival in NSCLC. Pre-clinical studies investigating the role of NEDD9, a SRC activator and intracellular scaffolding protein, in lung tumorigenesis, suggest a relationship with LKB1-AMPK-dependent autophagy in KRASMUT NSCLC. The purpose of this study was to investigate the association between NEDD9 expression and survival in a large real-world cohort of KRASMUT/STK11MUT-NSCLC (KS-NSCLC) with and without TP53 mutations.

Methods: 1852 (KS-NSCLC) specimens with DNA (592-panel/whole exome) and RNA (whole transcriptome) sequencing were profiled at Caris Life Sciences (Phoenix, AZ). Tumors were stratified into NEDD9-high/ low based on the median RNA expression in KRASMUT-NSCLC. Real-world overall survival (OS) was obtained from insurance claims and calculated from tissue biopsy to last contact. Hazard ratio (HR) was calculated using the Cox proportional hazards model. Statistical significance was determined using Chi-square, Fisher's Exact, Mann-Whitney U & log-rank tests and corrected for multiple comparisons where applicable (q<0.05).

Results: High-NEDD9 expression (vs low-NEDD9) was associated with improved OS in patients with both TP53WT and TP53MUT-KS-NSCLC. Interestingly, among high-NEDD9 tumors, mOS of TP53WT (22.9m) was superior to TP53MUT (14.5m), while mOS for low-NEDD9 tumors was similar independent of TP53MUT status (TP53WT:8.3m, TP53MUT:6.2m; Figure). Genomic analysis of these tumors revealed increased prevalence of KEAP1 and SMARCA4 mutations in low-NEDD9 tumors (vs high-NEDD9). Multivariate analysis revealed that NEDD9 was associated with favorable prognosis independent of KEAP1 and SMARCA4 mutations (TP53WT:HR=0.53, p<0.001; TP53MUT:HR=0.69, p<0.001) in KS-NSCLC independent of TP53MUT status. Although not the primary focus of the current study, this analysis was replicated in a KRASMUT/STK11WT-NSCLC cohort and high-NEDD9 expression was associated with improved mOS independent of TP53, KEAP1, and SMARCA4 co-mutations. PD-L1 positivity was inversely associated with NEDD9 expression and significantly different between NEDD9 high and low expressing tumors in the TP53WT KS-NSCLC cohort only (q < 0.001).

Conclusions: Using a large real-world cohort, high-NEDD9 expression is independently associated with improved OS and is an effective prognosticator in KS-NSCLC. Further elucidation of underlying mechanisms and treatment implications is warranted.

Keywords: NEDD9 expression, KRAS mutation, Non-small cell lung cancer



P1.06B PATHOLOGY AND BIOMARKERS - BIOMARKER
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P1.06B.08 The Prognostic Value of Histidine-rich Glycoprotein in Patients with Bronchial Carcinoid

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Introduction: Pulmonary carcinoids (PCs) are well-differentiated neuro-endocrine tumors with low metastatic potential. WHO classification designates two grades: typical and atypical carcinoid. The prognostic value of this grading system remains limited. In our previous work, we showed that addition of novel markers CD44/OTP to the WHO classification in combination with Ki-67 predicted the development of distant metastasis in approximately 50% of patients.

Methods: The discovery cohort included 28 surgically-resected PCs (12 metastasized, 16 without metastasis) profiled with liquid chromatography tandem-mass spectrometry (LC-MS/MS-based proteomics). Differentially expressed proteins were validated with immunohistochemistry (IHC) using H-score in a validation cohort of patients with available clinical follow up and OTP/CD44 IHC.

Results: The discovery cohort had a median follow up period of 50 months (IQR 32-72). The LC-MS/MS-based proteomics revealed 22 differentially expressed proteins ($p<0.001$) of which four were selected for IHC validation. Histidine-rich glycoprotein (HRG) was successfully validated and performed in 158 patients. In the validation cohort, 16 patients (10%) had lymph node metastasis and 11 patients (7%) developed distant metastases. HRG had a lower median H-score in patients with distant metastasis (0; IQR 0-50) versus no metastasis (140; IQR 90-200, $p<0.001$). Interestingly, HRG had also a lower median value in tumors with lymph node metastasis 0 (IQR 0-185, $p=0.005$), which was not the case for OTP/CD44. Loss of HRG was independently associated with a higher risk of distant metastasis in multivariate analysis ($p<0.001$). The log-rank test showed signficant differences in distant metastasis-free survival when mitotic count, Ki-67, HRG, CD44/OTP were combined in favorable and unfavorable profiles ($p<0.001$).

Conclusions: Loss of HRG showed promising prognostic value for development of distant metastasis in combination the widely used TC/AC classification, Ki-67 and OTP/CD44. Moreover, it is often lost in lymph node metastasis. This composite biomarker may guide a more tailored approach for the follow-up of patients with PC.

Keywords: Carcinoid, Biomarker, HRG

P1.06B PATHOLOGY AND BIOMARKERS - BIOMARKER
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P1.06B.09 Noninvasive Blood Biopsy of CRTAM-Type 3 Immune Axis Enables Dynamic Monitoring of Iraes Over the Course of Immunotherapy in Lung Cancer

S-C. Ma, Z-X. Rong, J-R. Lin, Z-P. Xu, D-H. Wu, Z-Y. Dong, Southern Medical University, Guangzhou/CN

Introduction: Immune checkpoint blockade (ICB)-based immunotherapy has become the first-line option for non-small cell lung cancer (NSCLC) without driver mutations. Nonetheless, the anti-tumor efficacy of immunotherapy comes at a cost of immune-related adverse events (irAEs) which leads to ICB withdrawal, reduced quality of life, and even patient deaths. A clinically scalable biomarker forecasting irAEs is urgently needed.

Methods: ICB-associated colitis, pneumonitis, and myocarditis were mimicked in preclinical models. Murine irAE vs control samples were subjected to RNA-sequencing for differential expression analysis. Genetic knockout mice were generated to explore the function and downstream signaling. An in-house NSCLC cohort was prospectively enrolled to evaluate blood biopsy for irAEs, where blood samples were divided into plasma and cell components. An external NSCLC cohort with plasma proteomics profiling was used for validation.

Results: Anti-PD-1 exacerbated the colitis and pneumonitis syndrome induced by dextran sodium sulfate (DSS) and whole lung radiotherapy (RT), respectively; and Pd1-/-Ctla4+/- exhibited spontaneous myocarditis in the preclinical setting. Integration of differential expressed genes of the irAE models pointed to CRTAM as a conserved biomarker. Crtam-/- mice exhibited compromised irAE phenotypes compared with Crtam+/+ mice after ICB induction (Figure 1). Transcription factor (TF) spectrum of Crtam-/- vs Crtam+/+ mice displayed a dampened expression of type 3 immune TFs. Our in-house cohort showed an upregulation of plasma IL-17 (type 3 immune effector) and CRTAM expression on T cells in irAE samples compared to those without irAEs. In the external cohort, plasma proteomics of irAE vs non-irAE revealed a concomitant increase of CRTAM and type 3 immune cytokines (IL-1 and IL-6) in baseline plasma samples from irAE patients (Figure 2).

Conclusions: Blood biopsy of the CRTAM-type 3 immune axis might be a promising non-invasive testing method for dynamic monitoring of the occurrence and development of irAEs during immunotherapy of NSCLC.

Keywords: immunotherapy, immune-related adverse events, non-small cell lung cancer

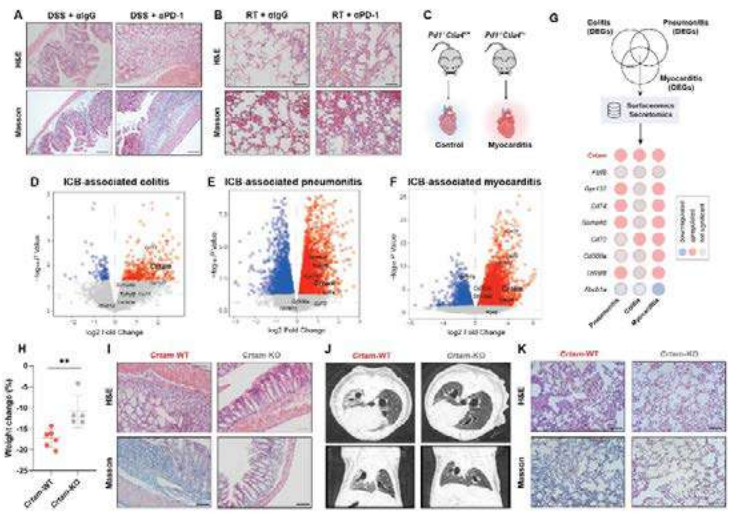

Fig 1. CRTAM as a conserved biomarker in irAE preclinical models. Anti-PD-1 exacerbated (A) DSS-induced colitis and (B) RT-induced pneumonitis syndrome. (C) Pd1-/-Ctla4+/- exhibited spontaneous myocarditis. (D-F) Differential analyses of ICB-associated colitis, pneumonitis, and myocarditis vs control. (G) Crtam as a conserved biomarker. Crtam-/- mice exhibited compromised irAE phenotypes in (H-I) colitis and (J-K) pneumonitis models.

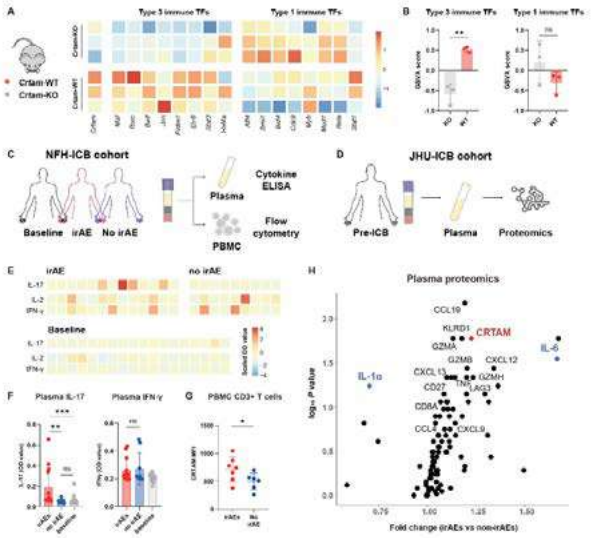

Fig 2. Blood Biopsy of CRTAM-type 3 Immune Axis monitors irAEs of NSCLC. (A-B) Transcription factor (TF) spectrum of Crtam-/- vs Crtam+/+ mice. (C-D) Diagram of blood biopsy in two independent cohorts. (E-G) Plasma cytokine profile and CRTAM expression on T cells of irAEs vs non-irAEs. (H) Plasma proteomics of irAEs vs non-irAEs.

P1.06B PATHOLOGY AND BIOMARKERS - BIOMARKER
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P1.06B.10 Post-hoc Biomarker Analysis of Adebrelimab Plus Chemotherapy and Sequential Radiotherapy as First-Line Therapy for ES-SCLC

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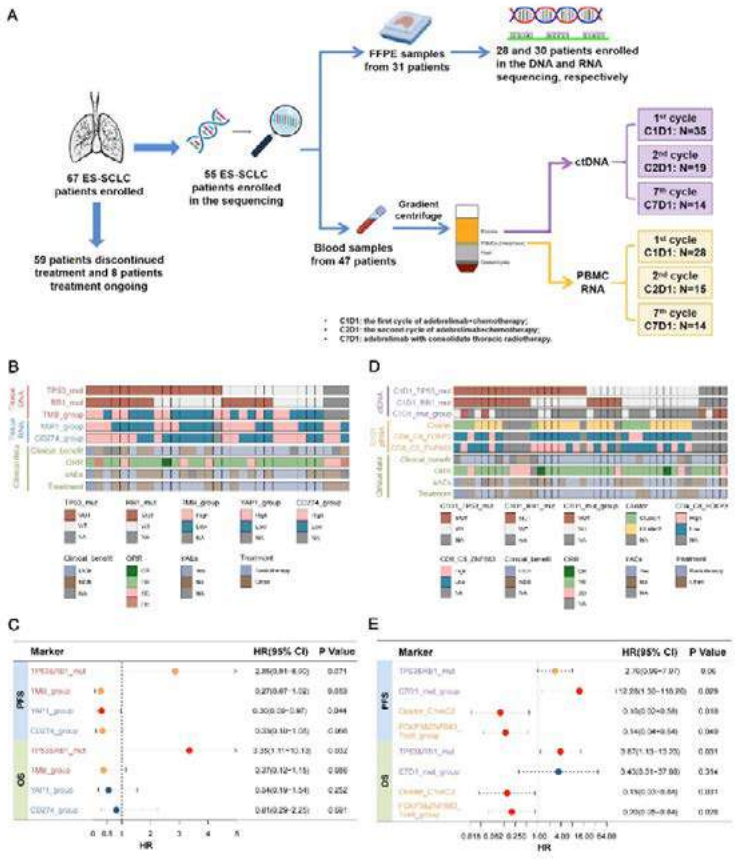
Introduction: A prospective trial investigating the efficacy and safety of adebrelimab plus first-line chemotherapy followed by sequential thoracic radiotherapy (TRT) combined with adebrelimab was designed (NCT04562337) in extensive-stage small cell lung cancer (ES-SCLC) patients. The improved clinical benefit of progression-free survival (PFS) and overall survival (OS) were reported (L. Wang, et al, ASTRO 2023: 65th Annual Meeting). An exploratory analysis was conducted revealing putative biomarkers indicating therapeutic efficacy.

Methods: Inclusion criteria and study endpoints were disclosed (L. Wang, et al, ASTRO 2023: 65th Annual Meeting). Biospecimens were collected from 55 patients (Figure A). FFPE biopsy tissues (n=31) before initiation of therapy were collected. Plasma and peripheral blood mononuclear cell (PBMC) from 41 patient were collected before 1st (C1D1), 2nd cycle (C2D1) of adebrelimab plus chemotherapy and adebrelimab with consolidate TRT (C7D1). Comprehensive genomic profiling of tissue and cfDNA was performed by 571 cancer-related genes (AmoyDx® Master Panel). Transcriptomic profiling on tissue and PBMC was conducted via RNA-seq (AmoyDx®).

Results: From October 2020 to April 2023, 67 patients with ES-SCLC were enrolled. The cut-off of follow-up was December 22, 2023. Balanced baseline characteristics was found between whole (n=67) and biomarker analysis population (n=55). Co-mutations of TP53/RB1 in tissue (n=28) and peripheral blood (n=35) indicated poorer efficacy (PFS, tissue, HR=2.85, P=0.071; ctDNA, HR=2.76, P=0.06; OS, tissue, HR=3.35, P=0.032; ctDNA, HR=3.87, P=0.031) (Fig B-E). Higher TMB level (≥10Muts/Mb) in tissue implied longer PFS and OS (HR=0.27, P=0.053 and HR=0.37, P=0.086) (Fig B,C). At C7D1 (n=14), ctDNA+ patients had worse PFS (HR=12.28, P=0.0069). Transcriptionally, either radiation sensitivity index (RSI) or GARD score associated with the efficacy of TRT with immunotherapy. While patients with higher expression of CD274 (HR=0.33, P=0.066) or YAP1 displayed longer PFS (HR=0.3, P=0.044) (Fig B, C). Further, two clusters, immune-regulatory (cluster 1) and pro-inflammatory (cluster 2) were categorized in baseline PBMC (Fig D). Two subpopulations of T cells were further revealed at baseline PBMCs indicating opposite response to investigated regimen (Cluster 2 vs 1: PFS, HR=0.15, P=0.01; OS, HR=0.15, P=0.031) (Figure D, E). Patients with higher baseline ZNF683+ CD8+ T cells (cluster 2) got more benefit than those with higher baseline regulatory T cells (PFS, HR=0.14, P=0.04; OS, HR=0.2, P=0.028) (Fig D, E).

Conclusions: Genomic and transcriptomic biomarkers of tissue and peripheral blood were discovered. These biomarkers displayed association with clinical benefit of adebrelimab plus chemotherapy and adebrelimab with consolidate TRT, but further verification was warranted.



P1.06B PATHOLOGY AND BIOMARKERS - BIOMARKER
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P1.06B.11 Plasma MicroRNAs Profiling to Monitor Immunotherapy Response in Advanced NSCLC Patients

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Introduction: Immune checkpoint inhibitors (ICIs) have radically changed non-small cell lung cancer (NSCLC) treatment significantly improving patients' outcome. However, about 80% of patients ultimately relapse due to primary or secondary resistance. In this context, the identification of minimally invasive biomarkers to monitor the response to treatment and personalize therapy remains an issue. In this study, we rely on longitudinal circulating microRNA profiling to model disease progression probability over time.

Methods: In the APOLLO trial, we collected clinical, biochemical, radiologic and molecular data, as well as plasma samples at predefined time-points from advanced NSCLC patients treated with ICI monotherapy. RECIST v. 1.1 criteria were used to evaluate radiological disease response. Using a custom RT-qPCR platform, we profiled 24-lung cancer related circulating microRNAs, generating 276 microRNA ratios. To model the probability of disease progression, we used generalized estimating equations (GEE), incorporating microRNA ratios and their interaction with time.

Results: We analyzed 454 plasma samples collected from 211 consecutive advanced NSCLC patients treated with ICI monotherapy at Istituto Nazionale dei Tumori of Milan. By principal component analysis at baseline, variables such as monocyte and leucocyte count, line of therapy, PD-L1 expression, presence of liver metastases and patient age were significantly related with the global microRNA profiling (Figure 1). Using GEE mathematical models, we identified nine circulating microRNA ratios (all featuring miR-145) as significant predictors of disease progression whose modulation was consistent with the radiologic response (Figure 2). Moreover, baseline values of miR-140-5p/miR-145, miR-145/miR-15b, miR-142-3p/miR-145, miR-145/miR-451, miR-145/miR-30b and miR-145/miR-30c were found to be associated with OS, but not with PFS.

Conclusions: Our findings highlight the role of dynamic microRNA profiles, especially miR-145, in response monitoring during ICI monotherapy in advanced NSCLC. Integrating minimally invasive microRNA-based liquid biopsy into clinical practice may help clinicians and improving treatment outcomes.

Keywords: microRNAs, Biomarkers, Immunotherapy

Figure 1: Radar plot reporting the association of baseline clinical variables with the first 3 principal components (PC) derived from PC analysis of plasma miRNA profiling.

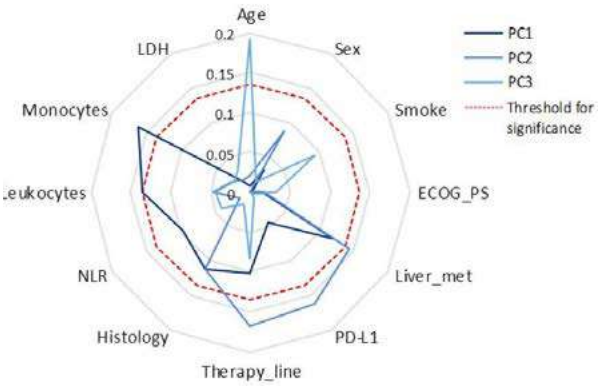
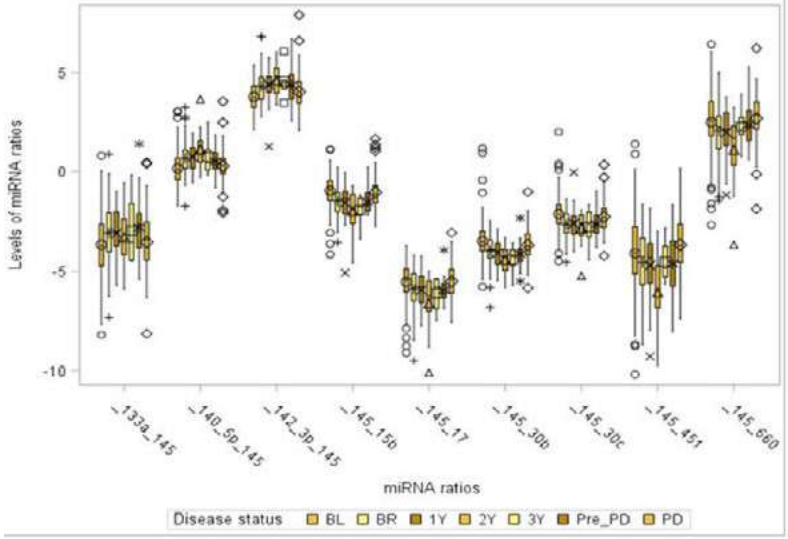


Figure 2: Distributions of 9 miRNA ratios consistent with the response to ICI by blood sample occurrences



P1.06B PATHOLOGY AND BIOMARKERS - BIOMARKER
SUNDAY, SEPTEMBER 8, 2024 - 12:00 - 14:00

P1.06B.12 Racial and Socioeconomic Disparities in Molecular Diagnostics for NSCLC Patients

S.J. Tuminello, M. Untalan, T. Ivic-Pavlicic, W. Turner, R. Flores, E. Taioli, Icahn School of Medicine at Mount Sinai, New York City/NY/USA

Introduction: Targeted therapies have substantially changed the landscape of non-small cell lung cancer (NSCLC) outcomes. These drugs work by inhibiting specific molecular pathways, such as the epidermal growth factor receptor (EGFR) tyrosine kinase, the anaplastic lymphoma kinase (ALK), KRAS, and BRAF oncogenic pathways. Approximately 30% of NSCLC patients will have tumors with eligible targetable mutations, but a molecular test must be conducted to assess eligibility to these treatments. Disparities in molecular testing could be partially responsible for the disproportionate utilization of targeted therapy across race and socioeconomic status (SES).

Methods: Surveillance, Epidemiology and End Results (SEER)-Medicare linked data was queried for NSCLC patients diagnosed from 2013 (the first year that standard guidelines for molecular testing in lung cancer were available) to 2016. Patients were limited to age over 66 years at diagnosis with continuous Part A and B coverage and no Part C coverage, for 1 year prior and 90 days post-diagnosis. The primary outcome was receipt of a molecular test based on claims data. Race, defined as white, Black or other, was the primary predictor variable. Demographic and clinical characteristics of those receiving vs not receiving a molecular test were compared using $\chi 2$ tests for categorical variables and t-tests for continuous variables. We also performed multivariable logistic regression to assess the association of molecular testing with race adjusting for sex, age, marital status, Charlson comorbidity index, histology, tumor site, stage, and census-level poverty indicator.

Results: There were 28,511 NSCLC patients, of which 9,639 (33.8%) received some type of molecular testing. Black patients were significantly less likely than white patients to have received a molecular test ($p<0.0001$). Only 23.9% of Black patients underwent any molecular testing, compared to 34.6% of white patients. Patients living in census tracts with at least 10% of residents living in poverty were also less likely to receive a molecular test ($p<0.0001$). Patients who were female ($p<0.0001$), married ($p<0.0001$), with fewer comorbidities ($p<0.0001$), adenocarcinoma histology ($p<0.0001$), tumors located in the lower lobe ($p<0.0001$), diagnosed at a later stage ($p=0.0001$) were more likely to have molecular testing. After adjustment, Black patients (ORadj [odds ratio]: 0.65; 95% CI [confidence interval]: 0.59-0.72) and those living in areas with greater poverty (ORadj: 0.87; 95% CI: 0.82-0.91) were statistically significantly less likely to have received molecular testing.

Conclusions: Disparities exist in comprehensive molecular diagnostics, and could explain, at least in part, the high mortality observed among Black NSCLC patients. Addressing barriers to molecular testing could increase uptake of targeted therapy treatment, decreasing disparities and improving patient outcomes.

Keywords: Molecular test, Race, EGFR

P1.06B PATHOLOGY AND BIOMARKERS - BIOMARKER
SUNDAY, SEPTEMBER 8, 2024 - 12:00 - 14:00

P1.06B.13 Blood-Based Loss of Heterozygosity in Human Leukocyte Antigen Class I Alleles Reveals Resistance to Immunotherapy in Non-Small Cell Lung Cancer

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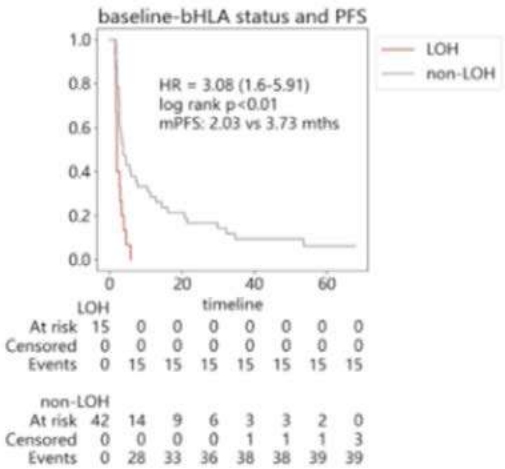
Introduction: Loss of heterozygosity in Human Leukocyte Antigen class I (HLA-LOH) leads to immune evasion and hints the status of tumor development and immunotherapy response, while studies on blood-based HLA-LOH (bHLA-LOH) remain blank.

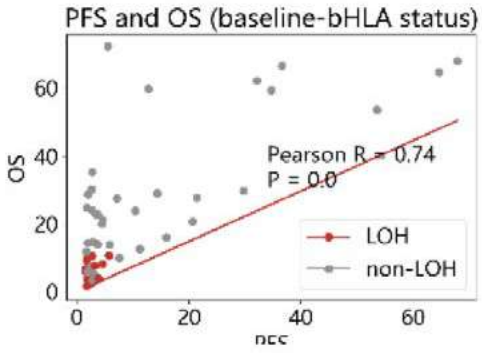
Methods: We explored bHLA-LOH characteristic based on 516 paired tissue-blood non-small cell lung cancer (NSCLC) specimens (GPD cohort) and detected baseline and dynamic bHLA-LOH status among 58 patients with advanced NSCLC receiving mono-immunotherapy (NCC cohort).

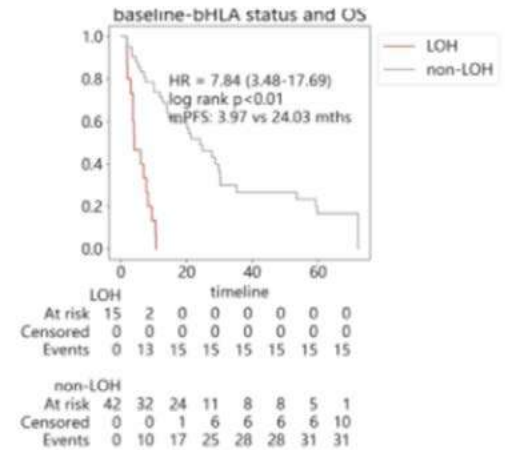
Results: In GPD cohort, the occurrence rates of tissue-based HLA-LOH (tHLA-LOH) and bHLA-LOH were 46.1% (238/516) and 14.9% (77/516) ,respectively. Similar with tHLA-LOH, bHLA-LOH group (n=439) included more patients with male gender (P = 0.001), smoking-history positive (P = 0.009) , and squamous carcinoma (P = 0.06) , characterized with higher blood-based tumor mutational burden (bTMB, P = 0.01), neoantigens (P = 0.09) and intra-tumor heterogeneity (ITH, P = 0.006) compared with non-bHLA-LOH group (n = 77). Surprisingly, in NCC cohort, patients with baseline bHLA-LOH showed significantly inferior clinical response (mPFS, 2.03 vs. 3.73mths, P < 0.01; mOS, 3.97 vs. 24.03mths, P < 0.01; primary resistance, P < 0.01), consistent with multi-factor analysis. Dynamic blood detection showed that bHLA-LOH was stably detected during immunotherapy(7/7), and three patients were detected with bHLA-LOH firstly as tumour progressed,indicating acquired resistance. Furthermore, baseline bHLA-LOH was associated with higher blood-based tumour mutation burden(bTMB, P < 0.01) and could stratified those with significantly worse response to immunotherapy in bTMB high group (mPFS, 2.03 vs. 3.47mths, P < 0.01; mOS, 3.97 vs. 13.9mths, P = 0.02).

Conclusions: We developed bHLA-LOH, a convenient, readily available, non-invasive predictive biomarker, which could effectively reveal primary and acquired resistance to immunotherapy in patients with NSCLC and guide clinical treatment decision, warranting future clinical trials.

Keywords: Human Leukocyte Antigen class I, HLA-I, Loss of heterozygosity, LOH, Non-Small Cell Lung Cancer, NSCLC







P1.06B PATHOLOGY AND BIOMARKERS - BIOMARKER
SUNDAY, SEPTEMBER 8, 2024 - 12:00 - 14:00

P1.06B.14 Optimal Cut-Off with NGS for Metamplification Andclinical Relevance to MET Inhibitor in Non-Small-Cell Lung Cancer

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Introduction: Current next-generation sequencing (NGS)-based assays lacked a unified standard on the cut-off value for MET amplification in non-small-cell lung cancer (NSCLC) patients. Identify the optimal cut-off with NGS for MET amplification could guide clinical decision.

Methods: We initiated a multiple-site jointing study to optimize cut-off value for MET amplification by using tumor tissue and NGS analysis. The study included two cohorts for training and validation. In training cohort, five NGS panels were used to detect MET gene copy number (GCN) and fluorescence in situ hybridization (FISH) was used as a reference. Receiver operating characteristic (ROC) analysis was used to identify the optimal cut-off with 100% specificity and optimal sensitivity. Result was validated in an independent validation cohort to explore the correlation between MET amplification and the efficacy of MET inhibitors in NSCLC patients. Univariate and multivariate Cox regression analysis was used to explore the association of baseline characteristics and MET amplification status by identified NGS cutoff with PFS of MET-directed therapy.

Results: The clinical and pathological characteristics of the patients in training cohort (n=21) and validation cohort (n=29) was similar. In the training cohort, an optimal MET GCN cut-off was determined by 6.55 (versus FISH GCN 5), yielding an area under curve of 0.9, corresponding to an accuracy of 85.7%. MET polysomy identified by FISH (n=2) was also detected by NGS. All five NGS panels demonstrated good concordance with FISH, with an accuracy ranging from 75.0% to 85.7%. In the validation cohort, NGS analysis also demonstrated good performance, with an accuracy rate of 79.3%. Patients with MET GCN ≥ 6.55 had a significantly longer median progression free survival than those with MET GCN < 6.55 (Figure 1). MET amplification identified by NGS with MET GCN ≥ 6.55 as independent factor was associated with significant PFS benefit in univariable and multivariable analysis. Besides, using MET GCN 10 as positive by FISH, the identified cut-off value of NGS MET GCN 8.63 was explored.

Conclusions: In this study, the optimal cut-off of MET GCN with NGS was 6.55 and patients with MET amplification positive identified with this cut-off had favorable survival benefit from targeted therapy. Future studies are warranted to confirm these results.

Keywords: MET amplification, Next-generation of sequencing, Non-small-cell lung cancer and Targeted therapy

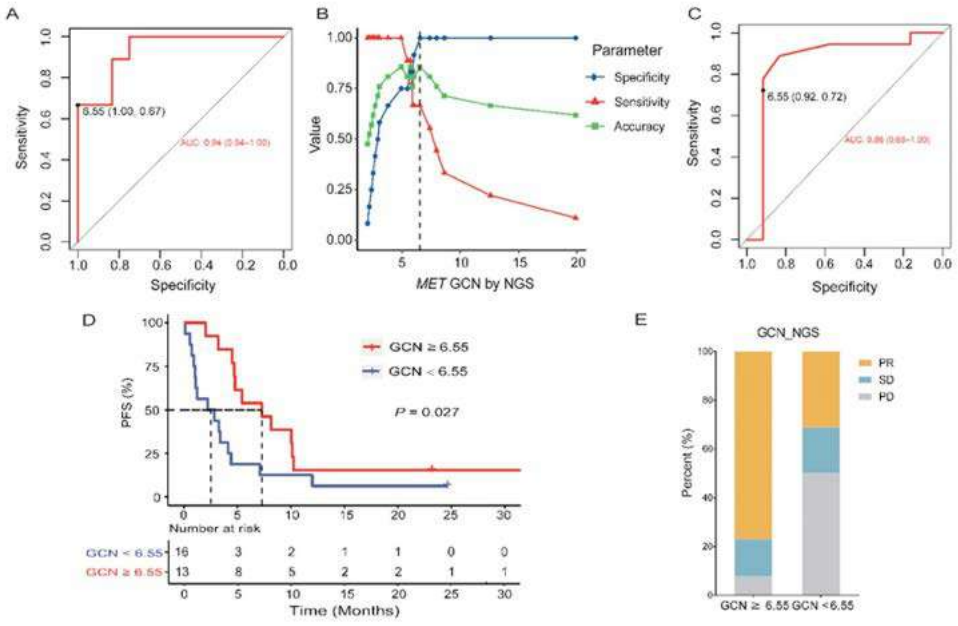

Figure 1: Identification and performance of the optimal cut-off value of MET GCN. (A): Receiver operating characteristic (ROC) curve showed the performance of MET GCN to define MET amplification based on NGS analysis. (B): Landscape of specificity, sensitivity and accuracy of different cut-off value of MET GCN to distinguish MET+ from MET- patients. (C): ROC curve showed optimal cutoff value of 6.55 by NGS in validation cohort. (D): Kaplan-Meier curve showed longer survival benefit from MET-directed therapy in patients with MET GCN≥6.55 by NGS (positive) than in those with MET GCN < 6.55 (negative). (E): Histogram show the better clinical response in MET positive patients than that in MET negative patients which grouped by NGS. AUC: area under curve; p: P value; PD: progressive disease; SD: stable disease; PR: partial response.

P1.06B PATHOLOGY AND BIOMARKERS - BIOMARKER
SUNDAY, SEPTEMBER 8, 2024 - 12:00 - 14:00

P1.06B.15 The Role and Clinical Significance of the MICOS Family in Lung Adenocarcinoma: A Focus on MIC19

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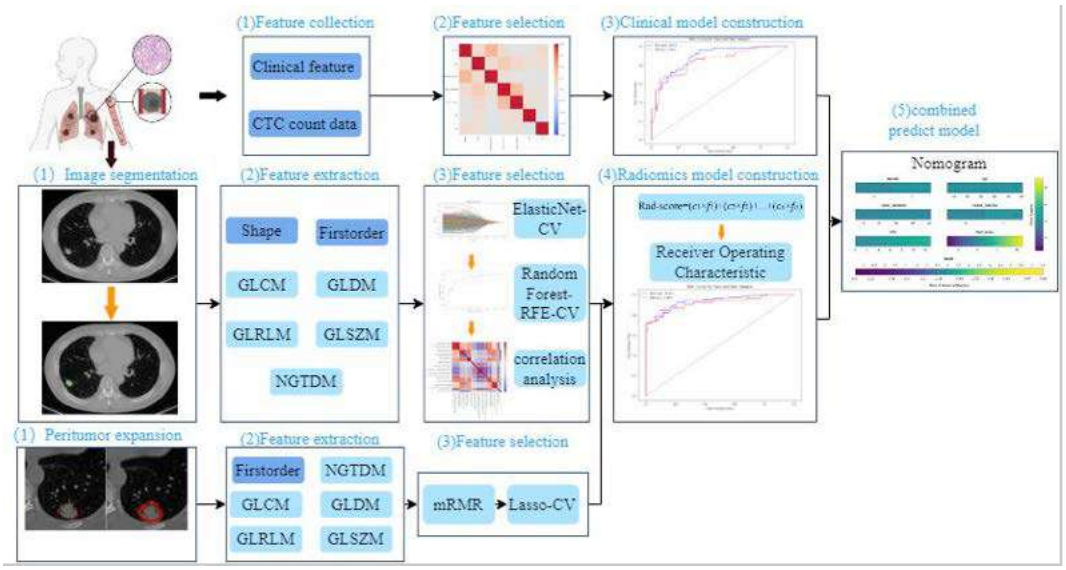
Introduction: The MICOS (Mitochondrial Contact Site and Cristae Organizing System) family comprises a group of protein complexes located on the inner membrane of mitochondria, primarily responsible for maintaining the integrity of mitochondrial inner membrane structure and regulating mitochondrial inner membrane morphology. Aberrations in mitochondrial morphology and function have been implicated in the onset, progression, and treatment resistance of tumors, including lung adenocarcinoma. This study aims to comprehensively investigate the function of the MICOS family in the occurrence and development of lung adenocarcinoma and its clinical significance, providing novel scientific insights and clinical guidance for the treatment and prognosis assessment of lung adenocarcinoma.

Methods: Lung adenocarcinoma samples were extracted from The Cancer Genome Atlas (TCGA) dataset. Multiple databases including UALCAN, HPA, and DAVID were utilized to explore the role of MICOS family genes in lung adenocarcinoma, including their modulation of the immune microenvironment. Additionally, we knocked down the expression of MIC19 in lung adenocarcinoma using siRNA and explored its effects on cell proliferation and migration through CCK8, EDU, Transwell, and colony formation experiments.

Results: Bioinformatics analysis revealed that all genes in the MICOS family are closely associated with the occurrence of lung adenocarcinoma, with MIC19 showing the closest correlation with malignant clinical features of lung adenocarcinoma. Furthermore, the expression of MIC19 was significantly correlated with the immune cell infiltration abundance in lung adenocarcinoma patients, suggesting its potential as a prognostic biomarker for lung adenocarcinoma patients. In vitro experiments demonstrated that MIC19 promotes the proliferation and migration of lung adenocarcinoma cells.

Conclusions: This study elucidates for the first time the role of MICOS family members in lung adenocarcinoma, highlighting the importance of MIC19 as a potential novel independent prognostic biomarker and therapeutic target in lung adenocarcinoma.

Keywords: MICOS, MIC19, Lung Adenocarcinoma



P1.06B PATHOLOGY AND BIOMARKERS - BIOMARKER
SUNDAY, SEPTEMBER 8, 2024 - 12:00 - 14:00

P1.06B.16 HER3 Expression Across Genomic Subsets of NSCLC

B. Gupta[1], Y. Baca[2], G. Hubbard[2], J.E. Reuss[1], S.C.M. Lau[3], A. Elliott[2], M.C. Garassino[4], A.M. Vanderwalde[2], P.C. Ma[5], B. Halmos[6], S.V. Liu[1], [1]Lombardi Comprehensive Cancer Center, Georgetown University, Washington/DC/USA ,[2]Caris Life Sciences, Phoenix/AZ/USA ,[3]Perlmutter Cancer Center, NYU Langone Health, New York/NY/USA ,[4]The University of Chicago, Chicago/IL/USA ,[5]Penn State Milton S. Hershey Medical Center, Hershey/PA/USA ,[6]Montefiore Einstein Comprehensive Cancer Center, Bronx/NY/USA

Introduction: Human epidermal growth factor 3 (HER3, ERBB3) is frequently expressed in NSCLC and is a target for novel antibody drug conjugates; while known to be highly expressed in tumors harboring mutations in EGFR, little is known about ERBB3 expression in other molecular subtypes of NSCLC. Here, we analyze ERBB3 expression patterns in multiple genomic driver subtypes of NSCLC, explore associations with survival, and characterize the impact of prior tyrosine kinase inhibitor (TKI) exposure on ERBB3 expression.

Methods: Next-generation sequencing of DNA (592-gene or whole exome) and RNA (whole transcriptome) was performed on NSCLC samples (n=52,690) submitted to a CLIA-certified lab (Caris Life Sciences, Phoenix, AZ). ERBB3 expression was reported in transcripts per million (TPM). Real-world overall survival (rwOS) information was obtained from insurance claims data and calculated from time of collection to last contact, while time-on-treatment (TOT) was calculated from date of first treatment to date of last of treatment. P values were calculated using the log-rank test.

Results: In 2,600 tumor specimens with common sensitizing EGFR mutations (exon 19 deletions, exon 21 L858R), the median ERBB3 expression was 71.82 TPM. Median ERBB3 expression was highest in specimens with ERBB2 (HER2) mutations (98.65 TPM, n=433), EGFR exon 20 insertion mutations (83.65 TPM, n=70), and KRAS mutations (73.53 TPM, n=7928). ERBB3 expression was higher in KRAS G12C mutant NSCLC than non-G12C (76.07 TPM, n=5766 versus 70.29 TPM, n=3162). ERBB3 expression was lower in tumors with a ROS1 fusion (60.22 TPM, n=186), an ALK fusion (58.86 TPM, n=665), or a MET exon 14 skipping variant (42.50 TPM, n=925). High ERBB3 expression (top quartile) was associated with improved overall survival in the EGFR L858R (35.5 vs 25.7 months, p=0.028), EGFR exon 19 deletion (36.5 vs 27.4, p=0.012), MET exon 14 skipping (32.0 vs 14.7 months, p<0.0001), and KRAS mutants (21.6 vs 13.8 months, p< .00001). Among EGFR mutant samples, ERBB3 expression was significantly higher in TKI-naive samples compared to TKI-exposed samples (median TPM 68.8 vs 57.2, p=0.001). Time on treatment with EGFR TKI did not vary by ERBB3 expression.

Conclusions: High ERBB3 expression was observed in multiple genomic subsets of NSCLC including those with EGFR, HER2 and KRAS mutations, though expression varies by specific mutation. Within EGFR mutant NSCLC, expression was highest in TKI-naive samples and in the exon 20 insertion mutation subset. High ERBB3 expression was associated with better survival. These data support the role of HER3 as a viable therapeutic target across multiple molecular subsets.

Keywords: HER3, EGFR, ERBB3

P1.06B PATHOLOGY AND BIOMARKERS - BIOMARKER
SUNDAY, SEPTEMBER 8, 2024 - 12:00 - 14:00

P1.06B.17 Combing Circulating Tumor Cell Associated Liquid Biopsy and Radiomics to Predict the Pathology Grade of LUAD Patients

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Introduction: Lung adenocarcinoma (LUAD) is a predominant cause of cancer-related mortality. Achieving accurate diagnostics and effective treatments remains a challenge. Emerging liquid biopsy markers and radiomics have shown promise in enhancing LUAD diagnostics.

Methods: To delineate lung nodules in patients with postoperative adenocarcinoma on low-dose CT (LDCT), 3D Slicer was used for accurate segmentation of the nodules and their peritumoral regions. Following segmentation, the pyradiomics library extracted radiomic features from these regions of interest (ROIs), encompassing shape, intensity, texture, and wavelet attributes. Feature selection and model development employed a combination of ElasticNet-CV, mRMR, Lasso-CV, Random Forest-RFE-CV, and correlation analysis to identify predictive features with minimal redundancy. These features were then integrated using a nomogram approach to construct robust predictive models. Model performance was assessed through ROC curve analysis, focusing on the area under the curve (AUC) to evaluate the models' ability to accurately predict lung adenocarcinoma presence based on radiomic signatures derived from LDCT.

Results: The radiomics model, the clinical model, and the combined model were evaluated for their predictive capabilities: In both training and test groups, the combined model demonstrated optimal performance with an AUC of 0.9420 and 0.9277, respectively. Precision-Recall curves further cemented the combined model's superiority, achieving AP values of 0.9731 for the training set and 0.9691 for the test set, surpassing the performance of the standalone models.

Conclusions: This study clarifies that a combined model integrating CTC counts, radiomics, and other clinical data holds immense promise in refining surgical decisions for LUAD treatment. However, for a holistic understanding and optimization of the diagnostic potential of genetic markers, further comprehensive research is paramount.

Keywords: Lung Adenocarcinoma, Circulating Tumor Cell, Radiomics

P1.06B PATHOLOGY AND BIOMARKERS - BIOMARKER
SUNDAY, SEPTEMBER 8, 2024 - 12:00 - 14:00

P1.06B.18 Pathologic Response Assessment of Resected NSCLC Neoadjuvant Therapy Specimens with Tumor Size Larger Than 3cm by Different Sampling Methods

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Introduction: Data on pathological evaluation of resected NSCLC specimens with tumor size>3cm after neoadjuvant therapy are limited. This study aims to investigate pathological assessment of resected NSCLC specimens with tumor size>3cm after neoadjuvant treatment using different sampling methods.

Methods: We conducted a retrospective study of resected NSCLC specimens with tumor size>3cm after neoadjuvant therapy between June 2020 and July 2023 at Shanghai Pulmonary hospital. The difference of residual viable tumor (RVT) and pathologic response between IASLC multidisciplinary recommendation for sampling (MRS) and complete sampling (CS) for tumor bed with tumor size>3cm was compared.

Results: This retrospective study enrolled 90 patients with Non-small cell lung cancer (squamous cell carcinoma, n=39; adenocarcinoma, n=51) treated with neoadjuvant therapy including chemotherapy (n=22), targeted therapy (n=14), and chemoimmunotherapy (n=54). In this cohort, there were 62 men and 28 women with an average age of 63 years (range 39 to 74); The average tumor bed size was 4.3cm (range 3.1 to 8.0), and the average number of sampled blocks was 8 blocks (range 5 to 16) and 15 blocks (range 8 to 36) per case by MRS and CS, respectively. The number of patients with major pathological response (MPR) defined as less than or equal to 10% RVT was 34 cases (MRS) and 30 cases (CS), respectively. Four cases showed inconsistent RVT between MRS and CS, including one case of squamous cell carcinoma and three cases of adenocarcinoma. The RVT% of the four inconsistent cases achieved 7% using MRS and 15% by CS, and the kappa value of MPR consistency evaluated by the two sampling methods was 0.893. According to MPR cutoffs of 65% for lung adenocarcinoma (ADC-MPR), 24 cases and 20 cases achieved ADC-MPR by MRS and CS, respectively. Of the four inconsistent cases, the RVT% by MRS was 60% in three cases and 65% in one case, whereas the RVT% by CS was 70%, and the kappa value of the two sampling methods was 0.741.

Conclusions: It's feasible and practical to apply the IASLC multidisciplinary recommendations for sampling of resected NSCLC specimens with tumor size larger than 3cm after neoadjuvant treatment. Further studies are needed to confirm the optimal sampling method for pathologic response assessment.

Keywords: IASLC multidisciplinary recommendation, complete sampling, major pathological response

Patients	Age	Gender	Subtype	Tumor Size(cm)	Blocks by MRS	RVT% by MRS	Blocks by CS	RVT% by CS
Case1	73	Male	Squamous cell carcinoma	3.8	8	7%	11	15%
Case2	72	Male	Adenocarcinoma	5.5	14	7%	23	15%
Case3	61	Male	Adenocarcinoma	4.2	10	5%	18	12%
Case4	65	Female	Adenocarcinoma	3.2	8	9%	12	18%

P1.06B PATHOLOGY AND BIOMARKERS - BIOMARKER
SUNDAY, SEPTEMBER 8, 2024 - 12:00 - 14:00

P1.06B.19 Effect of Gut Microbiota and Metabolites on Malignant Pleural Effusion of Lung Adenocarcinoma

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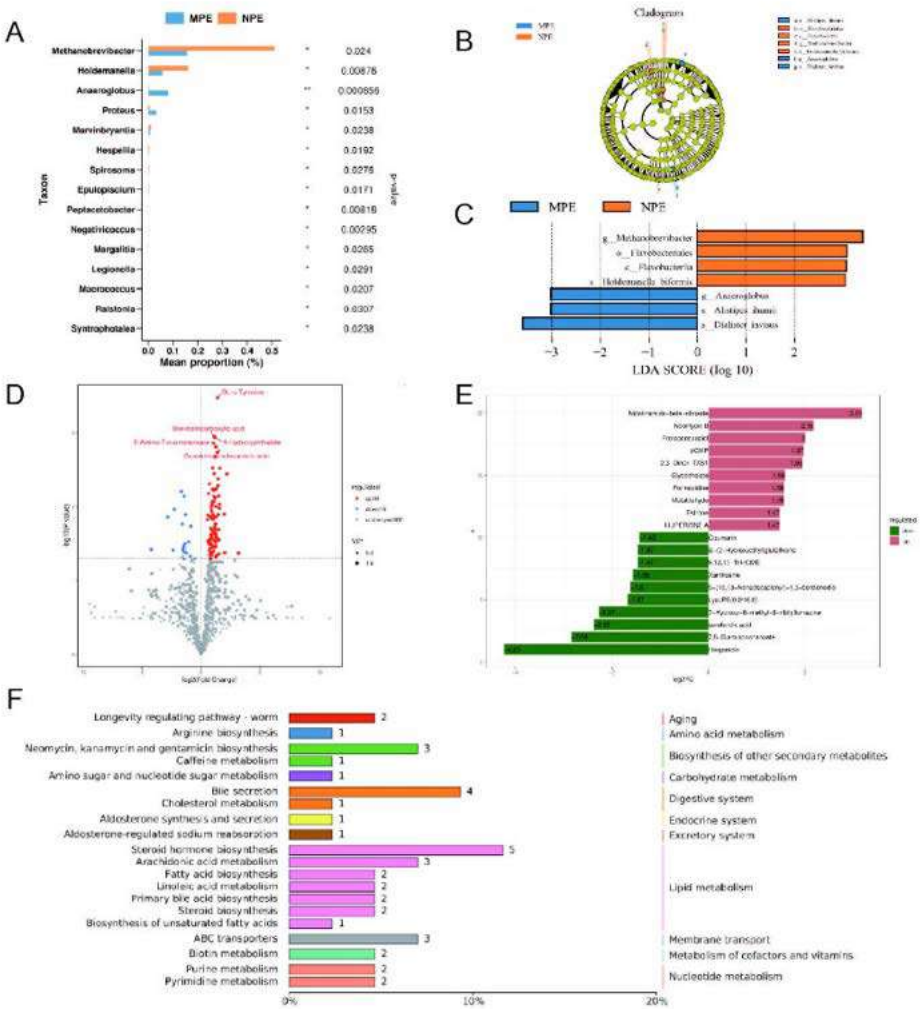
Introduction: Malignant pleural effusion (MPE) seriously threatens the quality of life of lung adenocarcinoma (LUAD) patients. Current studies have shown that human gut microbiome are closely related to the tumorigenesis, progression, diagnosis and prognosis of lung cancer. However, the relationship between gut microbiota and metabolites and MPE of LUAD remains unclear.

Methods: The study enrolled 122 newly diagnosed LUAD patients and collected baseline stool samples from all patients before treatment. Patients were divided into MPE group and NPE group according to the presence or absence of MPE at the time of diagnosis. Metagenomic and metabolomic tests were performed on stool samples from the two groups to compare the difference of gut microbiota abundance, metabolite diversity and metabolic pathway changes between the two groups.

Results: In the enrolled LUAD patient population, 53 patients had MPE and 69 patients did not. Our analysis found significant differences in gut microbiota and metabolite composition between the two groups. Compared with patients in the NPE group, the relative abundance of Methanobrevibacter (P=0.0203), Flavobacteriales (P=0.0386), Flavobacteriia (P=0.0358) and Holdemanella_biformis (P=0.0125) in the MPE group was reduced, while the relative abundance of Anaeroglobus (P=0.0003), Alistipes_ihumii (P=0.0317) and Dialister_ invisus (P=0.0163) increased. Metabolites such as DL-o-Tyrosine (P=0.0003) and Brevifolincarboxylic acid (P=0.0011) were up-regulated in MPE group. Kyoto Encyclopedia of Genes and Genomes (KEGG) database was used to enrich the differential metabolites, and the analysis showed that there were most significant differences in lipid metabolism related pathways, including steroid hormone biosynthesis, arachidonic acid metabolism, fatty acid biosvnthesis, etc.

Conclusions: This study suggests that LUAD patients with MPE have novel intestinal flora profiles and metabolic pathways, and these unique gut microbiota and metabolites may serve as potential biomarkers for the diagnosis and prognosis of MPE.

Keywords: LUAD, Malignant pleural effusion, Gut microbiota and metabolites



P1.06C PATHOLOGY AND BIOMARKERS - PATHOLOGY
SUNDAY, SEPTEMBER 8, 2024 - 12:00 - 14:00

P1.06C.01 Evaluation of Small Pulmonary Pathology Specimen Management in the Province of Quebec, Canada

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Introduction: The management of lung cancer patients has been revolutionized by the development of targeted therapies. Availability of tumor tissue is no longer vital for diagnostic purpose alone but also for biomarker evaluation. Small specimens such as tissue biopsies and cytology samples require strategic management now more than ever to ensure adequate treatment. The present study aims to investigate small specimen management in the province of Quebec, Canada.

Methods: Using pathological reports, data from 2164 small specimens diagnosed as lung adenocarcinoma, squamous cell carcinoma or non-small cell lung cancer favoring either were collected. Samples were submitted to a reference centre for molecular testing by 36 hospitals, categorized as academic centres, affiliated academic centres, and community hospitals, between 2022 and 2023. Based on the WHO Classification of Tumors of the Lung (2015, 2021), an algorithm was applied to categorize management of small specimens. Management was considered "adequate" when at least one immunohistochemistry stain was positive between TTF-1, Napsin A and/or Mucins (adenocarcinoma) or p40 and/or p63 (squamous cell carcinoma) only if no additional stain was performed. Thus, when one of the key stains was positive and additional stains were performed, management was considered "inadequate". When all the above were negative, management was categorized "adequate", regardless of the immunohistochemistry stains workup.

Results: In academic centres, the rate of adequate management of small specimens was higher (52.33% vs 39.25% vs 31.55%, p<0.0001), immunohistochemistry stains were less frequently performed (4.62 ± 0.15 vs 5.02 ± 0.12 vs 5.70 ± 0.16, p<0.0001), and turnaround times were faster (5.09 ± 0.16 vs 5.81 ± 0.10 vs 7.40 ± 0.18, p<0.0001) compared to affiliated academic centres and community hospitals, respectively (Figure 1). In the whole cohort, adequately managed specimens showed better turnaround times compared to inadequately managed ones (5.62 ± 0.14 vs 6.63 ± 0.12, p<0.0001). The rate of samples with enough tumor tissue for PD-L1 analysis differed between hospital settings (98.33% vs 95.60% vs 97.86% for academic centres, affiliated centres, and community hospitals, respectively, p=0.0041).

Conclusions: Our results show that a high proportion of small specimens were not managed adequately even close to 10 years after the publication of the WHO guidelines. In general, small specimen handling seems better in academic hospital centres compared to affiliated centres or community hospitals. With the growing need to preserve tumor tissue for molecular analyses, education to the pathology community is warranted to minimize the impacts on the patients.

Keywords: Pathology, Management, Small specimen

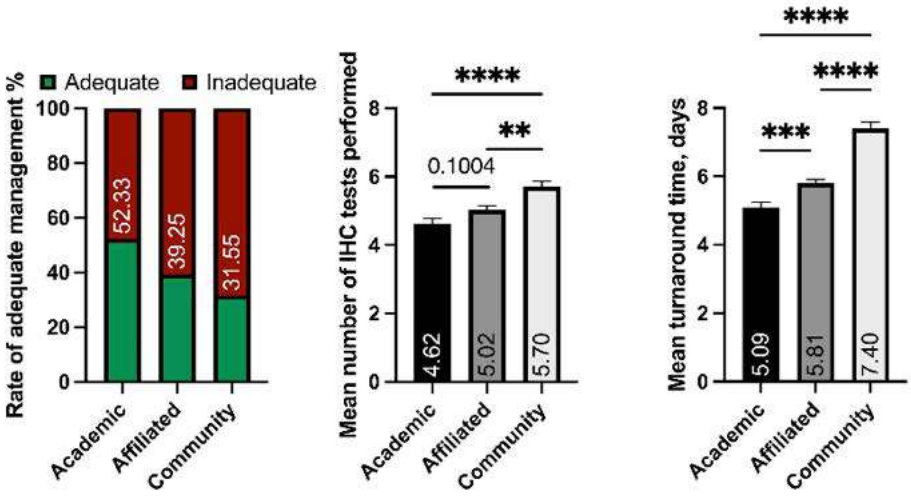


Figure 1. Small pulmonary pathology specimen management according to hospital settings.
Data are shown as rate (%) or mean ± SEM

P1.06C PATHOLOGY AND BIOMARKERS - PATHOLOGY
SUNDAY, SEPTEMBER 8, 2024 - 12:00 - 14:00

P1.06C.02 Description of A Single Center Thoracic Rapid Tissue Donation Program Experience

H. Ozakinci, G.S. Nazario, S. Acevedo-Acevedo, H. Trejo-Bittar, R. Macaulay, B. Pellini, J.M. Koomen, T.A. Rose, D-T. Chen, J.K. Teer, E.R. Flores, A.A. Beg, M.B. Schabath, E.B. Haura, T.A. Boyle, Moffitt Cancer Center, Tampa/FL/USA

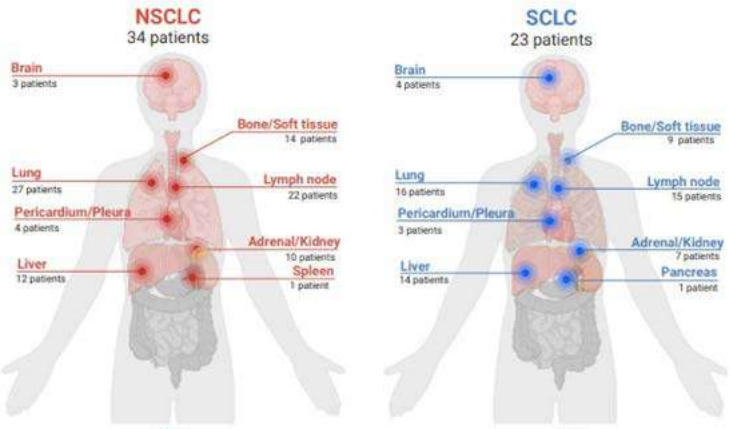
Introduction: The Moffitt Cancer Center Thoracic Rapid Tissue Donation (RTD) program offers significant opportunities for translational research in oncology. RTD has enabled the post-mortem donation of tumor tissue samples and body fluids from lung carcinoma patients to support translational research. These samples are particularly useful for studies of tumor evolution, heterogeneity, immune microenvironment, and treatment resistance mechanisms.

Methods: Between December 2015 and April 2024, 99 patients consented to participate in the RTD program as an alternative to organ donation, and samples from 58 donors were collected. The diagnosis of the donors included 32 with adenocarcinoma, 1 with squamous cell carcinoma, 1 with non-small cell lung cancer (NSCLC) not otherwise specified, and 23 with small cell lung cancer (SCLC), including 2 cases of SCLC transformed from NSCLC, and 1 case of mesothelioma. Tumoral and non-tumoral tissue samples, including formalin-fixed paraffin-embedded (FFPE), snap-frozen tissue, and fresh samples, were collected, processed, and stored. Special processing of fresh samples was performed to expand tumor-infiltrating lymphocytes and create 3D tumor microcultures. Multiple proteogenomic analyses were performed, including DNA sequencing, RNA sequencing, targeted gene expression analyses, immunohistochemistry, multiplex immunofluorescence, and mass spectrometry.

Results: The median interval between death and tissue collection was 10 hours (interquartile range: 5-19). A total of 789 FFPE, 737 snap-frozen, and 235 fresh samples were collected from 58 donors. The clinicopathological features of the 58 donors with lung cancer are summarized in Figure 1. Primary driver mutations were determined during clinical care and in the postmortem samples of 24 NSCLC donors, and only in postmortem samples of 3 NSCLC donors. Driver mutations included EGFR (N=3), KRAS (N=17), and NRAS (N=1) mutations, MET exon 14 skipping (N=1), and ALK (N=4) and ROS1 (N=1) fusions.

Conclusions: RTD enables the timely collection of high-quality tissue samples, allowing studies of tumor evolution, disease progression, therapeutic resistance, and heterogeneity within individual patients. Multiple lung cancer translational studies are in progress using these valuable post-therapy samples and data.

Keywords: rapid tissue donation autopsy, lung cancer, translational research



Female/Male (N)	19/15	9/14
Age (median, range)	62 (47-86)	68 (35-88)
Smoking history (N, %)	27 (79%)	21 (91%)
Overall survival (median, days)	944	379
Driver mutation (N, %)	27 (79%)	3* (13%)
Autopsy duration (median, hours)	13	8.5
Autopsy samples (N)		
Lung (FFPE)	35	31
Metastatic sites (FFPE)	185	150
Fresh samples for 3D tumor microculture	34	35

*3/23, including 2 that transformed from NSCLC, showed EGFR mutation.
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P1.06C PATHOLOGY AND BIOMARKERS - PATHOLOGY
SUNDAY, SEPTEMBER 8, 2024 - 12:00 - 14:00

P1.06C.03 Prediction of STAS by Intraoperative Frozen Section for cT1N0M0 Lung Adenocarcinoma: A Prospective, Multi-Center Clinical Trial (ECTOP-1016)

Y. Zhang, Fudan University Shanghai Cancer Center, Shanghai/CN

Introduction: Surgical decision-making based on frozen section (FS) diagnosis of tumor spread through air spaces (STAS) may be useful to prevent local control failure after sublobar resection. However, there is little evidence to demonstrate the diagnostic accuracy of identifying STAS as high-risk histologic features on FS.To investigate the value of intraoperative assessment of STAS on FS in peripheral small-sized lung adenocarcinoma.

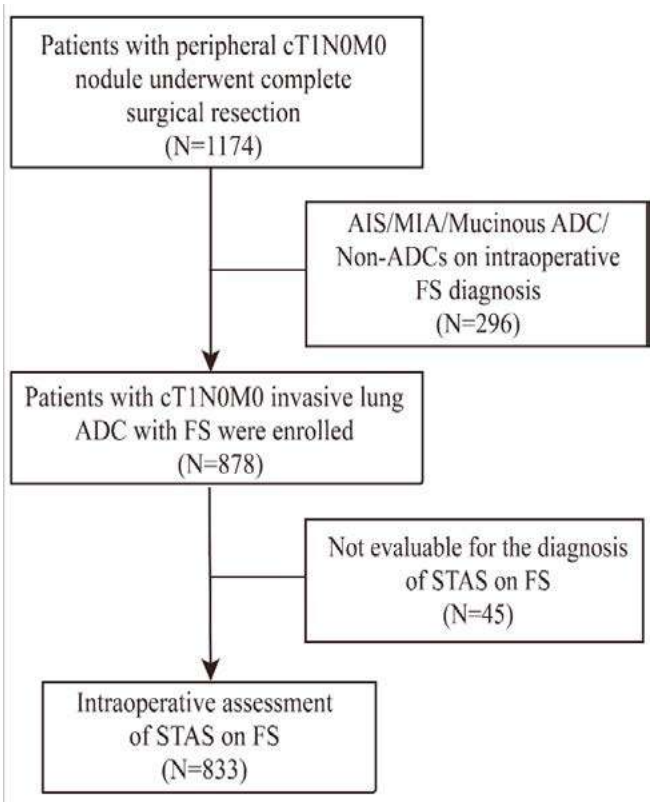
Methods: We conducted a prospective, multicenter (7 centers) study of consecutive patients with cT1N0M0 invasive lung adenocarcinoma to evaluate the accuracy of FS for intraoperative detection of STAS. The final pathology (FP) diagnosis of STAS was based on corresponding permanent paraffin sections. The inter-observer agreement for identifying STAS on FS was evaluated among three pathologists.

Results: The study included a cohort of 878 patients with cT1N0M0 invasive lung adenocarcinoma. 833 cases (95%) were assessable for STAS on FS. 26.4% of the cases evaluated positive for STAS on FP, whereas 18.2% on FS. The accuracy, sensitivity, and specificity of FS diagnosis of STAS were 85.1%, 56.4%, and 95.4%, respectively, with a moderate agreement (κ=0.575). Inter-observer agreement was substantial (κ=0.756) among three pathologists. Patients were further categorized based on tumor size or consolidation-to-tumor ratio for subgroup analysis of concordance, all with moderate agreement (κ: 0.54-0.58). After rigorous reassessment of false positive cases, the presence of artifacts may be the main cause of interpretation errors. Additionally, true positive cases showed more high-grade histological patterns and more advanced p-TNM stage than false negatives.

Conclusions: This is the largest prospective trial evaluating STAS on FS in cT1N0M0 invasive lung adenocarcinoma. FS is highly specific with moderate agreement but not sensitive for STAS detection. Appropriately reporting STAS on FS may provide surgeons with valuable information in intraoperative decision-making.

Keywords: STAS, Lung adenocarcinoma, Frozen section

	STAS (FP) +	STAS (FP) -	Total	
STAS (FS) +	124	28	152	Sensitivity=56.4%, NPV=85.9%
STAS (FS) -	96	585	681	Specificity=95.4%, PPV=81.6%
Total	220	613	833	Accuracy=85.1%, Kappa=0.575 (moderate)



P1.06C PATHOLOGY AND BIOMARKERS - PATHOLOGY
SUNDAY, SEPTEMBER 8, 2024 - 12:00 - 14:00

P1.06C.04 Low-Level Deletion of Chromosome 19p Genes May Be Sufficient to Drive Histology-Dependent Phenotypes in Lung Cancer

B. Henick, S. Mallick, N. Zhakula-Kostadinova, Y. Georgis, B. Herzberg, C. Concepcion-Crisol, A.M. Taylor, Columbia University, New York/NY/USA

Introduction: Deleterious mutations in chromosome 19p (chr19p) genes STK11/LKB1, KEAP1, and SMARCA4 have all been shown to contribute to lung adenocarcinoma biology and treatment response. However, the biological implications of low-level copy number deletion of chr19p have not been described.

Methods: We analyzed mutation, copy number, and gene expression data from non-small cell lung cancer cohorts in the Cancer Genome Atlas (TCGA), comparing lung adenocarcinoma with lung squamous cell carcinoma. For this dataset, we also evaluated immune infiltrate estimates calculated by methylation or gene expression patterns. In addition, we examined genomic data from immunotherapy-treated cohorts, including AACR Genie.

Results: Chr19p is frequently deleted across cancers in the TCGA dataset, with higher rates in lung adenocarcinoma. Immune infiltrate was significantly reduced in tumors with chr19p deletion when controlling for tumor type and overall copy number load; however, this was only observed in lung adenocarcinoma. The same was observed for low-level deletion of individual chr19p genes, including STK11 and KEAP1. Correlations of chr19p copy number and immune gene expression were also histology specific; chr19p loss significantly correlated with decreased immune signatures in lung adenocarcinoma and increased immune signatures in lung squamous cell carcinoma. Chr19p loss (or STK11 loss) also significantly correlated with STK11 deficiency based on gene expression patterns, again specific to lung adenocarcinoma. Based on these findings, we wanted to characterize the association between copy number of chr19p genes and immunotherapy response, turning to the AACR GENIE non-small cell lung cancer (NSCLC) biopharma collective (BPC) dataset. A subset of this cohort included patients treated with immunotherapy (atezolizumab, nivolumab, and/or pembrolizumab) and with copy number data available or GISTIC analysis of individual genes (n = 204). This subset largely comprised of lung adenocarcinoma patients. Here, deletion of any of these three chr19p genes correlated with worse overall survival, and this was statistically significant for STK11 deletion.

Conclusions: Overall, our analyses have found that (1) low-level copy deletion of chr19p genes can contribute to immune phenotypes and (2) there is a histology-specific effect of chr19p loss.

Keywords: genomics, immunobiology, histology

P1.06C PATHOLOGY AND BIOMARKERS - PATHOLOGY
SUNDAY, SEPTEMBER 8, 2024 - 12:00 - 14:00

P1.06C.05 The Impact of Lymphovascular Invasion as Prognostic Factor on Long-Term Survival in More Than 3500 Resected NSCLC Patients

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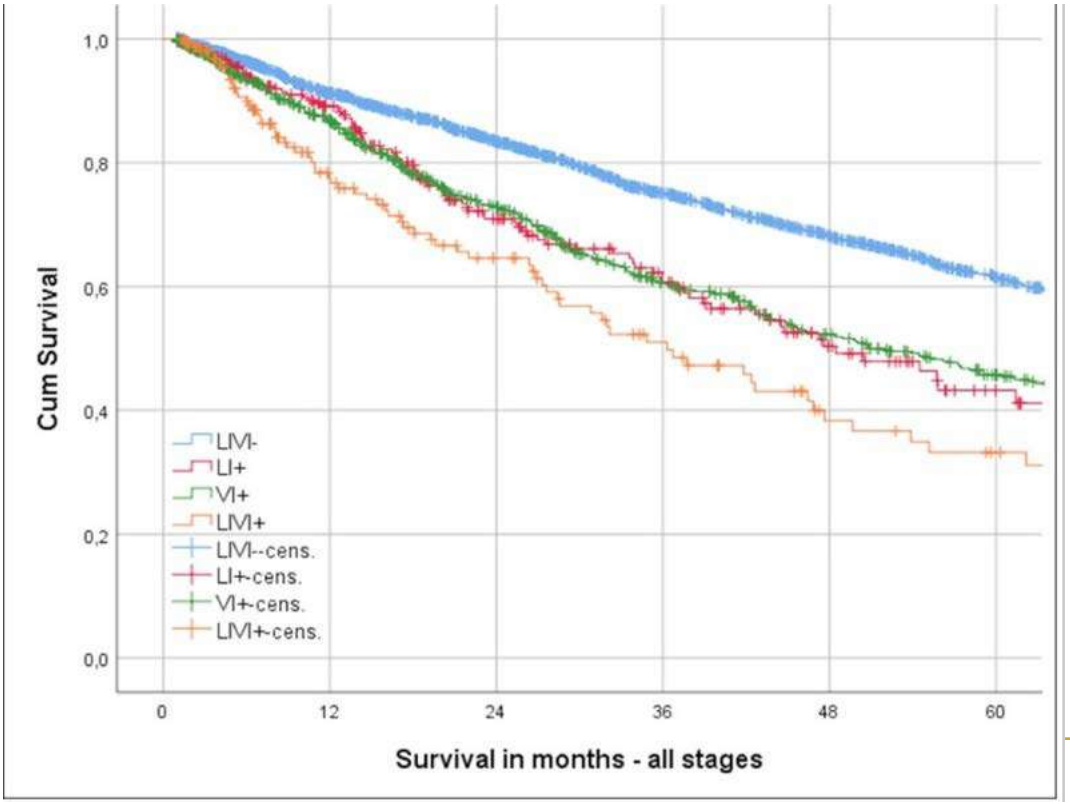
Introduction: The 9th edition of the IASLC TNM classification for NSCLC will not include lymphovascular invasion. We analyzed the significance of lymphovascular invasion and examined its influence on long-term survival in a large cohort of primary resectable NSCLC patients.

Methods: After applying the exclusion criteria (stage >IIIA, neoadjuvant therapy, positive resection margin, survival <90 days) we analyzed all consecutive adult patients who were resected at our institution between 2010 and 2022. Patients received adjuvant radio-/chemotherapy in accordance with current guidelines. We compared patients with lymphatic invasion (LI+), arterial/venous vascular invasion (VI+) and combined lymphovascular invasion (LIVI+) to a negative control group (LIVI-) after matching both cohorts according to the 8th edition of the IASLC TNM classification. Median-survival, 3- and 5- year survival rates and the hazard ratio (HR) for lymphovascular invasion were calculated.

Results: A total of 3,588 patients were included in this retrospective study. Mean age was 65.6±9.7 years and 56.6% (n=2031) of the patients were male. The right upper lobe was the most common tumor location (30.0%; n=1075) and adenocarcinoma (51.6%; n=1853) the most common histologic type. There were no significant differences between the groups (LIVI-: n=2409; LI+: n=279; VI+: n=735; LIVI+: n=165) in terms of stage, gender, age, histology, comorbidity and ECOG performance status. Stage-adjusted median survival in months was significantly longer for LIVI- patients (84.2±3.2) compared to patients with lymphovascular invasion (LI+: 48.5±5.3 vs VI+: 50.9±3.8 vs LIVI+: 36.3±5.3; p-value<0.0001). 3-year (LIVI-: 76.0% vs LI+: 59.6% vs VI+: 60.6% vs LIVI+: 48.5%; p-value<0.0001) and 5- year survival rates (LIVI-: 56.7% vs LI+: 25.4% vs VI+: 41.8% vs LIVI+: 25.0%; p-value=0.003) were significantly higher for patients without lymphovascular invasion. The hazard ratio (HR) for OS was 1.45 [95%-CI: 1.29-1.63] in case of lymphatic invasion, 1.27 [95%-CI: 1.19-1.35] in vascular invasion and 1.51 [95%-CI: 1.29-1.77] in a combined lymphovascular invasion. Survival was increased in node negative (LIVI-: 102.0±3.1 months vs LI+: 67.1±4.3 vs VI+: 66.5±7.0 vs LIVI+: 42.6±15.0; p<0.0001) versus node positive patients (LIVI-: 50.1±3.2 months vs LI+: 38.9±5.5 vs VI+: 41.3±4.2 vs LIVI+: 34.9±3.2; p=0.0029).

Conclusions: Our large single-institution analysis demonstrates the negative impact of lymphovascular invasion on long-term survival following NSCLC resection. While our findings are limited in their generalizability, this work could potentially serve as a foundation piece in advocating for the inclusion of lymphovascular invasion in subsequent IASLC classifications for NSCLC.

Keywords: NSCLC staging, lymphovascular invasion, long-term survival



P1.06C PATHOLOGY AND BIOMARKERS - PATHOLOGY
SUNDAY, SEPTEMBER 8, 2024 - 12:00 - 14:00

P1.06C.06 The Prognostic Impacts of Three Invasive Patterns in Pulmonary Peripheral Squamous Cell Carcinoma

H. Iguchi[1,2], Y. Hirai[1], T. Nakaya[1], A. Fusamoto[1], Y. Yata[1], Y. Mikasa[1], I. Matsuzaki[1], I. Hirai[2], S-I. Murata[1], Y. Nishimura[1], [1]Wakayama Medical University, Wakayama/JP ,[2]Naga Municipal Hospital, Kinokawa/JP

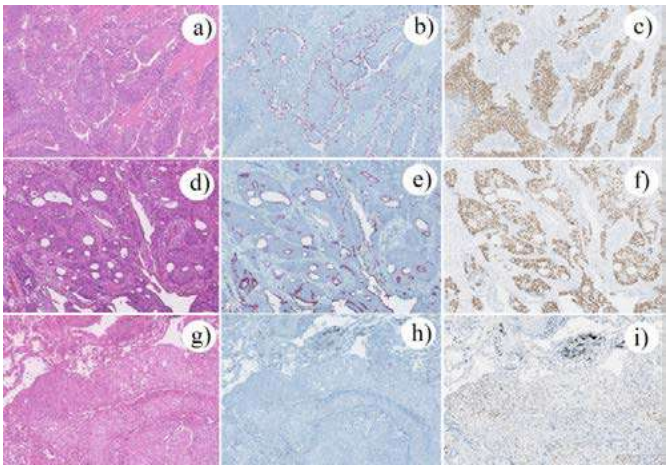
Introduction: Squamous cell carcinomas (SqCCs) account for ~20% of all non-small cell lung carcinomas. Despite advances in treatment strategies, SqCC prognosis is generally poor. Clinical trials have revealed the clinical utility of limited resection surgery for small pulmonary SqCCs. Therefore, determining the prognosis of surgically resected SqCCs is crucial. We explored the histopathological growth/invasive patterns of small SqCCs as a prognostic factor.

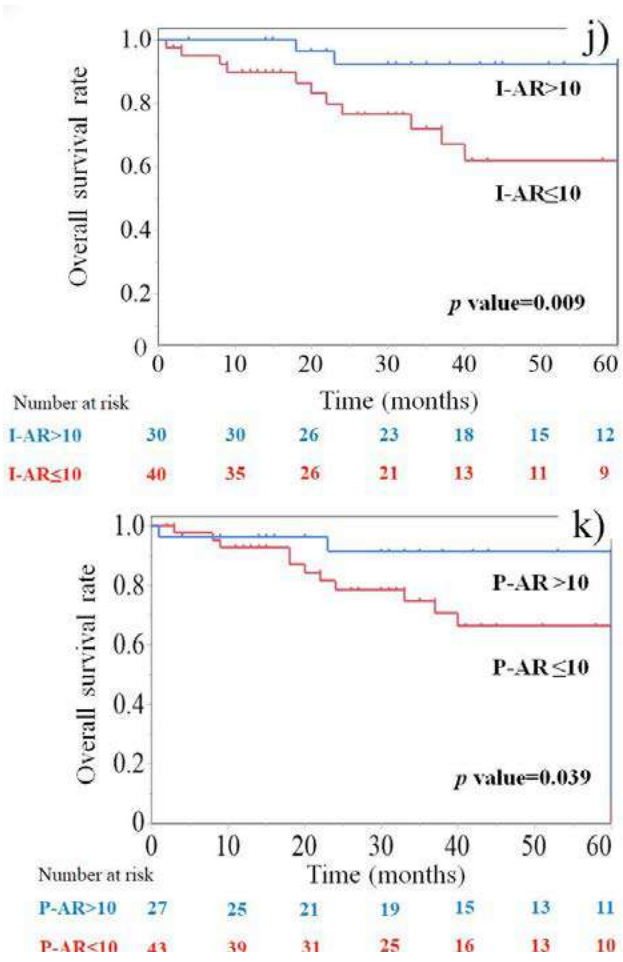
Methods: In this retrospective study, we analyzed data of 70 surgically resected cases of peripheral SqCCs at clinical stage I. We reviewed hematoxylin and eosin stained sections and TTF-1 and p40 immunohistochemically stained sections to evaluate peri- and intra-tumorous growth and invasive patterns in addition to quantitatively assessing the amount of alveolar structure remains.

Results: We found three distinct growth/invasive patterns of SqCCs with or without alveolar remains: intra-alveolar invasive pattern with alveolar remain (I-AR, Figure a-c), peri-alveolar invasive pattern with alveolar remain (P-AR, Figure d-f), and destructive invasive pattern with no alveolar remain (N-AR, Figure g-i) in 81.4%, 71.4% and 17.1% of the cases, respectively. Quantitative assessment of amount of intra-tumorous alveolar structure remains revealed that I-AR and P-AR values <10 and >11 showed significant differences in overall survival (p = 0.009 and 0.039, respectively, Figure j-k). Moreover, I-AR was an independent prognostic factor with excellent Hazard ratio (0.53). Pulmonary SqCCs show three distinct growth/invasive patterns with or without intra-tumorous alveolar remains. Amount of intra-tumorous alveolar remains is related with SqCC clinical prognosis.

Conclusions: This is the first report that growth/invasive patterns of SqCCs with intra-tumorous alveolar remains are strong prognostic factors.

Keywords: hide0512, hide0301, hide0710





P1.08A LOCAL-REGIONAL NON-SMALL CELL LUNG CANCER - ADJUVANT THERAPY
SUNDAY, SEPTEMBER 8, 2024 - 12:00 - 14:00

P1.08A.01 Identifying Candidates for Postoperative Radiotherapy in Patients with Non-Small Cell Lung Cancer: A Multicenter Study

Z. Ma[1], Z. Hui[1], [1]National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing/CN

Introduction: The value of postoperative radiotherapy (PORT) for patients with non-small cell lung cancer (NSCLC) is under great debate. This study aimed to evaluate the efficacy of a deep learning model in predicting disease-free survival (DFS) and to identify which patients could benefit from PORT.

Methods: Patients with histologically proven pN2 NSCLC who underwent complete resection were enrolled in one institution as the training set. Participants in the PORT-C randomized controlled trial were included as the test set. Patients across the other four independent medical centers were enrolled as external validation sets. A deep learning algorithm, DeepSurv, was trained on key clinicopathological variables. The model's performance was assessed using the concordance index (C-index). Patients were categorized into two subgroups based on DeepSurv recommendations: those recommended to receive PORT and those not. The clinical impact of model-recommended treatments was determined by comparing DFS in different subgroups of patients.

Results: The training, test, and external validation datasets comprised 1400, 364, and 841 individuals. DeepSurv demonstrated a C-index of 0.77 (CI, 0.75-0.78), 0.77 (CI, 0.74-0.79), and 0.70 (CI, 0.68-0.71) across these datasets, respectively. Patients were categorized into two subgroups based on DeepSurv recommendations: those recommended to receive PORT and those not. Within the training set, in the subgroup recommended for PORT, patients who received PORT demonstrated a significant improvement in median DFS (40.5 months, CI: 24.2-NA) compared to those who did not (24.9 months, CI: 18.5-31.6, P<0.01). Conversely, in the subgroup not recommended for PORT, no significant difference in median DFS was observed between those who underwent PORT (20.9 months, CI: 18.0 -36.8) and those who did not (24.9 months, CI: 21.4-32.3, P=0.74). The test and external validation set showed consistent results.

Conclusions: The deep learning model could predict DFS and tailor PORT for patients with NSCLC based on key clinicopathological variables.

Keywords: Survival, Surgery, Radiation therapy

P1.08B LOCAL-REGIONAL NON-SMALL CELL LUNG CANCER - BIOMARKERS FOR UNRESECTABLE NSCLC
SUNDAY, SEPTEMBER 8, 2024 - 12:00 - 14:00

P1.08B.01 Predicting Tumor Recurrence Risk in Locally Advanced NSCLC with Detectable ctDNA-Based Molecular Residual Disease: An Xgboost Model Analysis

Y. Pan[1], J-T. Zhang[1], X. Gao[2], Z-C. Jiao[2], Z-Y. Chen[1], H. Lin[1], S-Y.M. Liu[3], L-B. Tang[1], H-H. Yan[1], S. Dong[1], H-J. Chen[1], B-C. Wang[1], H-Y. Tu[1], X-N. Yang[1], J-J. Yang[1], W-Z. Zhong[1], Q. Zhou[1], Y-L. Wu[1,4], [1]Guangdong Lung Cancer Institute, Guangdong Provincial People's Hospital (Guangdong Academy of Medical Sciences), Southern Medical University, Guangzhou/CN ,[2]Geneplus-Beijing Institute, Beijing/CN ,[3]First Affiliated Hospital, Institute of Hematology, School of Medicine; Key Laboratory for Regenerative Medicine of Ministry of Education, Jinan University, Guangzhou/CN ,[4]Chinese Thoracic Oncology Group (CTONG), Guangzhou/CN

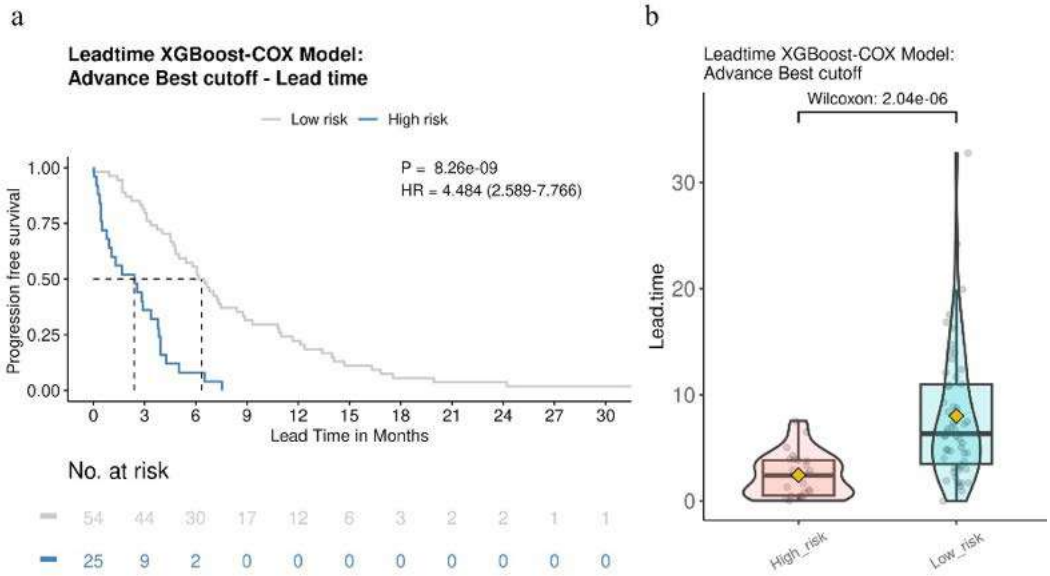
Introduction: Circulating tumor DNA (ctDNA)-based molecular residual disease (MRD) detection serves as a critical tool for monitoring disease recurrence after curative treatment in non-small cell lung cancer (NSCLC). Although detectable MRD indicates disease recurrence or progression, the variability in lead time, the interval from MRD detection to radiographical or clinical relapse, complicates its clinical utility, presenting a challenge for effective management.

Methods: We conducted an exploratory analysis within a cohort from our previous prospective study focused on dynamic ctDNA-MRD monitoring in locally advanced NSCLC patients undergoing chemoradiotherapy. This analysis included patients who presented with detectable MRD during surveillance. ctDNA alterations and their association with progression-free survival (PFS) and lead time were investigated. Significant variables were identified through univariate analysis and elastic net regression, followed by the development of a predictive model for lead time using the XGBoost algorithm.

Results: A total of 107 patients with detectable MRD were included, of which 79 experienced disease recurrence. The median age was 62(range 28-78), and 90.6% were male. The analysis revealed that higher ctDNA alteration copy numbers, increased tumor mutation burden (TMB), and the presence of pathogenic alterations were significantly associated with shorter lead time and poorer prognosis. Specifically, all 35 patients with a TMB ≥3 mutations per megabase experienced disease progression, demonstrating a notably shorter median lead time (4.97 vs. 7.12 months, p<0.0001) compared to those with a TMB <3. Furthermore, patients with pathogenic alterations identified in the ClinVar database at the time of MRD detection had a median lead time of 4.1 months, significantly shorter than those without such alterations. Multivariate analysis confirmed that ctDNA level, pathogenic alteration detection, and consistent detection of pathogenic alterations at both baseline and MRD detection were independent predictors of shorter lead time and adverse prognosis. A predictive model, empowered by a XGBoost algorithm-enhanced Cox regression, differentiated patients into high- and low-risk categories, where high-risk individuals had a shorter median lead time (2.4 vs. 6.3 months, HR=2.322 p<0.0001) and decreased 3-month PFS (36% vs. 80%, p<0.0001).

Conclusions: The clinical implications of detectable MRD in NSCLC may be different. High ctDNA levels and the presence of pathogenic alterations, especially those identified at both baseline and MRD detection, are associated with a higher likelihood ofrapid progression within 3 months. This study highlights the potential significance of ctDNA characteristics in stratifying recurrence risk and guiding clinical management strategies in NSCLC.

Keywords: circulating tumor DNA, molecular residual disease, lead time



P1.08B.02 Circulating T-Cell Immunosenescence in Patients with Unresectable Locally Advanced NSCLC: Preliminary Results of the SENLOAD Study

J.C. Benítez[1], M.v. SANCHEZ-BECERRA[2], N. Chaput[2], M. Naigeon[2], L. Cassard[2], L. Girard[2], D. Korera[2], N. Cozic[2], P. Lavaud[2], P. Abdayem[2], V. Albarragan-Artahona[2], A. Botticella[2], D. Planchard[2], J. Remon[2], F. Barlesi[2], C. Le Pechoux[2], B. Besse[2], A. Levy[2], [1]Gustave Roussy, Villejuif, Cedex/FR ,[2]Gustave Roussy Cancer Center, Villejuif, Cedex/FR

Introduction: Standard of care for patients with unresectable locally advanced (LA) non-small cell lung cancer (NSCLC) is concomitant platinum-based chemotherapy radiotherapy (CTRT) followed by anti-PD-L1 immune checkpoint blocker (ICB) durvalumab consolidation. The impact of T-cell immunosenescence, a mechanism of anti-PD-1/-L1 resistance in advanced NSCLC (aNSCLC), needs to be assessed in unresectable LA NSCLC. We present here the preliminary results of the SENLOAD study.

Methods: Blood samples at various timepoints were obtained for 60/117 planned patients enrolled within STING study (NCT04932525): baseline pre-CT (V0), before RT (V1), before ICB (V2), after 8 weeks of ICB (V3) and at progression (V4). The percentage of CD28-, CD57+, KLRG1+ among CD8+ T cells [senescent immune phenotype (SIP)] was assessed by blood flow cytometry. The primary goal is to evaluate SIP at baseline as prognostic factor of PFS in LA NSCLC receiving CTRT and ICB. A SIP cut-off of 39.5% was previously defined in aNSCLC.

Results: Median age was 62 (range, 38-77) years, most patients were male (63%) and the most frequent histology was adenocarcinoma (68%). Most tumors expressed PD-L1 (63%) and 20/60 of them (33%) were ≥50%. 48/60 patients (80%) received anti-PDL1 ICB and 12 (20%) did not receive ICB consolidation given progression or contraindication. 23/60 patients (38%) and 13/60 (22%) shown CRT- or ICB-related any grade toxicity. Median follow-up was 21 months. Mean PFS and OS were 23 months (95%CI 20-26.3) and 27 months (95%CI 24.6-29.8), respectively. The overall response rate of the whole cohort after CRT was 41.6% with a disease control rate of 75% for patients receiving durvalumab. The SIP+ results at each timepoint is shown in the Table 1. 30.4% and 14.2% SIP+ profile was found at baseline and at V2, respectively. Among 20 patients who experienced disease progression, 7 (35%) were SIP+ before ICB, including 2/20 (10%) who became SIP+ after CTRT. There were no differences between pts presenting ICB-related toxicity or not according to SIP+ profiles (15.4% vs 14.8%).

Conclusions: Circulating T-cell immunosenescence variations were observed along the course of treatment. We found 43% of senescence CD8-T during ICB progression. Assessment of Immunosenescence profile in stage III-NSCLC treatment strategy may contribute to improve personalization but did not seem related to toxicity. Further analyses are expected.

Keywords: unresectable stage III NSCLC, immunosenescnce, prognostic

SIP+ phenotype according to sample timepoints			
	N	SIP+	% SIP+
V0 (Pre-CT)	23	7	30.4
V1 (Pre-RT)	51	11	21.5
V2 (Post-RT)	42	6	14.2
V3 (8 weeks of ICB)	27	9	33.3
V4 (PD)	7	3	42.8

P1.08C LOCAL-REGIONAL NON-SMALL CELL LUNG CANCER - CLINICAL NEOADJUVANT
SUNDAY, SEPTEMBER 8, 2024 - 12:00 - 14:00

P1.08C.01 Targeted Therapy or Chemotherapy as Neoadjuvant Treatment for Resectable Stage II-IIIB EGFRm Lung Adenocarcinoma: A Study Between Four Cohorts

F-L. Lu, C. Lv, X. Yang, M.L. Zhuo, N. Wu, Beijing Cancer Hospital, Beijing/CN

Introduction: Neoadjuvant therapy is a promising strategy to reduce tumor size and increase the possibility of radical resection. Neoadjuvant chemotherapy and EGFR-TKIs therapy have both shown activity in previous studys. This study aimed to evaluate the efficacy of different neoadjuvant therapy for stage II-IIIB EGFR-mutant (EGFRm) NSCLC.

Methods: We selected two prospective study cohorts ("NEOS, ChiCTR1800016948" & "NEOIPOWER, NCT05104788") and retrospectively reviewed clinical records of stage II-IIIA lung adenocarcinoma patients treated with neoadjuvant targeted therapy or chemotherapy prior to surgery. The collected data were compared between the four groups of different neoadjuvant regimens: 1) chemotherapy group;2) first-generation EGFR-TKIs group;3) first-generation EGFR-TKIs plus chemotherapy group;4) third-generation EGFR-TKIs group.Tumor samples were collected for further sequencing analysis to explore resistance mechanisms.

Results: A total of 133 patients were enrolled, 32 patients in chemotherapy group;31 patients in first-generation EGFR-TKIs group;30 patients in first-generation EGFR-TKI (icotinib) plus chemotherapy group ("NEOIPOWER" study);40 patients in third-generation EGFR-TKI (Osimertinib) group ("NEOS" study). The baseline characteristics and clinical outcomes are shown in Table 1. Among all the four cohorts of patients who had completed the neoadjuvant treatment, the ORR as per RECIST were 40.6% (13/32), 45.2% (14/31), 83.3% (25/30) and 71.1 % (27/38). Logistic regression analysis identified neoadjuvant regimen significant correlation with ORR (p=0.001),while sex (p=0.467), smoking history(p=0.092), clinical staging (p=0.098) and EGFR mutation type (Exon 19 & 21, p=0.631) were not. Compared with neoadjuvant chemotherapy,the other three groups had higher ORR, with ORs of 1.204 (95% CI, 0.443-3.269), 7.308 (95% CI, 2.220-24.057) and 3.587 (95% CI, 1.327-9.699), in first-generation EGFR-TKIs, first-generation EGFR-TKI plus chemotherapy, and third-generation EGFR-TKI group, respectively. For pathological response assessment, 7.1% (2/28) and 10.7% (3/28) achieved a major pathological response (MPR) in first-generation EGFR-TKI plus chemotherapy group and in third generation EGFR-TKI monotherapy group, respectively. TRAEs were reported in 33 (82.5 %) of 40 patients in third-generation EGFR-TKI group, and in 25 (83.3 %) of 30 patients in first-generation EGFR-TKI plus chemotherapy group; of grades ≥3, 7.5 % occurred in third-generation EGFR-TKI group, and 13.3% occurred in first-generation EGFR-TKI plus chemotherapy group. No preoperative treatment-related AEs of grade 4 or 5 were observed.

Conclusions: Interim analysis from this study indicated that, compared with classical chemotherapy, neoadjuvant targeted therapy, especially third-generation EGFR-TKI and EGFR-TKI plus chemotherapy seemed to be more effective for patients with resectable stage II-IIIB EGFRm NSCLC, with higher radiographic response and tolerable toxic effects.

Keywords: Epidermal growth factor receptor mutation, neoadjuvant targeted therapy, neoadjuvant chemotherapy

	Chemotherapy	First-generation EGFR-TKIs	First-generation EGFR-TKI plus chemotherapy	Third-generation EGFR-TKI
No. of Patient	32	31	30	40
Median Age (years)	57.2(31,76)	62.5(46,79)	61(39,74)	63(47,76)
Sex				
Male	10	7	10	15
Female	22	24	20	25
Smoking				
Never	25	23	23	28
Previous	7	8	7	12
EGFR mutation				
Exon 19 del	15	17	12	20
Exon 21 L858R	13	13	18	20
Other	4	1	0	0
ECOG				
0	31	31	30	32
1	1	0	0	8
Clinical Staging				
II	10	17	15	14
III	22	14	15	26
Surgical resection				
R0	27	24	27	30
R1 / R2	5	7	1	2
Radiological Response				
PR	13	14	25	27
SD	19	17	4	11
PD	0	0	1	0
ORR	40.6%	45.2%	83.3%	71.1%

P1.08C LOCAL-REGIONAL NON-SMALL CELL LUNG CANCER - CLINICAL NEOADJUVANT
SUNDAY, SEPTEMBER 8, 2024 - 12:00 - 14:00

P1.08C.02 Revisiting the ACS 3N2 + 1N1 Mandate: Should Old Data Define Today's Standard?

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Introduction: In 2021, the American College of Surgeons Commission on Cancer introduced Operative Standard 5.8. The directive changed lymph node sampling recommendations from a total of 10 lymph nodes to 1 lymph node from a hilar (N1) station and another 3 from 3 separate mediastinal (N2) stations. Unfortunately, the research underlying this decision comes largely from a 2012 retrospective study of the SEER database from 1998 - 2002. The published findings reflect antiquated operative habits, and several metrics inconsistent with expected clinical outcomes. Worse, nothing in the study supports an oncologic principle that defines a specific number or pattern of required lymph nodes. We sought to reproduce this study with more current data and assist in clarifying surgical recommendations.

Methods: Data was queried from the SEER database. We collected information from 2018 - 2020 to ensure outcomes that shared staging criteria. We sought to emulate the 2012 study by evaluating survival in patients who underwent anatomic resection with and without mediastinal lymph node dissection.

Results: A total of 19,778 patients received a lobectomy or bi-lobectomy. Of those, 91.7% (n = 18,129) underwent MLD and 8.3% (n = 1,649) did not ($p < 0.0001$). There were another 531 patients who underwent pneumonectomy. Of those, 79.7% (n = 423) underwent MLD and 20.3% (n = 108) did not ($p < 0.0001$). Among patients who did not undergo MLD, 9.6% of patients were N1 (n = 229), and curiously 6% of patients were N2 (n = 114), and 12.2% of patients were N3 (n = 9). Additionally, 2.1% of patients undergoing MLD (n = 384) were classified as having stage IV disease. Patients who underwent MLD had significantly more lymph nodes removed at the time of surgery. The average number examined was 13.48 in patients who underwent MLD and 7.91 in patients who did not ($p < 0.0001$). Compared to patients who did not undergo MLD, patients who received a MLD were statistically significantly more likely to die from non-lung solid malignancy, cardiac disease, and other causes. They were less likely to die from lung cancer related causes, hematopoietic malignancy, and COPD. Performing a MLD carried a hazard ratio of 0.72 (95% CI 0.62 - 0.83). Though positive lymph nodes were associated with increased mortality (HR 1.06, 95% CI 1.04 - 1.08), there was no additional survival advantage to removing a greater quantity of lymph nodes (HR 0.99, 95% CI 0.99 - 1.00). Sub-group analysis will investigate the frequency of MLD in N0 and N1 patients, improved survival with MLD by N stage, and lung cancer specific mortality.

Conclusions: It comes as no surprise that MLD is associated with a decreased risk of mortality; lymph node sampling is essential for staging, procedural decision-making, and adjuvant therapy. However, the ACS has utilized a study to draw conclusions that are not supported and seeks to correct a problem that does not exist. Blanket policies have the potential to bottleneck safe surgical judgment and force hazardous dissection on vulnerable patients.

Keywords: Mediastinal Lymph Node Dissection, Lung Cancer, American college of surgeons

P1.08C LOCAL-REGIONAL NON-SMALL CELL LUNG CANCER - CLINICAL NEOADJUVANT
SUNDAY, SEPTEMBER 8, 2024 - 12:00 - 14:00

P1.08C.03 Updated Event-Free Survival of Tislelizumab Plus Chemotherapy Asneoadjuvant/adjuvant Therapy for Stage IIB-IIIC NSCLC (lungmark Study)

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Introduction: LungMark study is a phase II study investigating the feasibility of neoadjuvant PD-1 inhibitor tislelizumab with chemotherapy in patients with stage IIB-IIIC non-small-cell lung cancer (NSCLC). The preliminary results of this trial have been presented in 2023 ASCO abstract 8564, demonstrating a major pathological response (MPR) rate of 72.7% and a pathological complete response(pCR) rate of 47.7% in the surgical resection population. Here, we report the two-year event-free survival (EFS) rate of the study.

Methods: The study enrolled treatment-naïve patients with stage IIB-IIIC NSCLCs. Surgical resection was performed 4-6 weeks after 3~4 cycles of neoadjuvant PD-1 inhibitor tislelizumab (200mg), carboplatin (area under the curve 5), and pemetrexed (500 mg/m 2 for adenocarcinoma) or nab-paclitaxel (260 mg/m 2 for other subtypes) on day 1 of each 21-day cycle. Adjuvant tislelizumab monotherapy was followed for 1 year. The primary endpoint was the safety. EFS, MPR, pCR were set as secondary endpoints.This study is registered with ClinicalTrials.gov, NCT05244837.

Results: On March 15, 2024, the median follow-up duration was 24 (range: 12.8-20.0) months in the intention-to-treat population. Forty-four of the 53 (83.0%) enrolled patients underwent resection, in which 36 (67.9%) received tislelizumab monotherapy as adjuvant treatment following the operation with median 10 (range 1-13) cycles. Recurrence occurred in 36.1% of pts who had surgery. Possible reason for this result was that 23 patients (23/53, 43.4%) with stage IIIB/IIIC were enrolled in this trial. The median EFS was 30 (95%CI:23-NR) months in the intention-to-treat population, with a 12-month and 24-month EFS rates of 85.1% (95%CI:46.4-77.8) and 64.4%(95%CI:71.2-92.6), respectively. Patients who achieved MPR showed longer EFS as compared with those without MPR (median EFS: 39 vs.26 months).

Conclusions: Tislelizumab plus chemotherapy as a neoadjuvant treatment showed a promising pathological response and manageable TRAEs. Neoadjuvant and adjuvant tislelizumab combined with chemotherapy showed long-term EFS benefit in stage IIB-IIIC NSCLC.

Keywords: Neoadjuvant immunochemotherapy, Locally advanced NSCLC, Long-term survival

P1.08C LOCAL-REGIONAL NON-SMALL CELL LUNG CANCER - CLINICAL NEOADJUVANT
SUNDAY, SEPTEMBER 8, 2024 - 12:00 - 14:00

P1.08C.04 Delineating the Prognosis Spectrum: Disentangling Primary Tumor and Lymph Node Responses in NSCLC Following Neoadjuvant Immunotherapy

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Introduction: Neoadjuvant immunotherapy has emerged as a promising treatment paradigm for Non-Small Cell Lung Cancer (NSCLC). However, the discordance between primary tumor (PT) and lymph node (LN) response raises questions about their independent prognostic implications, especially considering that patients achieving pathological Complete Response (pCR) and Major Pathological Response (MPR) have shown better prognosis. This study aims to elucidate the independent prognostic implications of PT and LN response through semi-quantitative analysis.

Methods: In this retrospective study, we collated data from patients who received neoadjuvant immunotherapy between December 2018 and December 2023. A comprehensive record of demographics, disease characteristics, responses to neoadjuvant treatment, surgical techniques applied, post-operative outcomes, and survival rates was maintained. PT responses were meticulously categorized into eight groups based on the residual tumor burden: pCR (no residual tumor), 0-5%, 5%-10%, 10%-20%, 20%-30%, 30%-40%, 40%-50%, and over 50% residual tumor. LN responses were dichotomized into two broad categories: complete regression and incomplete regression. The impact of PT and LN responses on prognosis was assessed leveraging Cox regression model, which allowed us to estimate the independent effect of these variables on patient outcomes.

Results: The study population comprised 315 patients all treated with a uniform protocol of combinatory immunotherapy and chemotherapy. The R0 resection rate among these patients was remarkable, standing at 97.1% (306 patients). The median Disease-Free Survival (DFS) was 32.6 months (95% CI, 28.6-36.6). The median for Overall Survival (OS) was unreached. In six groups of patients with PT residual rates ranging from 0-5%, 5%-10%, 10%-20%, 20%-30%, 30%-40% to 40%-50%, there was an absence of tumor progression in patients demonstrating complete LN regression. Subsequently, patients were stratified into four groups: those with PT residual >50% and incomplete LN regression (PT>50%+nNpCR), those with PT residual >50% and complete LN regression (PT>50%+NpCR), those with PT residual <=50% and incomplete LN regression (PT<=50%+nNpCR), and those with PT residual <=50% and complete LN regression (PT<=50%+NpCR). Upon survival analysis, the median DFS for the four groups were reported as follows - PT<=50%+NpCR: 40.0 months (95% CI, 36.4-43.6), PT>50%+NpCR: 28.1 months (95% CI, 20.3-35.9), PT<=50%+nNpCR: 25.5 months (95%CI, 19.3-31.6), and PT>50%+nNpCR: 9.8 months (95% CI, 2.8-16.9).

Conclusions: The findings highlight the paramount significance of LN response over PT response in determining prognosis post-neoadjuvant immunotherapy in NSCLC. The beneficial influence of complete LN regression on survival outcomes underscores the need for further large-scale prospective studies to validate these findings. Additionally, mechanistic exploration targeting this phenomenon could lead to more personalized therapeutic interventions.

Keywords: Prognosis Spectrum, Neoadjuvant Immunotherapy, Quantitative Analysis

P1.08C LOCAL-REGIONAL NON-SMALL CELL LUNG CANCER - CLINICAL NEOADJUVANT
SUNDAY, SEPTEMBER 8, 2024 - 12:00 - 14:00

P1.08C.05 The Clinicopathological and Prognostic Significance of Skip-N2 Metastases: A Retrospective Multicenter Study

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Introduction: The skip N2 lymph node metastases, defined as mediastinal lymph node involvement (pN2) without hilar and intrapulmonary lymph nodes (pN1), frequently occur in non-small cell lung cancer (NSCLC). It has been reported that skip-N2 present a better prognosis compared to the non-skip-N2 metastases. However, the factors associated with skip-N2 remain controversial. This study aimed to investigate the clinicopathological features associated with skip-N2 and its impact on the survival in patients with clinical-N0 (cN0) NSCLC.

Methods: A retrospective multicenter study involving 22 institutions was conducted. The medical records of patients with cN0pN1-2 NSCLC between January 2012 and December 2021 were reviewed. Patients were categorized into three groups: pN1 group, skip-N2 group, and non-skip-N2 group (pN1N2), and clinical, radiological, and pathological findings were analyzed. Disease staging was reassigned according to the 8th edition of the TNM staging system.

Results: A total of 757 patients who underwent pulmonary resection with mediastinal lymph node dissection (ND2a-1 or ND2a-2) were enrolled. The median age at the time of surgery was 70 years (range, 28-90), and 473 patients were male. The clinical T categories were Tis (n = 1), T1 (n = 357), T2 (n = 307), T3 (n = 72), and T4 (n = 20). CT findings showed pure-solid tumors (n = 645), part-solid tumors (n = 111), and a ground-glass tumor (n = 1). Pleural attachment and indentation were observed in 552 cases. Tumors were located in the right upper lobe (n = 213), right middle lobe (n = 34), right lower lobe (n = 190), left upper lobe (n = 172), and left lower lobe (n = 148). Tumor histological types were adenocarcinoma (n = 554), squamous cell carcinoma (n = 153), and others (n = 50). The pathological nodal statuses were pN1 (n = 357) and pN2 (n = 400). Among pN2 cases, 175 cases (44%) were skip-N2. Tumor location on the right side (p = 0.003), contact with the pleura (p < 0.001), peripheral lesion (p = 0.007), pl-positive (pl1-3)(p = 0.004), Ly0 (p = 0.001), and v0 (p = 0.023) were significantly related to skip-N2. In total group, the median follow-up was 3.6 years, and the 3-, 5-year overall survival rates (OS) were 75.6% and 60.8%, respectively. The 5-year OS was 62.7% in pN1, 65.3% in skip-N2, and 54.3% in non-skip-N2. Skip-N2 had significantly better prognosis compared to non-skip-N2 (p = 0.010), and rather demonstrated a prognosis similar to pN1.

Conclusions: Skip-N2 disease occurs frequently and has a favorable outcome with curative surgical resection. Standard hilar and mediastinal lymph node dissection should be required, especially in the patients with NSCLC with pleural attachment on the right side.

P1.08D LOCAL-REGIONAL NON-SMALL CELL LUNG CANCER - UNRESECTABLE NSCLC
SUNDAY, SEPTEMBER 8, 2024 - 12:00 - 14:00

P1.08D.01 The Efficacy of Durvalumab after Concurrent Chemoradiotherapy for EGFR-Mutated Stage III Non-Small Cell Lung Cancer (NEJ063)

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Introduction: The consolidation therapy of durvalumab after chemoradiation therapy (CRT) has been shown to improve prognosis in unresectable stage III non-small cell lung cancer (NSCLC). However, the efficacy of durvalumab after CRT in EGFR-mutated NSCLC and the safety of EGFR-TKI after durvalumab is unknown. The aim of this study is to evaluate the efficacy and the safety of durvalumab after concurrent CRT (CCRT) in EGFR-mutated NSCLC patients (pts).

Methods: We conducted a multicenter (48 centers in Japan) retrospective cohort study of consecutive EGFR mutated stage III NSCLC patients who received radical CCRT between July 2015 to June 2022, and compared outcomes in patients who received durvalumab with those who did not. On survival analysis, we excluded pts whose genetic testing were performed after recurrence after CCRT and used propensity score matching based on prespecified explanatory variables. Furthermore, to align the observation periods as much as possible, we prespecified the maximum observation period was 3 years for the progression-free survival (PFS), 4 years for other analysis. In addition, we examined the safety of EGFR-TKI as posttreatments in both groups.

Results: A total of 207 pts were enrolled: pts with durvalumab were 134, pts with CRT alone were 73, 190 pts were eligible for survival analysis: pts with durvalumab were 123, pts with CRT alone were 67. After propensity score matching, there were no significant differences in patient background between pts with durvalumab (N=65) and pts with CRT alone (N=65): median (range) age 69 (44-85) vs 68 (40-84); 38 (58.5%) vs 41 (63.1%) female; 35 (53.8%) vs 36 (55.4%) Stage IIIA, 24 (36.9%) vs 25 (38.5%) IIIB, 6 (9.2%) vs 4 (6.2%) IIIC; 61 (93.8%) vs 62 (95.4%) Adenocarcinoma, 3 (4.6%) vs 2 (3.1%) Squamous cell carcinoma, 1 (1.5%) vs 1 (1.5%) Not otherwise specified; 31 (47.7%) vs 23 (35.4%) Exon 21 L858R, 26 (40.0%) vs 31 (47.7%) Exon 19 deletion, 1(1.5%) vs 1 (1.5%) Exon 20 insertion, 7 (8.8%) vs 10 (15.4%) other uncommon or compound. The median PFS of pts with durvalumab was significantly longer than that of pts with CRT alone (23.0 months (95%CI, 15.8-NA) vs 12.1 months (9.4-21.0); hazard ratio (HR) 0.56 (95%CI, 0.36-0.87); p=0.009). PFS rates of 1y, 2y, 3y, were 71.7% (95%CI, 58.9-81.1) vs 50.7% (37.8-62.3), 48.5% (35.6-60.3) vs 27.9% (17.1-39.7), 41.7% (28.7-54.2) vs 20.0% (10.7-31.4), respectively. There was no statistically significant difference in median overall survival (OS) between pts with durvalumab and pts with CRT alone (HR 0.63 (95%CI, 0.29-1.38); p=0.25). OS rates of 1y, 2y, 3y, 4y were 98.4% (95%CI, 89.3-99.8) vs 92.1% (82.0-96.6), 91.7% (81.2-96.5) vs 83.5% (71.4-90.8), 80.7% (66.6-89.3) vs 75.4% (61.8-84.7), 80.7% (54.1-79.4) vs 68.7% (54.1-79.4), respectively. There were no differences in the frequency of adverse events ≥CTCAE grade 3 of subsequent EGFR-TKIs between both groups (27.8% vs 26.0%, p=1.0).

Conclusions: In our real-world data for EGFR-mutated stage III NSCLC, durvalumab after CCRT improved PFS and did not increase the frequency of adverse events ≥CTCAE grade 3 of subsequent EGFR-TKI compared with CRT alone.

Keywords: NSCLC, EGFR, Durvalumab

P1.08D LOCAL-REGIONAL NON-SMALL CELL LUNG CANCER - UNRESECTABLE NSCLC
SUNDAY, SEPTEMBER 8, 2024 - 12:00 - 14:00

P1.08D.02 Survival after Salvage Treatment Following Durvalumab Consolidation in Locally Advanced Non-Small Cell Lung Cancer (LA-NSCLC)

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Introduction: PACIFIC established adjuvant durvalumab as standard of care in LA-NSCLC, but only about half of enrollees completed 1 full year of therapy due either to toxicity or progression. Data on practice patterns and outcomes after durvalumab treatment are limited. We sought to investigate nationwide treatment practices and survival in patients who received systemic therapy after consolidative durvalumab.

Methods: Our analysis included adult patients (pts) from the Flatiron Health electronic health record-derived database with LA-NSCLC who received at least one dose of consolidative durvalumab between 2017-2023 and had subsequent systemic therapy, classified as PD-(L)1 monotherapy, PD-(L)1+chemotherapy, chemotherapy alone, PD-(L)1+CTLA4, or targeted therapy (TT). Time to next treatment (TTNT) was analyzed from durvalumab start and finish to next line of therapy. Overall survival (OS), defined from start of post-durvalumab therapy to death or censoring at last contact, was analyzed using Kaplan Meier methodology.

Results: Our cohort included 751 pts, median age 68 (IQR 61-74), 53% female, 80% White, 91% ECOG 0-1, 90% smoking history, and 53% non-squamous histology. Of 482 pts with known PD-(L)1 expression, distribution of 0%/1-49%/≥50% was 41%/36%/23%, respectively. The most common post-durvalumab treatment was chemotherapy alone in 349 (46%), followed by PD-(L)1+chemotherapy in 147 (20%), PD-(L)1 monotherapy in 114 (15%), and TT in 104 (14%), which was most commonly osimertinib (24%) or alectinib (14%). Median duration of durvalumab treatment was 5.5 months (IQR 2.3-10.6); only 9% of patients received a full year of durvalumab, and 64% started next treatment within a year of durvalumab initiation. TTNT from durvalumab start/end was shorter in the chemotherapy and TT cohorts compared to the PD(L)1 +/- CTLA4 cohorts (Table 1). Median OS from post-durvalumab therapy initiation was 10.8 (5.6-18.8) mos in the chemotherapy cohort and 12.9 (6.0-24.2) mos in the chemoimmunotherapy cohort, versus 23.8 (8.7-34.5) mos in the PD-(L)1 monotherapy and 30.1 (9.5-NR) mos in the TT cohorts (p<0.001).

Conclusions: In a real-world cohort of pts receiving salvage therapy after durvalumab consolidation for LA-NSCLC, majority received less than 6 months of durvalumab, had subsequent therapy within a year of durvalumab initiation, and were treated with chemotherapy-based approaches. This cohort had a poorer mOS (10-13 months) compared to the expected contemporary mOS for pts with de novo recurrent/metastatic disease, likely reflecting poor prognosis in pts who were refractory or resistant to immunotherapy. Overall, this study shows a high prevalence of rapid disease progression after durvalumab, and highlights the need for better treatment strategies.

Keywords: locally-advanced NSCLC, post-durvalumab, overall survival

Treatment Category	Patients (n)	Median Mos from Durvalumab Start to Subsequent Therapy (IQR)	Median Mos from Durvalumab End to Subsequent Therapy (IQR)	Median Overall Survival from Start of Post-durvalumab Therapy, mos (IQR)
Chemotherapy	349	8.0 (4.4-13.0)	1.8 (0.9-5.2)	10.8 (5.6-18.8)
Chemotherapy + PD-(L)1	147	8.3 (3.9-17.7)	1.5 (0.9-7.2)	12.9 (6.0-24.2)
PD-(L)1 monotherapy	114	14.2 (6.2-20.8)	3.3 (1.4-11.6)	23.8 (8.7-34.5)
PD-(L)1+CTLA4	37	14.0 (8.5-21.9)	5.5 (1.7-13.2)	12.7 (4.5-20.7)
Targeted Therapy	104	7.6 (5.0-13.7)	1.9 (1.0-4.9)	30.1 (9.5-NR)

P1.08D LOCAL-REGIONAL NON-SMALL CELL LUNG CANCER - UNRESECTABLE NSCLC
SUNDAY, SEPTEMBER 8, 2024 - 12:00 - 14:00

P1.08D.03 Induction Durvalumab Followed by Chemoradiation and Consolidation Durvalumab for Stage III Non-Small Cell Lung Cancer (NSCLC)

R.E. Sanborn[1], D. Hanes[2], D. Shaker[3], M.J. Fidler[4], S. Gurubhagavatula[5], S-C. Chang[2], W.L. Redmond[1], [1]Earle A. Chiles Research Institute, Providence Cancer Institute, Portland/OR/USA ,[2]Providence Cancer Institute, Portland/OR/USA ,[3]Cancer Center of Kansas, Wichita/KS/USA ,[4]Rush University Medical Center, Chicago/IL/USA ,[5]Summit Health, Florham Park/NJ/USA

Introduction: Concurrent chemoradiation followed by consolidation durvalumab (D) is the current gold standard for patients (pts) with unresectable stage III NSCLC, based on the PACIFIC trial (including 12-month progression-free survival (PFS), measured starting after chemoradiation, reported as 55.9%). Our study evaluated the addition of induction D prior to concurrent chemoradiation and consolidation D to assess for potential improvement in 12-month PFS compared with PACIFIC as historical control.

Methods: This was a single arm study of 1 dose induction D, 1500 mg IV prior to concurrent chemoradiation, followed by consolidation D (1500 mg IV every 4 weeks) for up to 12 cycles after completion of radiation. Study plan was for safety run-in of 10 patients enrolled, followed by completion of accrual with 54 total planned patients. Primary objectives were 12-month PFS measured from completion of chemoradiation, safety, and feasibility. Exploratory objectives: Objective response rate (ORR); outcomes based on PD-L1, TMB status; banking for future correlative studies.

Results: Enrollment was halted after 10 pts were enrolled due to pandemic-related slow accrual. Pt characteristics included 6 male/4 female; mean age 67; 7 White/2 Black/1 Asian; 4 adenocarcinoma/1 adenosquamous/5 squamous. Chemotherapy: Carboplatin/paclitaxel (8); carboplatin/pemetrexed (1); cisplatin/etoposide (1). No pts progressed prior to consolidation, and all pts were able to receive consolidation D. Median number of consolidation D cycles was 7.5 (range 2-12). Outcomes: ORR: 70%; 12-mo PFS: 30%. There was no deepening of response during consolidation. 2 pts had complete response (CR) after chemoradiation and remain in CR. 7 pts progressed during consolidation. No signal relating to PD-L1 expression level and PFS was noted. All 3 pts who had high TMB (by institutional standard of care testing) were without progression at 12 months. All 7 pts with progression had tumors that were TMB low or unknown. No new safety signals were identified. Notable toxicities attributed to D included pneumonitis, hypothyroid, elevated creatinine, thrombocytopenia (1 pt each, grade 2), infusion reaction, dyspnea, neutropenia (1 pt each, grade 3), all during consolidation.

Conclusions: Conclusions are limited due to the small number of patients in this trial which closed early due to pandemic-related slow accrual. No new safety signals were seen with the addition of a single dose of induction D prior to chemoradiation and consolidation D. The initial 12-month PFS of 30% is disappointing, although not statistically significant as intended to compare with historical control. Interestingly, all 3 pts progression-free at 12 months had high TMB, without apparent relation to PD-L1 status.

Keywords: Induction, Durvalumab, Stage III

P1.08D LOCAL-REGIONAL NON-SMALL CELL LUNG CANCER - UNRESECTABLE NSCLC
SUNDAY, SEPTEMBER 8, 2024 - 12:00 - 14:00

P1.08D.04 The Clinical Outcomes of Contralateral Esophagus Sparing IMRT in Concurrent Chemoradiotherapy for Stage III Lung Cancer

H. LIM[1], K. Yang[1], J.M. Noh[1], H. Pyo[1], D.Y. Kwon[1], J.M. Kim[1], S.G. Ju[1], Y.C. Ahn[1], [1]Samsung Medical Center, Seoul/KR

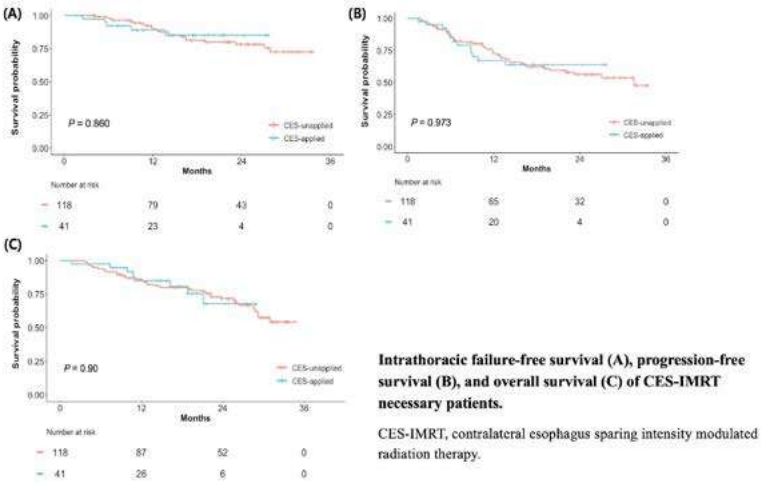
Introduction: Radiation esophagitis is frequent and annoying toxicity in high dose thoracic radiation therapy. Contralateral esophagus sparing intensity modulated radiation therapy (CES-IMRT) has been proposed to mitigate this problem, and this is to report impact of CES-IMRT in definitive concurrent chemoradiotherapy (dCCRT) for lung cancer patients.

Methods: From January 2021 till May 2023, 183 stage III non-small cell lung cancer patients underwent dCCRT. Esophagus was located within 1 cm from internal target volume in 159 patients. We comparatively evaluated frequency and severity of esophagitis by pain-killer usage, analgesic quantification algorithm (AQA) score, and failure patterns in 159 CES-necessary patients.

Results: All patients underwent dCCRT (66 Gy in 30 fractions with concurrent chemotherapy). Actual CES-IMRT application was determined based on discretion of responsible radiation oncologists: CES-applied in 41 patients; and CES-unapplied in 118. CES-applied patients experienced pain events less frequently (pain-killer usage: 53.7% vs. 77.1%, p=0.008) and less severely (AQA score of 2-3: 39.0% vs. 68.6%, p=0.002). On multivariate analyses, overlapping volume of esophagus and planning target (HR = 1.32, 95% CI 1.12~1.55, p=0.001) and CES-IMRT application (HR = 0.31, 95% CI 0.13~0.76, p=0.010) were associated with AQA score of 2-3 less frequently. There were no differences in failure pattern, progression-free survival, and overall survival.

Conclusions: CES-IMRT application resulted in less frequent and less severe pain events without compromising oncologic outcomes. Further studies, preferably in a randomized fashion, would be desired.

Keywords: Locally advanced non-small cell lung cancer, CES-IMRT, Radiation esophagitis



Intrathoracic failure-free survival (A), progression-free survival (B), and overall survival (C) of CES-IMRT necessary patients.

CES-IMRT, contralateral esophagus sparing intensity modulated radiation therapy.

**P1.09A METASTATIC NON-SMALL CELL LUNG CANCER &NDASH; LOCAL THERAPIES - RADIATION **
SUNDAY, SEPTEMBER 8, 2024 - 12:00 - 14:00

P1.09A.01 The Effectiveness of Split-course Stereotactic Body Radiation Therapy in Treating Large Thoracic Cancer

S. Tian[1], Y. Jie[2], L. Shang[1], C. Wang[1], M. E[1], A. Gu[1], [1]HarbinMedicalUniversityCancerHospital, Harbin/CN ,[2]Harbin Medical University Affiliated Fourth Hospital, Harbin/CN

Introduction: Single-course SBRT for large thoracic tumors often results in heavy injury to normal tissue. In this study, we investigated the effectiveness and safety of split-course stereotactic body radiation therapy (SBRT) in patients diagnosed with large thoracic cancer that is inoperable. The inclusion criteria were tumors larger than 5 cm, central and ultra-central large tumors, and the larger one in pulmonary oligometastases. Our aim is to achieve superior local tumor control while mitigating adverse events.

Methods: Based on tumor location, pathological and imaging evaluations, we designed personalized treatment plans, with most patients receiving doses ranging from 50 to 70 Gy in 10 fractions, split into two phases of radiotherapy with a gap of 3 weeks between them. Evaluations of local tumor control were conducted during treatment, at 4 weeks post-treatment, and then every 3 months thereafter. The Kaplan-Meier method was used to calculate local control (LC), local area control (LRC), progression-free survival (PFS), overall survival (OS), and treatment-related toxicity.

Results: From April 2023 to February 2024, 52 patients were enrolled in our study. By the end of March 2024, 44 of these patients had completed split-course SBRT. The median follow-up is 3.2 months. The proportions of complete response (CR), partial response (PR), and stable disease (SD) were 45.5%, 47.7%, and 2.3%, respectively. In terms of long-term efficacy, due to the limited follow-up time, the local control rate at 6 months was 95.8%. The 6-month recurrence-free survival rate (PFS) was 70.8%. In terms of toxicity and side effects, some patients (36.4%) only had grade 1-2 toxicity, and only 1 patient (2.3%) had grade 3 dyspnea toxicity.

Conclusions: Split-course SBRT effectively enhances local control for large thoracic cancers, with minimal toxicities. However, the integration of biomarkers is essential to evaluate tumor local-contorl in future.

Keywords: stereotactic body radiation therapy (SBRT), large thoracic tumors, split-course radiation therapy

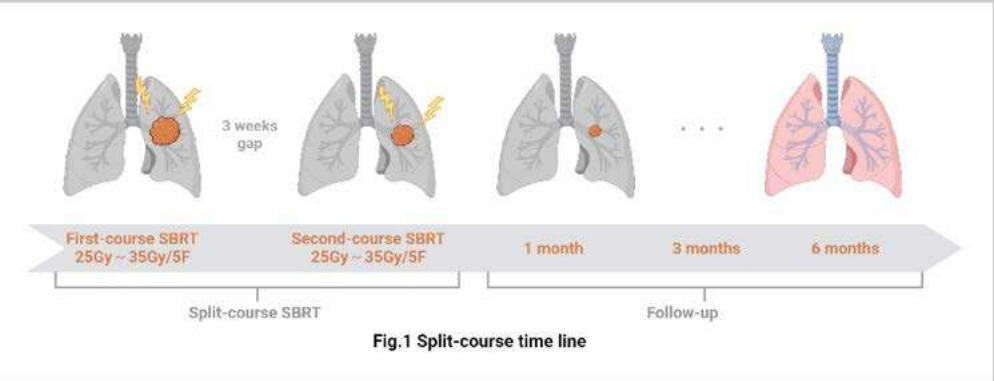


Fig.1 Split-course time line

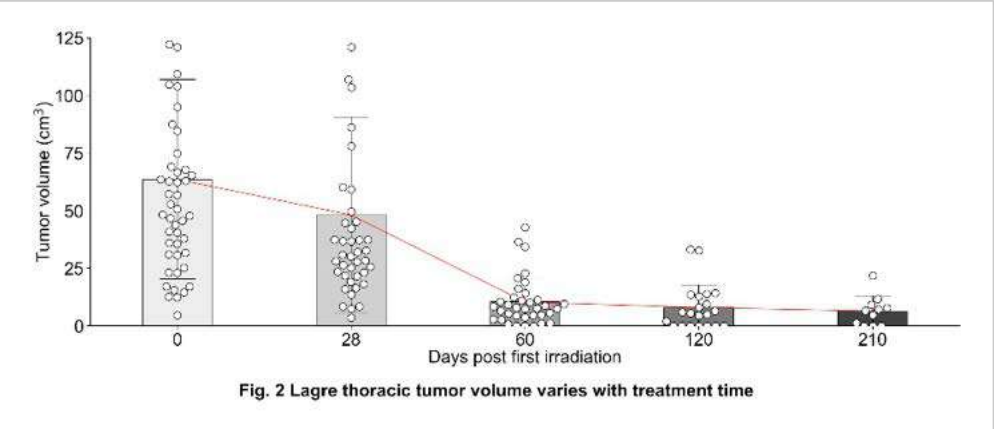


Fig. 2 Lagre thoracic tumor volume varies with treatment time

**P1.09A METASTATIC NON-SMALL CELL LUNG CANCER &NDASH; LOCAL THERAPIES - RADIATION **
SUNDAY, SEPTEMBER 8, 2024 - 12:00 - 14:00

P1.09A.02 Pathologic Tumor Positivity vs Only Necrosis in Clinically Suspected Recurrent Brain Metastasis Post-Radiation

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Introduction: For recurrent brain metastasis (RBM), determining progression after previous radiation therapy (RT) by imaging alone can be challenging, and on pathology, necrosis and tumor frequently co-exist. To better understand the rate of pathologic tumor positivity (TUM+) vs necrosis without tumor (TUM-), we examined frozen section results in a cohort of patients with prior same site RT undergoing resection of presumed RBM.

Methods: We examined the rates of intraoperative pathology disclosing tumor (TUM+) or necrosis without tumor (TUM-) in patients with presumed RBM and prior same-site RT undergoing a planned resection. All cases had been prospectively enrolled on a multi-institution registry of patients undergoing resection and intraoperative placement of cesium-131 collagen tile brachytherapy (NCT04427384) (GammaTile, GT Medical Technologies, Tempe AZ, USA). Preoperative evaluation varied by center; we also examined patient demographics, primary site, lesion size, and prior therapies.

Results: From Oct2020 to Feb2024, 60 patients with 64 lesions and prior same-site RT underwent open resection and intraoperative pathology evaluation. Per patient, primary sites were lung in 53%, melanoma 15%, breast 13%, renal 7%, and other 10%. Median age was 62 (range 28-81), F:M 31:29, maximum preoperative diameter was 2.9 cm (range 1.4-5.7), and median KPS was 80 (range 50-100). Time from last RT was 15.4 months (range 1-69). On a per patient basis across all histologies, TUM+ was found in 88% (53/60) and TUM- in 12% (7/60). Per patient rates of TUM- varied by cancer primary, with lung showing the highest rate at 16%, breast 13%, and melanoma 11% (Table 1). Taken together, the TUM- rate for non-lung primary metastasis was 7% vs 16% for lung origin. All TUM- patients received RT+prior chemotherapy, immunotherapy, or both.

Conclusions: This multi-institutional sample of previously irradiated metastasis, the frozen section pathology demonstrated a 12% rate of TUM- for all cancers and 16% for lung cancer. As they necessitated surgery, the adverse event RT injury grading would be > Gr 4. These findings highlight the importance of pathologic confirmation before undertaking re-irradiation, as the optimal treatment of RT injury is not additional radiation.

Keywords: Brain, Necrosis, Radiotherapy

TABLE 1

Primary sites, findings	# patients/#operated lesions	% patients/lesions
All:	60/64	100/100% of series
--TUM+:	53/56	88/87%
--TUM-:	7/8	12/13%
Lung primary:	32/33	53/52% of series
--TUM+:	27/27	84/82%
--TUM-:	5/6	16/18%
Non-Lung primary:	28/31	47/48% of series
--TUM+:	26/29	93/94%
--TUM-:	2/2	7/6%
Melanoma:	9/10	15/16% of series
--TUM+:	8/9	89/90%
--TUM-:	1/1	11/10%
Breast:	8/10	13/16% of series
--TUM+:	7/9	88/90%
--TUM-:	1/1	13/11%
Renal:	4/4	7/6% of series
--TUM+:	4/4	100/100%
--TUM-:	n/a	0/0%
Other*:	6/6	10/9% of series
--TUM+:	5/5	100/100%
--TUM-:	n/a	0/0%

*2 Colon, 2 Uterine, 1 GIST, 1 Cervical

**P1.09A METASTATIC NON-SMALL CELL LUNG CANCER &NDASH; LOCAL THERAPIES - RADIATION **
SUNDAY, SEPTEMBER 8, 2024 - 12:00 - 14:00

P1.09A.03 Concurrent Combination of EGFR-TKIs and Thoracic Radiation Therapy for Metastatic Non Small Cell Lung Cancer Patients

M. Yoshida, T. Fujii, K. Shida, C. Osumi, T. Fujii, A. Kawata, T. Kishigami, Y. Nishimoto, M. Hasegawa, M. Kikuchi, T. Gomi, Toho University Ohashi Medical Center, Tokyo/JP

Introduction: Epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) has asignificant therapeutic effect in the treatment of metastatic non-small-cell lungcancer (NSCLC) patients with EGFR mutations.In addition, EGFR-TKIs exhibits a radiosensitizing effect in preclinical models.However, the tolerability and the efficacy of EGFR-TKIs plus concurrent thoracicradiation therapy has not been well investigated.

Methods: We conducted this retrospective study to review medical records and database of patients who received radiation therapy from October 2018 to December2023.We extracted the patients from the database who underwent the concurrent combination of EGFR-TKIs and thoracic radiation therapy and analyzed the treatment outcomes and toxicities.

Results: Among 157 NSCLC patients who were treated with radiation therapy fromOctober 2018 to December 2023, 3 cases underwent the concurrentcombination of EGFR-TKIs and thoracic radiation therapy. One patient who had exon 19 deletion mutation underwent radiation therapy for mediastinal lymph nodes with intake of erlotinib. Another patient who had exon 21 L861Q mutation underwent radiation therapy for lung, and later formediastinal lymph nodes with intake of osimertinib.The median follow-up period was 19.0 (range 7-33) months. ECOG performance status (PS) 0/1/2 were 1/1/1 respectively.The prescribed radiation dose was 60-66 Gy in 30-33 fractionations usingvolumetric modulated arc therapy.The median lung V5, lung V20, MLD (Mean Lung Dose), MHD (Mean HeartDose) and MED (Mean Esophagus Dose) were 51.3 (range 27.1-77.6) %, 15.4(range 6.7-34.2) %, 10.7(range 5.0-17.9) Gy, 3.3(range 1.2-15.2) Gy, and11.5(range 7.0-30.4) Gy respectively. The first patient underwent elective nodal irradiation for mediastinal lymphnodes metastases, therefore high dose was irradiated to lung, heart, andesophagus.No acute and late toxicities were observed including radiation dermatitis,esophagitis, and radiation pneumonitis.The median overall survival time was 19.0 (range 7-33) months.No local recurrence was observed in the irradiated volume.

Conclusions: This retrospective study revealed the well-tolerability and the efficacy of EGFR-TKIs plus concurrent thoracic radiation therapy in patients with metastaticNSCLC having EGFR mutations.

Keywords: Radiation therapy, EGFR-TKIs, Concurrent targeted therapy and radiation therapy

P1.09B METASTATIC NON-SMALL CELL LUNG CANCER &NDASH; LOCAL THERAPIES - SURGERY SUNDAY, SEPTEMBER 8, 2024 - 12:00 - 14:00

P1.09B.01 Surgical Reduction at the Peak of Response Before Disease Progression in Patients with Metastatic EGFR-Mutated Lung Cancer

F.V. Moiseenko[1,2], D. Stroyakovskiy[3], E. Levchenko[4], M. Fedyanin[5], A. Gabina[1], A. Danilova[3], A. Allakhverdiev[6], E. Stepanova[1], A. Oganesian[1], S. Belukhin[1], M. Stepanova[1], E. Artemeva[1], A. Myslik[1], N. Volkov[1], A. Bogdanov[1], T. Shuginova[1], K. Krukov[1], V. Khenshtein[1], I. Zaberezhny[3], N. Levchenko[4], E. Slugin[4], O. Lopushanskaya[4], E. Kuligina[4], S. Aleksakhina[4], A. Iyevleva[4], A. Ivantsov[4], N. Savelov[3], D. Sehniaidze[3], Y. Akhmadiyarova[3], M. Popov[3], E. Imyanitov[4], V. Moiseyenko[1], [1]N.P. Napalkov City Cancer Center, St.Petersburg/RU ,[2]N.N. Petrov National Medical Research Center of Oncology, Ministry of Public Health of the Russian Federation, St-Petersburg, Russian Federation, St.Petersburg/RU ,[3]Moscow City Hospital №62, Moscow/RU ,[4]N.N. Petrov National Medical Research Center of Oncology, Ministry of Public Health of the Russian Federation, St-Petersburg/RU ,[5]Moscow clinical center «Kommunarka», Moscow/RU ,[6]The Loginov Moscow Clinical Scientific Center, Moscow/RU

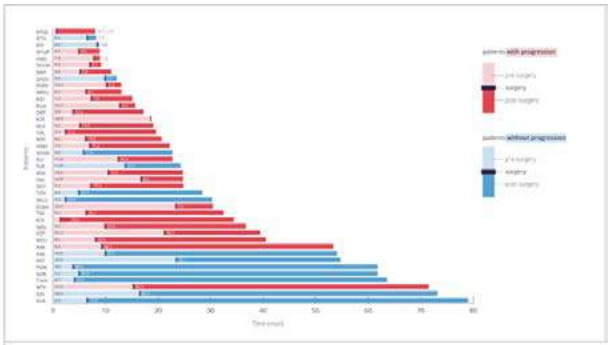
Introduction: NSCLC with EGFR mutations represents one of the malignancies benefiting the most from targeted therapies. Still hardly any patient might be cured with contemporary targeted approach. The reason for failure is resistant population that either arise or reside in the residual tumor tissue after response nadir is achieved. We suggested that surgical excision of the «persister» tissue might augment the maturation of resistant clone and postpone disease progression

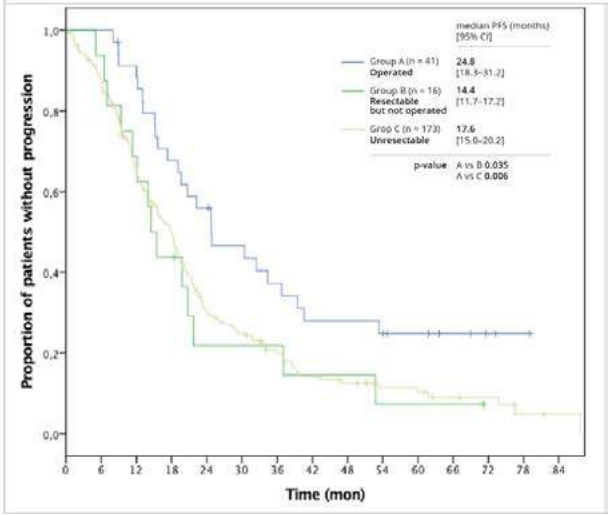
Methods: Out of 230 EGFR associated NSCLC patients treated with 1st line TKI we identified 41 (17%) case who underwent surgical cytoreduction during the response to TKI before radiographic progression

Results: mPFS was significantly longer in operated patients (Group A) - 24.8 mon [18.3-31.2] than in resectable at nadir but not operated (Group B) - 14.4 mon [11.7-17.2], p = 0.035 or unresectable (Group C) - 17.6 mon [15.0-20.2], p = 0.006. mOS was also longer in Group A - 62.1 mon [45.9-78.2] versus Group B - 37.1 mon [11.8-62.4], p = 0.010 versus 44.7 mon [27.8-61.6], p = 0.041, respectively. Median time to surgery from TKI start was 7.3 mon [0.5-24.2]. Post-surgical complication rate was 36.5%. Propensity score matching analysis confirmed statistically significant advantage in OS (56.0 mon [35.5-76.5] versus 37.1 mon [11.8 - 62.5], log rank p = 0.045) and numerical in PFS (24.7 mon [21.2-28.3] and 14.4 mon [11.7-17.2] in operated group over non operated. 26 of 41 operated patients had disease progression in distant sites (21/26), regional (1/26) and both (4/26). 14/41 patients are without progression after surgery at the median follow-up of 54.1+ mon. (8.23 - 79.07).

Conclusions: Complete cytoreduction at nadir of response to 1st line TKI is feasible for pts with locally advance or metastatic NSCLC and leads to survival advantage in a proportion of patients.

Keywords: Lung cancer, targeted therapy, local treatment





**P1.09B METASTATIC NON-SMALL CELL LUNG CANCER &NDASH; LOCAL THERAPIES - SURGERY **
SUNDAY, SEPTEMBER 8, 2024 - 12:00 - 14:00

P1.09B.02 Double Lung Transplantation in Patients with Metastatic Lung-limited Non-Small Cell Lung Carcinoma (NSCLC).

Y.K. Chae, T. Demir, L.I-Y. Chung, W. Woo, C. Moloney, B. Sanson, R. Dwyer, C.M. Jung, R. Tomic, A. Bharat, Feinberg School of Medicine, Northwestern University, Chicago/IL/USA

Introduction: Double lung transplantation (DLT) may offer curative treatment for metastatic lung-limited NSCLC patients without extrapulmonary disease. We present a case series of consecutive NSCLC patients who underwent DLT.

Methods: Patients treated with DLT were identified between 09/2021 and 04/2024 at Canning Thoracic Institute of Northwestern University. All patients had enrolled in the DLT registry aimed for lung-limited malignancies (DREAM) study cohort A (NCT05671887). Exclusion criteria includes presence of extrapulmonary disease.

Results: Seven patients with stage IVA NSCLC who underwent lung transplantation were included. Six (85.7%) patients underwent double lung, and one (14.3%) patient single lung transplantation. Five (71.4%) patients had invasive mucinous, and two (28.6%) had invasive non-mucinous adenocarcinoma histology. One of the two invasive non-mucinous patients had acinar, and the other had mixed lepidic, papillary, and acinar histology. Patients were aged 56-71; one (14.3%) was Asian, six (85.7%) were White, four (57.1%) were male, and three (42.9%) had a history of smoking. One (14.3%) patient had a past medical history of interstitial lung disease (ILD) and chronic obstructive pulmonary disease (COPD). The median pretransplant treatment lines were 3 (1-5). All patients had high oxygen requirements before DLT due to cancer progression. Pre-transplant endobronchial ultrasound and evaluation of bilateral pneumonectomy lungs found no lymph node involvement (pN0). One patient had an epidermal growth factor receptor (EGFR) mutated cancer but had failed relevant targeted therapy prior to transplant. All patients had disease progression on standard of care treatments with/without clinical trials. The indication for DLT was respiratory failure or refractory cancer for all patients. After DLT, one patient had a recurrence of the disease at 18 months with a 1cm solid nodule and was treated with stereotactic body radiotherapy (SBRT). Both original and recurrent tumors had invasive mucinous adenocarcinoma histology, negative PD-L1 expression, and the same JAK3 c.2174C > T, P725L mutated clone. It suggests that the recurrence likely arose from the original cancer. Transplant rejection did not occur in any of the cases. Following the transplant, there was no requirement for oxygen therapy for any patient. All patients are alive with 30, 20, 10, 10, 8, 6 and 1-month posttransplant follow-up.

Conclusions: Seven patients underwent DLT successfully without significant complications. All patients were alive and in good health. Ongoing DREAM study will continue to investigate the role of DLT in metastatic lung-limited NSCLC patients (especially in pN0).

Keywords: Stage IVa, Non-small cell lung carcinoma, Double Lung transplantation

**P1.09B METASTATIC NON-SMALL CELL LUNG CANCER &NDASH; LOCAL THERAPIES - SURGERY **
SUNDAY, SEPTEMBER 8, 2024 - 12:00 - 14:00

P1.09B.03 Ex-Situ Lung Transplantation without Heparinization: A Novel Surgical Approach for Locally Advanced and Central Lung Carcinoma

H. Pan[1], S. Yang[1], C. Zheng[1], K. Shi[1], W. Han[1], [1]The First Affiliated Hospital, Zhejiang University School of Medicin, Hangzhou/CN

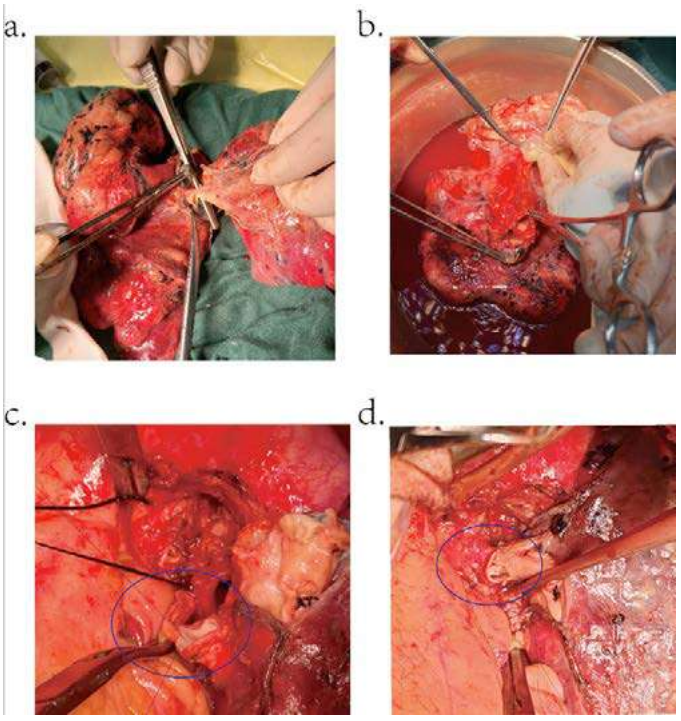
Introduction: Ex-situ lung transplantation represents an unconventional surgical intervention for patients with central lung cancer invading critical helium structures and compromised lung function. Previous reports on ex-situ lung transplantation have predominantly employed heparinization. This study presents our experience with ex-situ lung transplantation in patients with central lung cancer, conducted without heparinization.

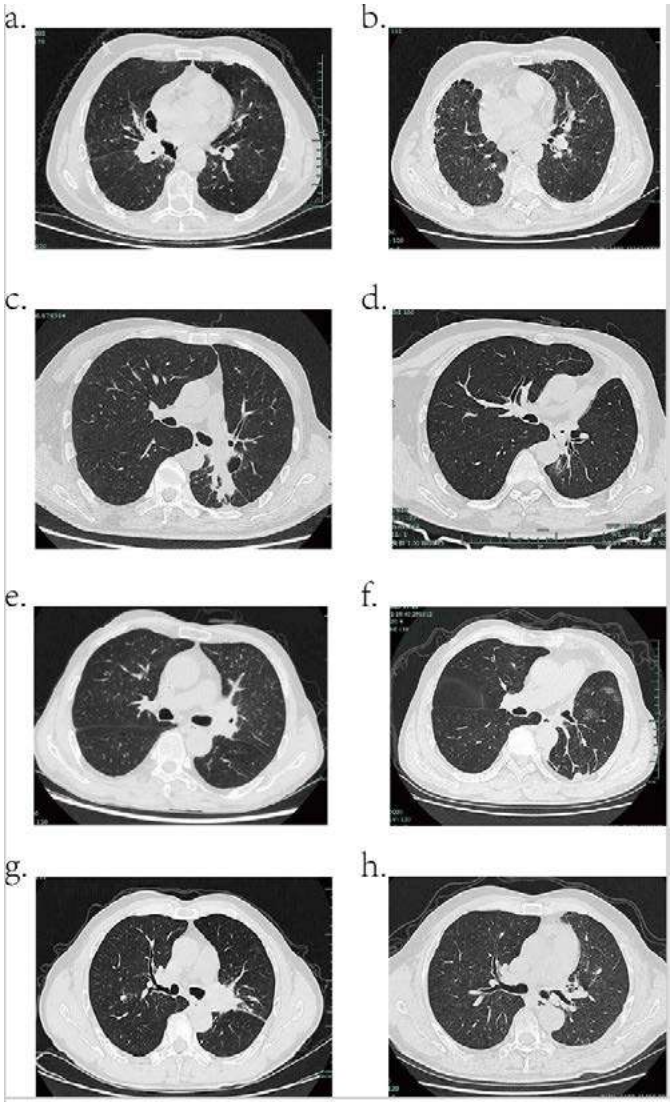
Methods: Ethical approval for all surgical procedures was obtained from the ethics committee of the First Affiliated Hospital, Zhejiang University School of Medicine. The fifth intercostal lateral thoracotomy approach was uniformly employed. Careful dissection of the pulmonary hilum was performed. Without heparinization, occlusion of the pulmonary artery and vein was achieved using a pulmonary artery clamp(Fig.1a). Subsequently, the affected lung was excised, and the lesion removed ex vivo. All patients underwent R0 resection confirmed by intraoperative cryopathology. Ex-vivo lung perfusion was conducted using Perfedex(Fig.1b). Veins and bronchus were sutured with 4-0 prolene(Fig.1c), end-to-end anastomosis, while 5-0 prolene was used for end-to-end anastomosis of the pulmonary artery(Fig.1d).

Results: Four patients who underwent ex-situ transplantation were included. The median age of the patients was 69 years. All patients were diagnosed with stage III squamous cell lung cancer following biopsy. Neoadjuvant treatment was administered to all patients. Preoperative planning, guided by CT imaging(Fig.2a,c,e,g), facilitated successful ex-situ transplantation in all cases. The median surgery duration was 337 minutes, with a median blood loss of 100 ml. Median postoperative intubation time was 1 day, and median hospital stay was 9 days. One patient experienced a non-fatal partial branch embolism of the contralateral pulmonary artery. At the 3-month postoperative follow-up, all patients were asymptomatic(Fig.2b,d,f,h).

Conclusions: Ex-situ lung transplantation emerges as a superior alternative to pneumonectomy for patients with locally advanced lung cancer. Our findings suggest that heparinization may not be necessary for this procedure.

Keywords: Ex-vivo Lung Transplantation, Surgical Techniques, Central Lung Cancer





**P1.09B METASTATIC NON-SMALL CELL LUNG CANCER &NDASH; LOCAL THERAPIES - SURGERY **
SUNDAY, SEPTEMBER 8, 2024 - 12:00 - 14:00

P1.09B.04 Impact of BMI on TTFields in Patients with Mnsclc: Post-hoc Analysis from the Phase 3 LUNAR Study and Simulation Model Data

C. Rolfo[1], D.E. Gerber[2], R. Kotecha[3], J. Ward[4], W. Akerley[5], A. Naveh[6], N. Shapira[6], T. Leal[7], C. Langer[8], [1]Center for Thoracic Oncology, The Tisch Cancer Institute Icahn School of Medicine at Mount Sinai Mount Sinai Health System, New York/NY/USA ,[2]Harold C. Simmons Comprehensive Cancer Center, UT Southwestern Medical Center, Dallas/TX/USA ,[3]Miami Cancer Institute, Baptist Health South Florida, Miami/FL/USA ,[4]Washington University School of Medicine, St. Louis/MO/USA ,[5]Huntsman Cancer Institute University of Utah, Salt Lake City/UT/USA ,[6]Novocure Ltd, Haifa/IL ,[7]Winship Cancer Institute of Emory University, Atlanta/GA/USA ,[8]Abramson Cancer Center, Perelman School of Medicine, University of Pennsylvania, Philadelphia/PA/USA

Introduction: Tumor Treating Fields (TTFields) are electric fields that disrupt processes critical to cancer cell viability and tumor progression and are delivered non-invasively to the tumor site via skin-placed arrays. Recently, the randomized, pivotal (phase 3) LUNAR study (NCT02973789) demonstrated improved overall survival (OS) for TTFields therapy (150 kHz) delivered continuously until progression or intolerable toxicity together with an immune checkpoint inhibitor (ICI) or docetaxel (DTX) vs ICI/DTX alone in patients with metastatic non-small cell lung cancer (mNSCLC) following progression on or after platinum-based therapy (HR 0.74 [95% CI, 0.56-0.98]; P=0.035). The effects of TTFields are dependent on several factors, including intensity, frequency, and distribution, all of which may be affected by tissue conductivity and array layout used. We therefore evaluated the effect of body mass index (BMI) on the delivery of TTFields to the lungs using clinical data from the LUNAR study and data from a simulation study.

Methods: We performed a post-hoc analysis of the LUNAR study to evaluate OS in patients with varying BMIs. A simulation study was also conducted to evaluate TTFields intensity and distribution using 2 array sizes (small and large) in computerized phantom models with healthy (BMI 22 kg/m2), overweight (BMI 26 kg/m2), and obese (BMI 30 kg/m2) BMIs.

Results: Of the 276 patients included in the intent-to-treat population of the LUNAR study, BMI data was available for 259 patients (94%). Mean ± standard deviation BMI was 24.7 ± 5.3 kg/m2 in the TTFields + ICI/DTX arm (n=131) and 26.0 ± 4.9 kg/m2 in the ICI/DTX arm (n=128). In the BMI <25 kg/m2 subgroup (n=140), median OS (95% CI) was 11.6 months (8.5-16.1) in the TTFields + ICI/DTX arm compared with 8.2 months (6.1-14.3) in the ICI/DTX arm (hazard ratio [HR] 0.70 [95% CI, 0.47-1.04]; P=0.08). In the BMI ≥25 kg/m2 subgroup (n=119), median OS (95% CI) was 13.9 months (9.7-23.3) in the TTFields + ICI/DTX arm compared with 10.2 months (8.9-14.7) in the ICI/DTX arm (HR 0.74 [95% CI, 0.49-1.13]; P=0.27). Therapeutic electric field intensities (amplitude in the order of >1 V/cm) were achieved in all lobes of the lung for all simulation models when using the appropriately sized arrays.

Conclusions: This post-hoc analysis of the LUNAR study did not identify a difference in OS benefit between patients with a BMI <25 kg/m2 vs BMI ≥25 kg/m2 receiving TTFields therapy. The simulation-based study demonstrated the feasibility of delivering TTFields therapy at a therapeutic intensity to the lungs of patients with varying BMIs. These data suggest TTFields are delivered adequately to the lungs of patients and provide clinical benefit across a range of BMIs.

Keywords: Tumor Treating Fields, Body mass index, Metastatic non-small cell lung cance

**P1.09B METASTATIC NON-SMALL CELL LUNG CANCER &NDASH; LOCAL THERAPIES - SURGERY **
SUNDAY, SEPTEMBER 8, 2024 - 12:00 - 14:00

P1.09B.05 Improved Survival of Primary Tumor Resectionfor Metastatic Non Small Cell Lung Cancer:a Propensity Score-matched Analysis

J. Wu[1,2], F. Qin[1,2], X. Qin[1,2], Y. Zheng[1,2], H. Zheng[1,2], J. Chen[1,2], Z. Liu[1,2], B. Jian[1,2], G. Wang[3], H. Liao[1,2], [1]Department of Thoracic Surgery, The Sixth Affiliated Hospital, Sun Yat-sen University, Guangzhou/CN ,[2]Biomedical Innovation Center, The Sixth Affiliated Hospital, Sun Yat-sen University, Guangzhou/CN ,[3]Zhongshan School of Medicine, Sun Yat-sen University, Guangzhou/CN

Introduction: Lung cancer is the second most common malignancy, and about 85% of those patients are non-small cell lung cancer (NSCLC). For NSCLC patients with distant metastases such as lung or liver lesions, primary tumor resection (PTR) whether should be considered is still controversial. The study aims to assess the survival effect of PTR on NSCLC patients with synchronous lung or/and liver metastases.

Methods: NSCLC patients with synchronous lung or/and liver metastases were identified from the SEER database from 2010 to 2015. And 1:1 propensity-score matching(PSM) analysis were used to minimize heterogeneity between PTR and no-PTR groups. The cox models were used to identify predictors of overall survival (OS) and cancer-specific survival (CSS) for those metastatic NSCLC patients.

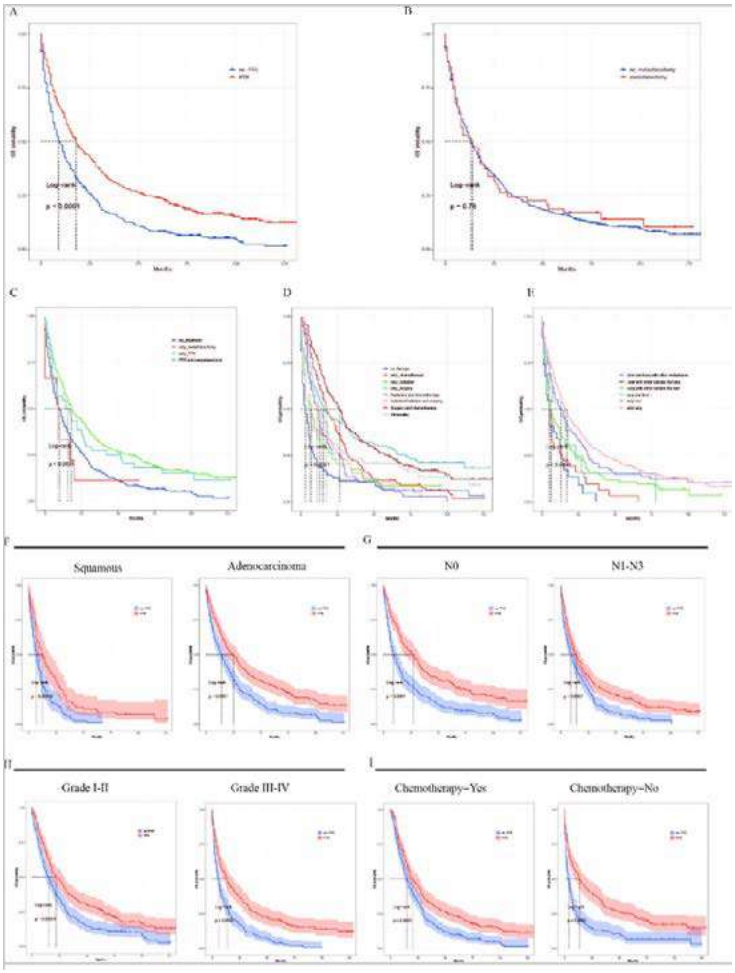
Results: Of 7660 NSCLC patients with synchronous lung or/and liver metastases, 788 were enrolled in the PSM cohort. Patients underwent PTR had a better median OS (18.0 months vs. 9.0 months, p < 0.001) and median CSS (13.0 months vs. 7.0 months, p < 0.001) than those patients did not in PSM cohort.

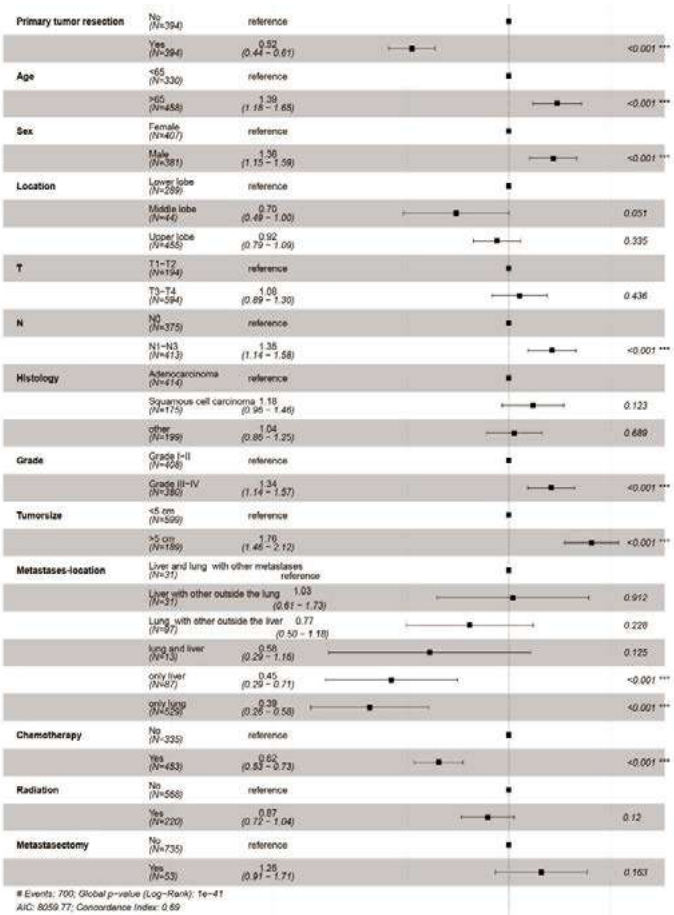
Additionally, multivariable cox analysis similarly demonstrated that PTR was a significantly protective factor for those metastatic NSCLC patients in OS (HR: 0.52; 95% CI, 0.44 to 0.61, P < 0.001). Also, multivariate cox analysis identified the independent risk factors for those metastatic NSCLC patients as as follows: no primary resection surgery, age >65 years, male, N1-N3, tumor size>5 cm, worse differentiation, no systemic therapy. However, metastasectomy is not a significantly protective factor.

In stratified analyses by N stage, tumor differentiation, tumor histology and systemic therapy, those patients with PTR had a better prognosis. And PTR combined with chemotherapy and NSCLC patients with only lung metastases was associated with the greatest treatment effect.

Conclusions: Primary tumor resection can improve the survival of NSCLC patients with synchronous lung or/and liver metastases.

Keywords: primary tumor resection, non small cell lung cancer, synchronous lung / liver metastases





P1.09C METASTATIC NON-SMALL CELL LUNG CANCER – LOCAL THERAPIES - CLINICAL TRIALS IN PROGRESS
SUNDAY, SEPTEMBER 8, 2024 - 12:00 - 14:00

P1.09C.01 A Multicenter, Randomized, Phase II Trial of EGFR TKI with Primary Tumor Resection for EGFR-Mutant Metastatic NSCLC Patients

P-H. Chen[1,2], H-H. Hsu[3], T-H. Young[1], J-S. Chen[2], [1]Institute of Biomedical Engineering, College of Medicine and College of Engineering, National Taiwan University, Taipei/TW ,[2]National Taiwan University Hospital, Taipei/TW ,[3]National Taiwan University Cancer Centor, Taipei/TW

Introduction: Several phase II trials have investigated the use of combination local consolidation therapies in EGFR-mutant advanced lung cancer to potentially improve survival. However, there has been no specific trial design for on evaluating the efficacy of primary thoracic tumor resection with EGFR TKI before disease progression.Our hypothesis posits that surgery, targeted at eradicating pre-existing resistant subclones or reducing tumor burden resulting from drug-induced resistance, could significantly improve outcomes related to non-progression intervals by reducing the chance of subsequent resistance development. This approach aims not to cure the disease but to achieve a superior control effect, exceeding the results achievable with standard EGFR TKI therapy alone.

Methods: We are conducting a two-arm, phase II clinical trial to assess the impact of primary tumor resection in patients with EGFR-mutant advanced non-small cell lung cancer (NSCLC) that is suitable for thoracic surgery, utilizing data from two major centers in Taiwan. The goal is to enroll 100 stage IV patients to evaluate their response to treatment.

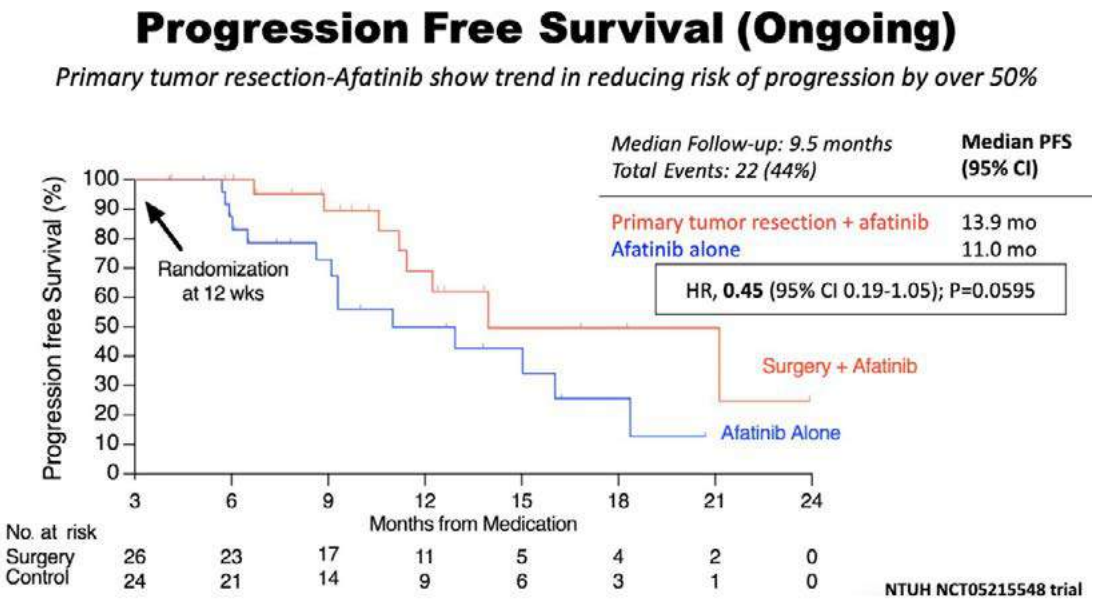
Eligible patients must have an Eastern Cooperative Oncology Group (ECOG) performance status of ≤1 and be considered candidates for surgery with curative intent at at least one disease site. Additionally, patients must exhibit NSCLC with either an EGFR exon 19 deletion or an L858R mutation. Patients exhibiting progressive disease (PD) will be excluded. Following an initial 12 weeks of afatinib (40mg,day) therapy, participants will be randomized (1:1) to receive either afatinib monotherapy or primary tumor resection and/or radiation therapy targeting residual distant disease.

The primary goal of thoracic surgery is to achieve optimal locoregional disease control and potentially secure a negative resection margin. Those in the surgical arm will continue with afatinib post-surgery. The radiation therapy will be administered at the discretion of the multidisciplinary team of investigators, which is will be completed after first dose of afatinib. The primary endpoint of this trial is the two-year progression-free survival (PFS). Secondary endpoints include progression-free survival and overall survival (OS), involving a total of 100 subjects.

Results: Initial results (Fig.1) suggest that combining primary tumor resection with EGFR TKI may reduce the risk of disease progression by more than 50% compared to EGFR TKI alone.

Conclusions: This trend points towards a potential increase in benefit, which could become statistically significant with longer follow-up.

Keywords: Salvage Thoracic Surgery, EGFR TKI, Metastatic NSCLC



P1.09C METASTATIC NON-SMALL CELL LUNG CANCER – LOCAL THERAPIES - CLINICAL TRIALS IN PROGRESS
SUNDAY, SEPTEMBER 8, 2024 - 12:00 - 14:00

P1.09C.02 SiCARIO: A Phase I/II Study of Split Course Adaptive Radioimmunotherapy for the Treatment of Oligometastatic Non-Small Cell Lung Cancer

R. Whitaker, K. McComas, E. Osmundson, Vanderbilt University Medical Center, Nashville/TN/USA

Introduction: The current standard of care (SOC) for non-driver mutation oligometastatic NSCLC involves treatment with cytotoxic chemotherapy alone, chemotherapy combined with immune checkpoint blockade (ICB), or ICB alone based on tumor PD-L1 expression level. While improvements associated with addition of ICB have been observed in this cohort, local and/or distant failure remains a near certainty. New strategies are needed to enhance the efficacy of these agents to provide more durable responses and in select patients, potentially curative approaches. Increasing pre-clinical data supports synergy between radiotherapy (RT) and immune-based therapies; however, radiation treatment paradigms have not been updated to better harness the potential biologic interactions between RT and the immune system. This study seeks to determine if high-dose per fraction, split course, anatomically and biologically adapted RT timed concurrently with immunotherapy containing systemic regimens can improve outcomes. Emerging clinical evidence supports concurrent treatment with high-dose per fraction RT as an optimal approach to induce antitumor immunity in combination with ICB. Use of a split course approach may improve the therapeutic window of RT in this setting, and act to sequentially re-prime the immune system to the evolving antigenic signature of the tumor and micro-environment.

Methods: This is a phase I/II, single institution, open label clinical trial in patients with de novo non-driver mutation metastatic NSCLC with up to 10 sites of extracranial metastases. Patients with brain metastases which can be addressed with surgery and/or stereotactic radiosurgery are eligible. Patients receive RT to all sites of extracranial disease and thoracic primary in 8 Gy fractions every 3 weeks to a total dose of 40 Gy in 5 fractions concurrent with SOC (chemo)immunotherapy. RT plans are adapted between fractions as needed using a novel, CT-linac-based adaptive RT platform (Varian Medical Systems). Planned enrollment is 25 patients to observe an improvement in best overall response rate (ORR) to 75% compared to historical controls. The primary objectives are to assess safety, tolerability and ORR of the SiCARIO regimen combined with SOC systemic therapy. Secondary objectives include PFS, OS and new metastasis free survival. Exploratory objectives include serum biomarkers of response (ctDNA and immune profiling) and imaging biomarkers including 18F-FDG PET and 18F-FSPG PET response. This study will also serve as a practical evaluation of a CT-linac-based adaptive platform for development of efficient clinical workflows integrating both anatomic and functional imaging data to deliver complex, multi-site RT plans. Enrollment is currently ongoing with potential for future expansion pending initial outcomes.

Keywords: Radiation, Immunotherapy, Oligometastasis

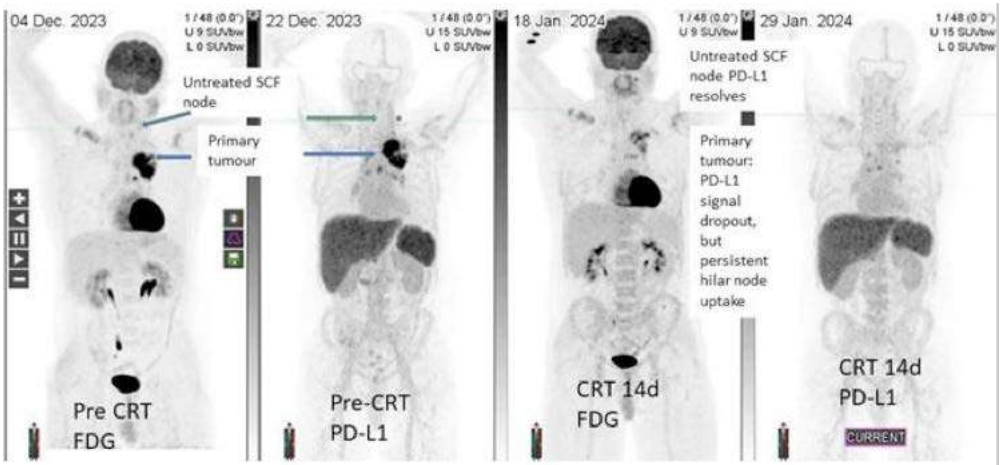


Figure 1: ^{89}Zr-Durva PET scans taken at baseline and 14 days into Chemoradiotherapy. Patient PD-L1 70% on initial biopsy.

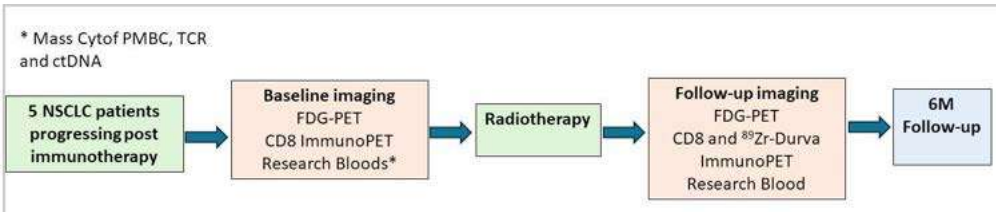


Figure 2: Trial Design

P1.09C METASTATIC NON-SMALL CELL LUNG CANCER – LOCAL THERAPIES - CLINICAL TRIALS IN PROGRESS
SUNDAY, SEPTEMBER 8, 2024 - 12:00 - 14:00

P1.09C.03 IMMUNOResist: Defining the Immunophenotype of Immunotherapy Resistance with PD-L1 and CD8 Novel Tracer PET

F. Hegi-Johnson, T. Akhurst, T. John, A. Scott, S. Parakh, B. Blyth, S. Wong, M. MacManus, Peter MacCallum Cancer Centre, Melbourne/AU

Introduction: IMMUNOResist is a multicentre, single arm pilot study investigating the use of the ImmunePET tracers 89Zr-DFO-Sq-durvalumab (89Zr-durva) and 89Zr-89 crefmirlimab berdoxam (CD8) PET/CT to interrogate PD-L1expression and infiltration of CD8 T-cells in non-small cell lung cancer(NSCLC) patients undergoing radiotherapy after progression on immunotherapy. We have established that 89Zr-durva PET/CT can provide information about PD-L1 expression in patients who are progressing on immunotherapy and receiving radiotherapy (See Fig1)[1].

Methods: This is a prospective, observational, single arm open-label pilot study of 5 patients with NSCLC who are receiving radiotherapy to progressive disease after 1st line immunotherapy. ECOG 0-1 NSCLC patients of any PD-L1, EGFR, ALK or ROS mutation status and histology are eligible. Patients have CD8-PET/CT before and after radiotherapy, and 89Zr-durva PET/CT after radiotherapy. Patients also undergo liquid biopsy before the first day and after the completion of radiotherapy. Baseline tissue genomic analysis, analysis of blood samples with mass cytometry of PBMC, TCR characterization and cytokine profiling will be performed. Please see Figure 2 for details of study design.

Aims: To use dual 89Zr-durva and CD8 ImmunoPET imaging to investigate PD-L1 expression and activated T-cell infiltration NSCLC progressing after immunotherapy who are receiving radiotherapy to progressive disease. To interrogate the host immune response with Tissue DNA analysis, PBMC mass cytometry, TCR and cytokine profiling.

Endpoints: 1.Qualitative evaluation of 89Zr-durva and CD8 PET/CT imaging will be compared with FDG PET/CT. 2.Quantitative measures, including SUVmax, SUVmean, SUVpeak & %ID will be compared. 3.Comparison of 89Zr-durva uptake and CD8-PET/CT with PD-L1 IHC on tissue 4.PD-L1 expression and CD8 T-cell recruitment seen on PET/CT will be compared with host immunity interrogated with PBMC, TCR and cytokine analysis **Conclusions:** We have previously demonstrated the feasibility of ImmunePET imaging in a multicentre trial, and will use this pilot study to evaluate whether dual CD8 and 89Zr-Durva PET imaging may enable characterisation of the immunophenotype during radiotherapy treatment.

References: 1.10.1016/j.ijrobp.2023.05.019.

Keywords: Immunotherapy Resistance, PET Imaging, Radiotherapy

P1.12A METASTATIC NON-SMALL CELL LUNG CANCER - TARGETED THERAPY - EGFR
SUNDAY, SEPTEMBER 8, 2024 - 12:00 - 14:00

P1.12A.01 Real-World Outcomes and Treatment Patterns after First-Line Osimertinib in Patients with Advanced NSCLC and Uncommon EGFRm

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Introduction: Uncommon EGFR mutations (ucEGFRm), a highly heterogenous group of alterations within exons 18-21, represent about 10% of all EGFR mutations that are detected in patients with advanced NSCLC. Multiple clinical practice guidelines recommend osimertinib as a treatment option for patients with advanced NSCLC and ucEGFRm; however, data on the real-world effectiveness of first-line osimertinib in this setting are lacking. We characterized outcomes and subsequent treatment patterns after first-line osimertinib in a U.S. cohort of patients with advanced NSCLC and ucEGFRm.

Methods: Patients with advanced NSCLC and ucEGFRm who were treated with first-line osimertinib between April 01, 2018 and March 31, 2020 were identified from the Flatiron Health Spotlight Database. Patients were divided into two subgroups: those with multiple mutations comprising a combination of common mutations and ucEGFRm (Group A) and those with ucEGFRm only (Group B). Time-to-next treatment or death (TTNTD), time-to-treatment discontinuation (TTD), real-world progression-free survival (rwPFS), real-world overall survival (rwOS), and second-line treatment patterns were described for the overall cohort and in the ucEGFRm subgroups (Groups A and B).

Results: Among 61 patients in the overall cohort, median age was 71 years (interquartile range [IQR]: 63-77), 77% were female, 67% were White, 52% had a history of smoking, 57% had an ECOG score of 0-1, 31% had brain metastasis, and median follow-up after first-line treatment was 10 months (IQR: 3-29). Group A represented 31% of patients (n=19) and Group B 69% (n=42). The table shows median TTNTD, TTD, rwPFS, and rwOS for the overall cohort and the ucEGFRm subgroups. At the end of study follow-up, 13% (n=8) of patients remained on osimertinib (Group A: 26%, Group B: 7%), 54% (n=33) discontinued osimertinib because they had died (Group A: 37%, Group B: 62%), and 33% (n=20) received subsequent treatment (Group A: 37%, Group B: 31%). Of the 20 patients who received second-line treatment, 35% received chemotherapy, 25% received osimertinib combination therapy, 15% received immunotherapy alone, 15% received EGFR-TKIs (including osimertinib), 5% received immunotherapy with chemotherapy, and 5% received clinical study drug.

Conclusions: Our study represents the largest set of patients with advanced NSCLC and ucEGFRm treated with first-line osimertinib. Our results support current clinical guidelines that recommend first-line osimertinib as a treatment option for patients with advanced NSCLC and ucEGFRm.

Keywords: Real-World, Second-Line, Uncommon mutations

ucEGFRm Subgroup	Median TTNTD, months (95% CI)	Median TTD, months (95% CI)	Median rwPFS, months (95% CI)	Median rwOS, months (95% CI)
Overall (N=61)	11.4 (8.3, 28.3)	9.9 (5.6, 24.8)	8.2 (5.1, 14.8)	27.0 (11.0, 40.3)
Group A, common + ucEGFRm (n=19)	24.0 (10.3, NE)	10.7 (6.5, 34.0)	13.2 (10.0, 41.7)	36.1 (10.3, NE)
Group B, ucEGFRm only (n=42)	9.5 (5.5, 26.5)	8.8 (5.1, 24.8)	6.2 (4.2, 12.3)	20.0 (9.2, 32.9)

Abbreviations: CI, confidence interval; NE, not estimable; rwOS, real-world overall survival; rwPFS, real-world progression-free survival; TTD, time-to-treatment discontinuation; TTND, time-to-next treatment or death; ucEGFRm, uncommon epidermal growth factor mutation

P1.12A METASTATIC NON-SMALL CELL LUNG CANCER - TARGETED THERAPY - EGFR
SUNDAY, SEPTEMBER 8, 2024 - 12:00 - 14:00

P1.12A.02 Efficacy of EGFR-Tyrosine Kinase Inhibitors in Patients with NSCLC Harboring EGFR Exon 19 Insertions: A Report from the LC-SCRUM-Asia

Y. Uehara[1,2], H. Izumi[1], I.S. Kobayashi[3], S. Matsumoto[1], Y. Hosomi[2], T. Okuno[4], J. Sugisaka[5], N. Takase[6], K. Taima[7], S. Sasaki[8], S. Teranishi[9], S. Miyamoto[10], M. Mori[11], C. Nakashima[12], S. Asano[13], Y. Zenke[1], K. Yoh[1], D.B. Costa[3], S.S. Kobayashi[3,14], K. Goto[1], [1]National Cancer Center Hospital East, Kashiwa/JP ,[2]Tokyo Metropolitan Cancer and Infectious Diseases Center, Komagome Hospital, Tokyo/JP ,[3]Beth Israel Deaconess Medical Center, Boston/MA/USA ,[4]Shimane University Faculty of Medicine, Izumo/JP ,[5]Sendai Kousei Hospital, Sendai/JP ,[6]Takarazuka City Hospital, Takarazuka/JP ,[7]Hirosaki University Graduate School of Medicine, Hirosaki/JP ,[8]Juntendo University Urayasu Hospital, Urayasu/JP ,[9]Yokohama City University Medical Center, Yokohama/JP ,[10]Japanese Red Cross Medical Center, Tokyo/JP ,[11]NHO Osaka Toneyama Medical Center, Toyonaka/JP ,[12]Saga University, Saga/JP ,[13]Japan Community Health Care Organization Chukyo Hospital, Nagoya/JP ,[14]National Cancer Center, Kashiwa/JP

Introduction: EGFR exon 19 insertions occur in 0.1-0.4% of NSCLC and the most common variant is K745_E746insIPVAIK. Due to their rarity, the clinical-genomic characteristics and outcomes with EGFR-tyrosine kinase inhibitors (TKIs) remain uncertain.

Methods: We evaluated the clinical-genomic characteristics and outcomes of EGFR-TKI therapies for NSCLC with EGFR exon 19 insertions in this multi-institutional prospective lung cancer genomic screening project (LC-SCRUM-Asia), using targeted next-generation sequencing (Oncomine Comprehensive Assay or Oncomine Precision Assay). We also studied preclinical Ba/F3 models expressing EGFR-K745_E746insIPVAIK (Ba/F3-IPVAIK) and EGFR-delE746_A750 (Ba/F3-Del19) to investigate the sensitivity to 1st-generation (gen) (gefitinib and erlotinib), 2nd-gen (afatinib, dacomitinib, and poziotinib), 3rd-gen (osimertinib), and EGFR exon 20 insertion active TKIs (mobocertinib, sunvozertinib, and zipalertinib).

Results: In LC-SCRUM-Asia, 16,204 NSCLC patients were enrolled from March 2015 to December 2023. EGFR exon 19 insertions were detected in 13 samples (0.1% of NSCLC and 0.4% of EGFR-mutated NSCLC). The median age was 72 years (range, 38 to 80), patients were predominantly female (77%) and never-smokers (62%). Twelve patients (93%) had adenocarcinoma histology and one had adenosquamous carcinoma. Three patients (23%) had brain metastasis at diagnosis. When compared to patients with major EGFR mutations (1,359 patients) from LC-SCRUM-Asia, no distinct differences in clinical characteristics were observed. Twelve patients (93%) had EGFR-K745_E746insIPVAIK, and one (7%) had EGFR-K745_E746insVPVAIK. The most frequent concomitant mutation was TP53 (62%), followed by EGFR amplification (15%), CDKN2B amplification (15%), PIK3CA mutation (8%), and FGFR mutation (8%). No patients had any other driver alterations. Eleven patients received EGFR-TKIs; four (36%) experienced a partial response. The median progression-free survival (PFS) of EGFR-TKIs and overall survival (OS) were 7.4 months (95% confidence interval [CI], 6.0-not reached [NR]) and 29.6 months (95%CI, 21.4-NR), respectively. When broken down by EGFR-TKI generation, response rates for 1st, 2nd, and 3rd-gen TKIs were 50% (1/2), 60% (3/5), and 0% (0/4), respectively. The median PFS for 1st, 2nd, and 3rd-gen TKIs was 8.7 months (95% CI, 7.4-NR), 13.8 months (95% CI, 7.2-NR), and 3.9 months (95% CI, 1.0-NR), respectively. The median OS for 1st, 2nd, and 3rd-gen TKIs was 25.5 months (95% CI, 21.4-NR), NR, and NR, respectively. In the preclinical study, Ba/F3-IPVAIK showed the highest sensitivity to 2nd-gen EGFR-TKIs (IC50 range: 0.57-0.95 pM) compared to other EGFR-TKIs (IC50 range: 1st-gen, 61-158 nM; 3rd-gen, 13.8 nM; exon 20 insertion active, 1.78-21.3 nM). The preclinical therapeutic window of Ba/F3-IPVAIK and Ba/F3-Del19 for all the 2nd generation TKIs were similarly favorable, whereas Ba/F3-IPVAIK had much unfavorable therapeutic windows to other EGFR-TKIs compared to Ba/F3-Del19.

Conclusions: Our clinical and preclinical findings indicate 2nd-gen EGFR-TKIs are more effective than 1st and 3rd-gen EGFR-TKIs in patients with EGFR exon 19 insertions.

Keywords: I740_K745dup, Afatinib, K745_E746insIPVAIK

P1.12A METASTATIC NON-SMALL CELL LUNG CANCER - TARGETED THERAPY - EGFR
SUNDAY, SEPTEMBER 8, 2024 - 12:00 - 14:00

P1.12A.03 Outcome and Transcriptomic Features of Dual EGFR and MET Blockade in NSCLC

D.D-W. Lee[1,2], W.P. Ng[2,3], S.F. Ang[2], D.P. Lau[2], L.Y. Wang[2], G.G.Y. Lai[2,4], M.Y.W. Boey[2], T.K.H. Lim[2], D.S.W. Tan[2,4], [1]University of Malaya, Kuala Lumpur/MY ,[2]National Cancer Center Singapore, Singapore/SG ,[3]Genome Institute of Singapore, Singapore/SG ,[4]Duke-NUS Medical School, Singapore/SG

Introduction: MET alterations are known resistance mechanisms to EGFR tyrosine kinase inhibitors (TKI). Dual EGFR and MET inhibition have shown promise in overcoming EGFR resistance post EGFR TKI. We present the outcome of patients treated with MET inhibitors with or without EGFR TKI after EGFR TKI failure.

Methods: NSCLC patients with both MET alterations (amplification, polysomy, and mutation) and EGFR mutation who received crizotinib, capmatinib, or tepotinib with or without an EGFR TKI after progression on EGFR TKI in our database were included in this study. MET alterations were detected by FISH or next-generation sequencing. We performed whole exome sequencing (WES) and RNA-seq for 6 tissue samples available.

Results: From 2012 to 2020, 46 patients who fulfilled our search criteria were identified. The median age of diagnosis was 60 years old (31 - 80), 58.7% were male and 76% were never smokers. The MET alterations detected were MET amplification (50%, 23/46), MET polysomy (47.8%, 22/46), and MET mutation (2.2%, 1/46). Notably, 17 patients fulfilled the criteria of primary EGFR resistance (Progression-free survival of less than 6 months on EGFR TKI). Thirteen patients received single-agent MET inhibitors and 33 patients received dual EGFR/MET inhibitors. The overall median duration of response (DOR) was 2.8 months (2.0 months for MET blockade and 4.2 months for dual MET and EGFR blockade). Among patients with MET polysomy, the median DOR was 5.8 months versus 1.9 months in those with MET amplifications. In evaluable patients, 54% (20/37) had disease progression, 27% (10/37) had a partial response and 19% (7/37) had stable disease. All patients who had partial response received dual EGFR/MET inhibitors. Six tissue samples among patients that received both EGFR and MET inhibitors - 3 from responders (DOR > 2 months) and 3 from non-responders (DOR < 2 months) were evaluated with WES and RNA-seq. All responders were female and all non-responders were male. Responders showed higher tumor content (purity estimate by PUREE). All responders show TRU (terminal respiratory unit) subtype, whereas non-responders show either PI (proximal-inflammatory) or PP (proximal proliferative) subtypes. There were no remarkable differences in mutational signatures, CIBERSORT, and GEP scores.

Conclusions: Our data suggest the possible benefit of adding MET inhibitor while continuing EGFR TKI for patients harboring both EGFR and MET alterations. Other possible predictive factors are MET polysomy, high tumor content, and TRU subtype. We suggest further investigation to define MET amplification cut-off and patient selection based on responsiveness to EGFR TKI.

Keywords: EGFR Resistance, MET alterations, Transcriptomics

P1.12A METASTATIC NON-SMALL CELL LUNG CANCER - TARGETED THERAPY - EGFR
SUNDAY, SEPTEMBER 8, 2024 - 12:00 - 14:00

P1.12A.04 Socioeconomic Disparities and Overall Survival Differences Among Ethnic-Minority Patients with EGFR-Mutated NSCLC Treated with Osimertinib

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Introduction: Osimertinib (Osi) is a key treatment for EGFR-mutated NSCLC, yet knowledge gaps persist regarding treatment adherence and clinical outcomes in ethnic minorities. Building upon previous research at our institution demonstrating inferior survival among black patients before the wide use of Osi, this study aims to provide updated insights into the impact of race/ethnicity, adherence and other demographic, socioeconomic and clinical factors on outcomes for NSCLC patients treated with Osi.

Methods: We conducted a retrospective cohort study involving 168 patients (pts) with EGFR mutated NSCLC who were prescribed Osi from 1/1/16-3/31/24, including 60 pts within Montefiore's specialty pharmacy with comprehensive claims data. Adherence was measured using proportion of days covered (PDC). Primary endpoint was overall survival (OS) along with secondary endpoints of progression-free survival (PFS) and treatment duration from the start of Osi, compared minority vs non-minority using log-rank testing and survival analysis with cox proportional models.

Results: This cohort constituted of 26.2% of Non-Hispanic Black (NHB), 32.7% Hispanics, 28.6% non-Hispanic Whites (NHW) 28.6%, and 12.5% non-Hispanic Asians with a median age of 70 years. Treatment adherence based on PDC did not differ between Blacks (76%) vs non-Blacks (84%) or Hispanics (86%) vs non-Hispanics (78%). The average out of pocket cost for our pts was $78 (USD) per month, significantly lower for minority patients with lower median household incomes. With a median follow-up time was 16.3 months (mons), in a univariate analysis, significantly higher OS is associated with an income of >50,000 (USD) compared to <50,000 (USD), and Medicare insurance compared to Commercial insurance. NHB showed Inferior OS compared to NHW (12.1 mons vs 22.6 mons, p=0.035), also with a trend towards lower OS in Hispanics (22.6 mons vs 16.6 mons, p=0.054) despite no differences in duration and adherence of Osi. PFS was longer in Medicare patients compared to commercial insurance (p=0.010), and worse in Uncommon non-sensitizing EGFR alterations (p=0.045), although no OS differences. Multivariate results confirmed higher mortality and progression risk in NHB compared to NHW (p<0.05). Further results are summarized in Table 1.

Conclusions: Our study demonstrates that although Osi adherence and treatment duration were similar across racial/ethnic groups, a persistent inferior OS was observed in NHB, and Hispanics compared to NHW. This underscores the need for further investigation into underlying mechanisms impacting outcomes of EGFR-mut NSCLC, particularly in NHB pts, and exploration of how income and insurance disparities may contribute to these disparities in clinical outcomes.

		OS			PFS		
Characteristics		HR	95% CI	p-value	HR	95% CI	p-value
Univariate Model							
Gender	Male	-	-	-	-	-	-
	Female	1.24	0.81, 1.92	0.321	1.02	0.66, 1.57	0.919
Age	<65	-	-	-	-	-	-
	≥65	1.03	0.69, 1.55	0.875	0.82	0.55,12.3	0.333
Language	Non-English	-	-	-	-	-	-
	English	0.85	0.55, 1.31	0.460	1.16	0.74, 1.81	0.521
Race/Ethnicity	Non-Hispanic White (NHW)	-	-	-	-	-	-
	Non-Hispanic Black (NHB)	1.75	1.04, 2.94	0.035	0.93	0.54, 1.62	0.802
	Hispanic	1.66	0.99, 2.77	0.054	1.07	0.65, 1.77	0.790
	Asian	1.81	0.96, 3.40	0.068	0.82	0.42, 1.59	0.549

Smoking status	Smoker (Active/Former)	-	-	-	-	-	-
	Never Smoker	1.12	0.76, 1.64	0.570	1.13	0.75, 1.68	0.565
BMI	Underweight/Healthy (<25)	-	-	-	-	-	-
	Overweight/Obese (≥25)	0.94	0.64, 1.39	0.764	1.06	0.71, 1.58	0.783
Insurance	Commericial	-	-	-	-	-	-
	Medicare only	0.73	0.45, 1.18	0.198	0.52	0.31, 0.85	0.010
	Medicaid only	1.16	0.64, 2.12	0.616	0.68	0.36, 1.27	0.226
	Dual (Medicare/Medicaid)	1.50	0.20, 11.2	0.691	3.12	0.91, 10.8	0.071
Histology	Adenocarcinoma	-	-	-	-	-	-
	Squamous	0.86	0.32, 2.35	0.773	0.48	0.17, 1.32	0.155
Common vs uncommon *EGFR* mutations	Common/Typical *EGFR* (Exon 19 deletions and exon 21 L858R substitutions, T790M)	-	-	-	-	-	-
	Uncommon *EGFR* (G719X, S768I, L861Q, exon 20 insertions, and complex mutations)	1.44	0.73, 2.87	0.295	1.98	0.91, 4.31	0.086
Multivariate model							
Age	<65	-	-	-	-	-	-
	≥65	1.89	0.69, 5.19	0.22	2.91	0.30, 28.6	0.36
Race/Ethnicity	Non-Hispanic White (NHW)	-	-	-	-	-	-
	Non-Hispanic Black (NHB)	3.08	1.12, 8.49	0.030	21.6	1.74, 268	0.017
	Hispanic	1.58	0.51, 4.83	0.42	12.9	0.94, 176	0.056
	Asian	0.96	0.28, 3.31	0.95	1.63	0.08, 33.3	0.75
PDC adherence (PDC ≥80%)	Yes	-	-	-	-	-	-
	No	0.38	0.14, 1.08	0.070	1.83	0.38, 8.87	0.45
Annual Household Income by Zip Code	<50K (USD)	-	-	-	-	-	-
	≥50K (USD)	1.01	0.45, 2.24	0.99	8.39	1.55, 45.4	0.014

Annual Household Income by Zip Code	<50K (USD)	-	-	-	-	-	-
	≥50K (USD)	1.01	0.45, 2.24	0.99	8.39	1.55, 45.4	0.014
Weight (kg)		1.00	0.98, 1.03	0.68			
Insurance	Commercial	-	-	-	-	-	-
	Medicare only	0.41	0.11, 1.51	0.18	0.03	0.00, 0.59	0.022
	Medicaid only	0.90	0.29, 2.76	0.85	0.24	0.02, 3.27	0.29
	Dual (Medicare/Medicaid)	0.60	0.06, 6.47	0.68	0.45	0.05, 4.56	0.50
Histology	Adenocarcinoma	-	-	-	-	-	-
	Squamous	2.47	0.61, 10.0	0.21	0.49	0.04, 5.85	0.57
Type of *EGFR*	Common/Typical *EGFR* (Exon 19 deletions and exon 21 L858R substitutions, T790M)	-	-	-	-	-	-
	Uncommon *EGFR* (G719X, S768I, L861Q, exon 20 insertions, and complex mutations)	1.68	0.47, 6.02	0.42	30.0	1.38, 653	0.030

P1.12A METASTATIC NON-SMALL CELL LUNG CANCER - TARGETED THERAPY - EGFR
SUNDAY, SEPTEMBER 8, 2024 - 12:00 - 14:00

P1.12A.05 Aumolertinib in Treatment-Naïve EGFR-Mutant NSCLC Patients with Brain Metastases:Efficacy and Safety Data from the ARTISTRY

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Introduction: Brain metastases (BMs) are the most common site of distant metastasis in non-small cell lung cancer (NSCLC), and the patients have a poor prognosis. Epidermal growth factor receptor (EGFR) gene are one of the main driver genes in NSCLC, and the incidence of brain metastases is higher in EGFR mutation-positive patients (44%-63%). Therefore, it is of great clinical significance to investigate the optimal treatment of BMs in patients with EGFR-mutated NSCLC. The third-generation EGFR-TKI is the optimization regimens of EGFR-mutated patients with BMs. The third-generation EGFR-TKIs showed significant efficacy and safety in patients with BMs harboring EGFR-sensitive mutations compared with first-generation EGFR-TKIs in FLAURA and AENEAS trial. The Bloom study proved it high dose of EGFR-TKIs have superior efficacy of EGFR-mutant NSCLC patients with leptomeningeal metastases. ARTISTRY (NCT04778800) is an ongoing dose-escalation study evaluating third-generation EGFR-TKI aumolertinib in three cohorts of EGFR-mutant NSCLC patients with brain/leptomeningeal metastases. The primary efficacy and safety data was previously presented at WCLC 2022. Here, we report update efficacy and safety data of the brain parenchyma metastases cohort 1 from the ARTISTRY.

Methods: Treatment-naïve EGFR-mutant NSCLC patients with brain parenchyma metastases received aumolertinib 110mg orally once daily. The dose was then escalated to 165mg in case of only intracranial progression. Assessments were performed every 4 weeks and then every 8 weeks after 2 consecutive disease control until extracranial progression as per RECIST v1.1. Endpoints included intracranial objective response rate (iORR), intracranial disease control rate (iDCR), ORR, DCR, progression free survival (PFS) and safety.

Results: At data cut-off (March 15, 2024), a total of 26 patients were enrolled and the median follow-up time was 23.4 months (range, 1.3-39.7). In the 110 mg group, the iORR was 88.5% (23/26; 95% CI: 76.2-100), the iDCR was 96.2% (25/26; 95% CI: 88.8-100), the ORR was 88.5% (23/26; 95% CI: 76.2-100), the DCR was 96.2% (25/26; 95% CI: 88.8-100), and the median PFS was 18.5 months (95% CI: 15.0-30.9). Total 5 patients dropped out due to lung lesions progression, but the brain lesions remained partial response (PR); 2 patients dropped out because of lung and brain lesions progression. In the 165mg group, the iORR and iDCR were 20% (1/5) and 80% (4/5), respectively, and the mPFS was 7.4 months (95% CI:2.0-15.2). The most common grade 1-2 adverse events (AEs) in all patients were elevated creatine kinase, alanine aminotransferase increased, glutamic aminotransferase increased.

Conclusions: Aumolertinib showed superior antitumor activity with a manageable safety profile as first-line therapy in EGFR-mutant NSCLC patients with brain metastases, and patients with brain metastases progression still benefit from high dose Aumolertinib. Enrollment for this trial will continue, and further analyses are warranted to determine longer-term outcomes.

Keywords: Brain metastases, dose escalation, aumolertinib

P1.12A METASTATIC NON-SMALL CELL LUNG CANCER - TARGETED THERAPY - EGFR
SUNDAY, SEPTEMBER 8, 2024 - 12:00 - 14:00

P1.12A.06 A Phase II 80 Mg Osimertinib in Patients with Leptomeningeal Metastases Associated with EGFR Mutation-Positive NSCLC (BLOSSOM)

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Introduction: Leptomeningeal metastases (LM) exhibit a high incidence in patients with EGFR-mutated non-small cell lung cancer (NSCLC) post-treatment with first- or second-generation EGFR tyrosine kinase inhibitors (TKIs). This investigation evaluates the efficacy, safety, and pharmacokinetics of 80 mg osimertinib in LM patients resistant to prior first- or second-generation EGFR TKIs.

Methods:

In this Phase II multicenter, open-label, single-arm study, 80 mg osimertinib was administered to patients with EGFR-mutated NSCLC who had developed LM subsequent to treatment with prior EGFR TKIs. The primary endpoint was overall survival (OS), assessed alongside objective response rate by the blinded independent central review (BICR) and a pharmacokinetic analysis of plasma and cerebrospinal fluid (CSF) on the first day of cycles 3 and 6.

Results: A total of 73 patients diagnosed with LM were treated with osimertinib, including 64 patients evaluable for the LM efficacy set—T790M negative (n=62) and T790M positive (n=2). The median OS in the full-analysis set was 15.6 months (95% CI: 11.5-20.2). The objective response rate for LM was 51.6%, including a 15.6% complete response rate, and the disease control rate was 81.3% by BICR in the LM efficacy evaluable set. The median LM progression-free survival was 11.2 months (7.7-15.3), the duration of response was 12.6 months (7.6-17.7), and OS was 15.0 months (11.3-18.7). Pharmacokinetic analysis showed that the CSF to free plasma osimertinib ratio was 22%. Most safety profiles were grade 1 and 2.

Conclusions: The study demonstrates significant intracranial efficacy and survival benefits of 80 mg osimertinib in NSCLC patients with LM. The data support considering 80 mg of osimertinib as a treatment option for EGFR-mutated NSCLC patients with LM, irrespective of T790M mutation status.

Keywords: Osimertinib, Leptomeningeal metastasis, EGFR

P1.12A METASTATIC NON-SMALL CELL LUNG CANCER - TARGETED THERAPY - EGFR
SUNDAY, SEPTEMBER 8, 2024 - 12:00 - 14:00

P1.12A.07 A Phase 1 Study of TY-9591 in Advanced Non-Small Cell Lung Cancer (NSCLC) Patients with EGFR Positive Mutation.

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Introduction: TY-9591 is an efficient, ATP competitive, irreversible, oral third-generation EGFR-TKI with antitumor effects on both EGFR-sensitizing mutations and EGFR T790M resistance mutations. This study aimed to evaluate the safety and efficacy of TY-9591 in patients with locally advanced or metastatic EGFRm+ NSCLC.

Methods: In this study, 105 patients with EGFRm+ advanced NSCLC were assigned to receive TY-9591 (19 patients in the "3+3" dose-escalation phase, at a dose of 20-200 mg once daily, and 86 patients in the dose-expansion phase, at a dose of 80, 120, 160 mg once daily) (NCT04204473). 79 of 86 patients in the dose-expansion phase were EGFR-TKIs treatment naïve and EGFR sensitizing mutated (exon 19 deletion or exon 21 L858R substitution). The primary efficacy end point was objective response rate (ORR) assessed every 6 weeks by investigator based on RECIST v1.1.

Results: As off May 18, 2023, median follow-up time during the dose-escalation phase and expansion phase was 29.1 and 23.7 months respectively. No DLT was observed and MTD was not reached. For the intention-to-treat population (n=105), most common treatment-related adverse events (TRAEs) (≥10%) were hematologic toxicity, such as white blood cell count decreased (54.3%) , anaemia (39.0%), platelet count decreased (37.1%), lymphocyte count decreased(19.0%), diarrhea (30.5%), rash (17.1%) , etc, and most of them were Grade 1 or 2. Grade 3-4 TEAEs were occurred in 43.8% patients. Treatment-related SAEs were reported in 7.6% of patients. No interstitial lung disease (ILD), cardiomyopathy and keratitis was reported. The exposure level of metabolite (TY-9591-D1) was approximately 4.76% to 6.36% of that of the original drug. For the efficacy-evaluable treatment naive population with EGFR sensitizing mutation (n=78), the overall confirmed ORR of all doses (80/120/160mg) was 85.9% (95% confidence interval [CI]: 76.2-92.7). The median duration of response (DOR) was 20.2 months (95% CI: 15.9, -). The disease control rate (DCR) was 94.9% (95% CI:87.4-98.6). The median depth of response (DepOR) was 50.46% (95% CI: 9.8-84.3), which was above 30% in 72 patients. In the 160 mg dose group (n=12), the confirmed ORR was 91.7% (95% CI: 61.5-99.8), the median DOR was not reached, the median DCR was 100.0% (95% CI: -, -). The median progression-free survival (PFS) was 21.5 months (95% CI: 17.3-27.3) , which of exon 19 deletion and exon21 L858R subgroups was 25.7 months (95%CI:17.5-) and 19.3 months (95%CI:13.1-23.5) , respectively. The median OS has not been reached. Among patients diagnosed with disease progression through radiology, 7 patients (8.9%) experienced progression due to brain metastases, most of them (6/7 patients) have baseline brain metastases. Among 11 patients with measurable intracranial lesions, the intracranial ORR (iORR) based on RECIST v1.1 was 90.9% (4 patients achieved CR, 6 patients achieved PR and 1 patient remained SD), most response occurred in the 160mg dose group (iORR was 100.0%, n=8).

Conclusions: TY-9591 is a highly effective and well-tolerated third-generation EGFR TKI for patients with EGFR sensitizing mutation advanced NSCLC, especially for patients with L858R mutations or with brain metastases. Pivotal phase 2 (NCT05948813) and phase 3 trials (NCT05382728) are onging.

Keywords: TY-9591, EGFR sensitizing mutation, Third-generation EGFR-TKI

P1.12A METASTATIC NON-SMALL CELL LUNG CANCER - TARGETED THERAPY - EGFR
SUNDAY, SEPTEMBER 8, 2024 - 12:00 - 14:00

P1.12A.08 The Mechanism Study on a Novel CD3-EGFR Bispecific Antibody Combo Improves Osimertinib-Resistant NSCLC Tumor Environment

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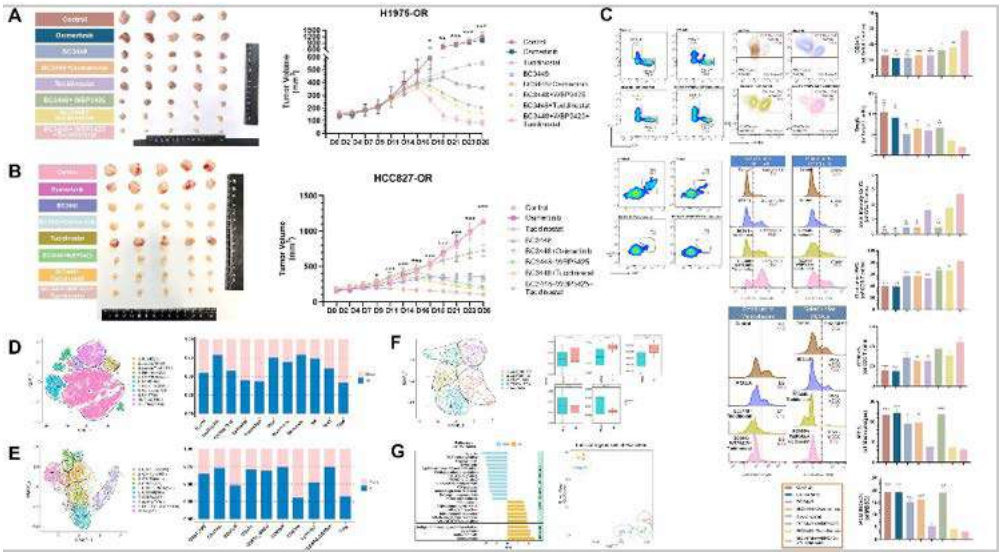
Introduction: Mechanisms of Osimertinib resistance are unclear in 50% of cases, highlighting the urgent need for novel therapeutic strategies. We reported the antitumor effect of BC3448 (CD3×EGFR) in Osimertinib-resistant NSCLC cell lines and xenograft tumors (WCLC 2024, MA04.04). Here, we propose a combinational therapy with Tucidinostat (HDAC inhibitor) and WBP3425 (4-1BB Agonist) to target resistant tumors and remodel the tumor microenvironment.

Methods: Osimertinib-resistant cell lines (H1975-OR and HCC827-OR) were established via stepwise escalating exposure and maintaining in 1M Osimertinib. HuHSC-NOG-EXL mice were purchased from Charles River Laboratories. Experimental mice were divided into seven groups, with the exposure of following drugs including Osimertinib (5 mg/kg, i.g., qd), BC3448 (0.3 mg/kg, i.p., biw), Tucidinostat (12.5 mg/kg, i.g., qd), and WBP3425 (10 mg/kg, i.p., biw). At the endpoint, we performed scRNA-seq for humanized mouse tumors with BD Rhapsody Single-Cell Analysis System.

Results: In vivo, BC3448 effectively suppressed the growth of these tumors, with added WBP3425 and Tucidinostat boosting efficacy (Fig. 1A and 1B). However, combining BC3448 with Osimertinib did not overcome resistance. Flow cytometry analysis revealed that the triple drug therapy involving BC3448, WBP3425, and Tucidinostat activated more CD8+ T cells, facilitated the differentiation of stem memory T cells, and reduced the infiltration of Treg, M2, and PNM-MDSC populations (Fig. 1C). scRNA-seq) demonstrated that compared to BC3448 mono-therapy (Mono), the triple therapy (Tri) recruited more mast cells, monocytes, monocyte-derived macrophages (mono.mac), NK T cells, cycling NK, with reduced fibroblast and tissue-resident macrophage (TRM) infiltration (Fig. 1D). Regarding T cell subtypes, the Tri group showed a dominance of interferon-stimulated gene (ISG)-CD4 T, CD4 central memory T (Tcm), CD4 naïve T (Tn), FCER1G-CD4 effector T (Teff), and CD8 Teff cells, while CD4 exhausted T (Tex) and Treg cells were more prevalent in the Mono group (Fig. 1E). In terms of cycling T cell subtypes, cycling CD4 Tcm, cycling CD4 Teff, and cycling CD4 Tn significantly increased in the Tri group, while cycling Treg and cycling CD8 Tex did not show notable changes (Fig 1E). Comparatively, Mono.mac in the Tri group upregulated pathways related to antigen processing and presentation, antitumor (AT) responses, and macrophage recruitment to the tumor, while downregulating angiogenesis pathways (Ang) as demonstrated in Figure 1G.

Conclusions: The additional combination of WBP3425 and Tucidnostat with BC3448 demonstrated a synergistic efficacy to Osimertinib-resistant tumors via a multidimensional reshaping of the microenvironment, potentially offering a comprehensive approach to combat NSCLC resistance.

Keywords: Bispecific Antibody, EGFR, NSCLC



P1.12A METASTATIC NON-SMALL CELL LUNG CANCER - TARGETED THERAPY - EGFR
SUNDAY, SEPTEMBER 8, 2024 - 12:00 - 14:00

P1.12A.09 A Phase 1b Study of the MER Tyrosine Kinase Inhibitor, MRX-2843, in Combination with Osimertinib in Advanced EGFR Mutant Non-Small Cell Lung Cancer

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Introduction: The 3rd generation EGFR TKI, osimertinib, is an effective treatment of EGFRm NSCLC, but resistance eventually develops. MER tyrosine kinase (MERTK), a member of the TAM (TYRO3, AXL, MERTK) family of receptor tyrosine kinases mediates resistance to osimertinib. MRX-2843 is a novel small molecule MERTK TKI; we conducted a phase Ib study to evaluate the safety and efficacy of MRX-2843 in combination with osimertinib in participants (pts) with EGFRm NSCLC.

Methods: Pts were enrolled in cohorts of 3 during the dose escalation phase to test the combination of osimertinib (80mg orally once daily) along with increasing doses of MRX-2843 (orally once daily) using an escalation with overdose control (EWOC) design with a target toxicity level of 0.33. The activity of this combination is being investigated in the dose expansion cohorts of 20 pts with EGFRm NSCLC who are osimertinib naive and another with osimertinib resistance.

Results: The first pt enrolled in February 2021. Dose escalation cohorts of MRX-2843 at 60, 80, 100 and 120 and 160mg (dose levels 1-5, respectively) with osimertinib 80mg have completed enrollment. Overall, 20 pts have enrolled in the dose escalation phase. Baseline characteristics include: median age 70 years (range 51-80), 17 were female and 12 White/5 Black/3 Asian participants.There were no DLTs in dose levels 1-4. A total of 9 patients were enrolled in dose level 5, MRX-2843 160 mg. Three patients experienced DLTs at dose level 5; therefore, this was determined to be the MTD of the combination, according to the EWOC design. These DLT included G2 nausea/vomiting causing patient to receive <75% MRX-2843; G4 hyponatremia and G3 pneumonitis. Table 1 demonstrates the adverse events. In the dose escalation phase, though there was no CR/PR; 60% had disease stabilization by RECIST 1.1 and 25% were free from progression at 6 months.

Conclusions: The combination of MRX-2843 and osimertinib is safe at doses up to 160 mg/d and 80 mg/d respectively. Based on suggestion of preliminary evidence of efficacy, expansion cohorts to include both treatment-naïve and osimertinib-resistant patients is currently underway. (NCT # 04762199)

Keywords: EGFR

Treatment Related Adverse Events (TRAE)	Treatment Arm (n =20)	
	All Grade	Grade 3-4
Total Subjects with any Event	*14 (70.00)*	*1 (5.00)*
Alkaline phosphotase increased	1 (5.00)	0
Anemia	2 (10.00)	0
Aspartate aminotransferase increased	3 (15.00)	0
Aspartate aminotransferase increased (intermittent)	1 (5.00)	0
Creatinine increased	3 (15.00)	0
Decreased appetite	1 (5.00)	0
Dysgeusia	3 (15.00)	0
Fatigue	3 (15.00)	0
Hyperglycemia	1 (5.00)	0
Hyperpigmented spots (pea sized)	1 (5.00)	0
Hypertension	1 (5.00)	1 (5.00)
Hypokalemia	3 (15.00)	1 (5.00)
Hypomagnesemia	2 (10.00)	0
Ill defined cutaneous lesion to left shin	1 (5.00)	0
Nausea	7 (35.00)	0
Neck cramp	1 (5.00)	0
Rash	2 (10.00)	0
Shingles	1 (5.00)	0
Alanine aminotransferase increased	2 (10.00)	0
Anorexia	1 (5.00)	0
Constipation	2 (10.00)	0
Diarrhea	6 (30.00)	1 (5.00)
Dizziness	1 (5.00)	0
Mouth sensitivity	2 (10.00)	0
Rash maculo-papular	1 (5.00)	0
Vomiting	2 (10.00)	1 (5.00)
Dry mouth	1 (5.00)	0
Hypokalemia	1 (5.00)	0
Hypocalcemia	1 (5.00)	0
Lymphocyte count decreased	1 (5.00)	1 (5.00)
Pneumonitis	0	1 (5.00)
Platelet count decreased	1 (5.00)	
Hyponatremia	2 (10.00)	1 (5.00)
Burning sensation in throatand stomach	1 (5.00)	0

P1.12A METASTATIC NON-SMALL CELL LUNG CANCER - TARGETED THERAPY - EGFR
SUNDAY, SEPTEMBER 8, 2024 - 12:00 - 14:00

P1.12A.10 Effect of De Novo Co-Mutations on Clinical Outcomes in Patients Receiving First-Line Osimertinib for EGFR-Mutated NSCLC

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Introduction: Osimertinib remains the standard-of-care first-line therapy for most patients with EGFR-mutated advanced non-small cell lung cancer (NSCLC). Since FLAURA2, and with other novel therapeutic combinations on the horizon, identifying patients at higher risk for inferior outcomes to first-line osimertinib may enable more appropriate selection for treatment intensification and improve prognostic assessment. While the negative prognostic impact of TP53 co-mutations has been previously characterized in general and in the setting of earlier EGFR-targeted therapies, here we seek to expand on the impact of de novo co-mutations among patients receiving first-line osimertinib for metastatic NSCLC.

Methods: This multicenter retrospective study across 3 U.S. sites included adult patients with metastatic NSCLC and classic sensitizing EGFR mutations (exon 19 deletion, exon 21 L858R) receiving first-line osimertinib monotherapy and with tissue-based next-generation sequencing at diagnosis. Clinicopathologic characteristics, including frequency of co-occurring pathogenic or likely pathogenic genetic alterations, were collected. Kaplan-Meier survival analyses and Cox regression were used to estimate time-to-treatment failure (TTF) and overall survival (OS) by number of co-mutations, individual mutations, and molecular pathways of interest (P53, cell cycle, AKT/PI3K, WNT/beta-catenin, epigenetic modification, and EGFR amplification).

Results: 180 eligible patients were included (median age 68, 62% female, 72% never smokers, 98% adenocarcinoma histology, 51% CNS metastases at diagnosis). Patients with 2 or more co-occurring genetic alterations had increased risk of death (HR 1.9, p=0.023), shorter median OS (25.7 vs 48.6 months), and numerically inferior median TTF (15.9 vs 20.9 months, p=0.25) compared to those without co-mutations. The OS difference remained significant on multivariate analysis accounting for primary EGFR mutation. There were no significant OS or TTF differences for those with only 1 co-mutation, compared to no co-mutations. TP53 was most frequently co-mutated (59%), followed by EGFR amplification (11%), RB1 (8%), PIK3CA (7%), CTNNB1 (7%), and CDKN2A (6%). Conversely, KEAP1 (0%) and STK11 (1%) mutations were infrequent in this cohort. Co-mutation of both TP53 and PIK3CA (TP53mut/PIK3CAmut) demonstrated inferior OS compared to TP53 mutation alone (TP53mut/PIK3CAwt) or TP53 and PIK3CA wild-type (TP53wt/PIK3CAwt) (21.9 vs 40.4 and 41.8 months, p=0.04), with similar numerical trend for median TTF (14.1 vs 20.9 and 24.5 months, p=0.17). No such differences were identified for other TP53 co-mutation pairs. Among molecular pathways, the presence of co-mutations in genes involved in epigenetic modification (ARID1A, IDH1/2, MYC) was associated with shorter median OS (19.9 vs 39.8 months, p=0.03) and numerically shorter median TTF (11.6 vs 20.9 months, p=0.24) compared to those without these alterations.

Conclusions: The presence of 2 or more de novo co-mutations, particularly co-mutation of TP53 and PIK3CA, as well as alterations in epigenetic pathway genes, was associated with inferior OS in EGFR-mutated NSCLC patients receiving first-line osimertinib. While TTF on osimertinib trended similarly, we hypothesize that tumors with these findings at baseline have increased propensity for mutagenesis and therapeutic resistance to both first-line osimertinib and subsequent therapies. Given the evolving landscape of EGFR-mutated NSCLC, these high-risk subgroups may reap particular benefit from combination treatment strategies such as the addition of chemotherapy or amivantamab to first-line tyrosine kinase inhibitors.

Keywords: co-mutation, osimertinib, EGFR-mutated NSCLC

P1.12A METASTATIC NON-SMALL CELL LUNG CANCER - TARGETED THERAPY - EGFR
SUNDAY, SEPTEMBER 8, 2024 - 12:00 - 14:00

P1.12A.11 Analysis of Uncommon EGFR Exon 19 Alterations Identified by Liquid Biopsy in Advanced Non-Small Cell Lung Cancer (NSCLC)

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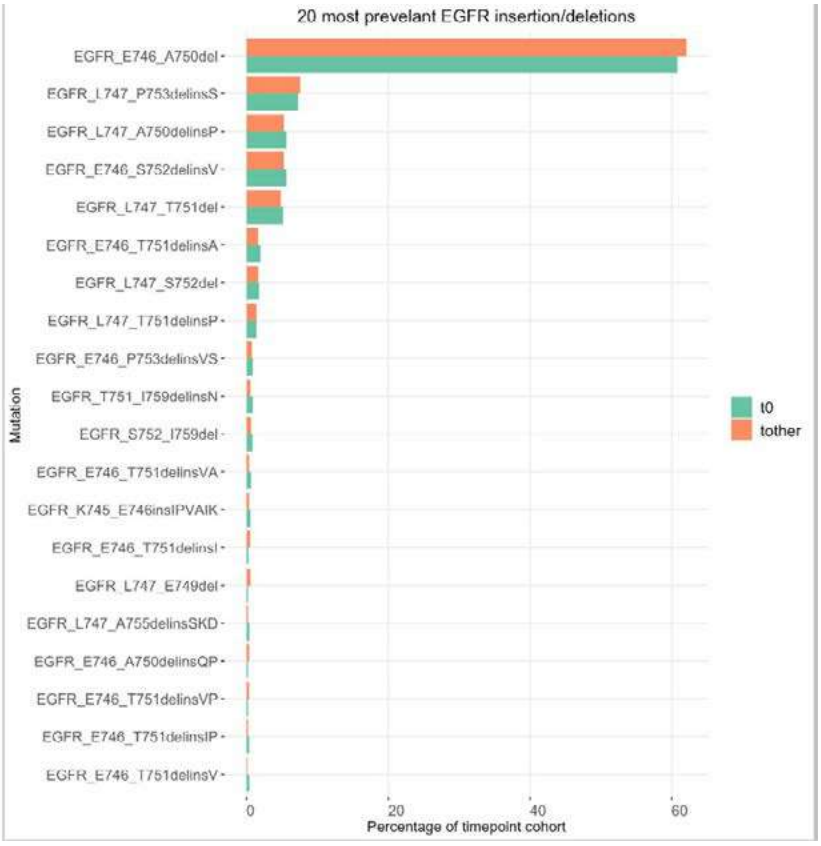
Introduction: EGFR exon 19 deletions (ex19del) are heterogeneous and comprised of >40 distinct insertion/deletions (indels). Uncommon ex19dels studied pre-clinically show mixed response to EGFR tyrosine kinase inhibitors (TKI), with limited literature on co-alterations and resistance mechanisms. Following observation of two uncommon EGFR ex19del cases (L747_P753delinsS and L747_A750delinsP) at the West Cancer Center/Guardant Health molecular tumor board, discussion proved optimal selection of EGFR TKI in this scenario is challenging. As such, we assessed uncommon EGFR ex19del alterations identified by liquid biopsy and herein report a large dataset describing prevalence and co-alterations to inform clinical decision-making.

Methods: Patients with NSCLC and >1 EGFR ex19del identified as part of clinical Guardant360 testing from 02/2015-09/2023 were queried to assess prevalence of uncommon ex19del and co-alterations. Mutations were profiled as “common” or “uncommon” based on public sources in cBioPortal, including TCGA and MSK datasets. Co-alterations were analyzed in cohorts of common EGFR L746_A750del (n=4540), uncommon EGFR ex19del (n=2733), treatment naive timepoint (T0, n=1816), and other time points (Tother, n=3088); groups were compared using Fisher’s Exact Test (significance defined as p<0.05).

Results: EGFR ex19del were identified in 8% of patients with cfDNA alterations detected similar to published rates (9.1%, AACR GENIE). EGFR ex19indels were identified in 7273 unique patients, with common EGFR L746_A750del observed in (62%) and uncommon ex19del variants observed in 38% (Figure 1). Frequencies of common / uncommon ex19del and co-alterations, such as TP53, EGFR, PIK3CA variants and EGFR copy number amplifications (CNA), did not vary by T0/tother timepoints. EGFR SNVs T790M, C797S, and G724S were the most prevalent co-occurring alterations within the Tother cohort and nearly absent in the T0 cohort, likely due to their association with acquired resistance. Significant co-alteration differences between common / uncommon ex19del groups were noted in BRAF SNVs (p=0.003), ALK indels (p= 0. 001), FGFR2 fusions (p=0.005) and other genes. Co-alterations in 15 genes were significantly different in prevalence between T0 and Tother cohorts, including MET amplifications and SNVs in BRAF, PIK3CA and MET (all p <0.0001), all with increased frequency in Tother, likely due to their association with EGFR TKI resistance.

Conclusions: To our knowledge, this is the largest liquid biopsy analysis comparing common/uncommon ex19dels in NSCLC and shows similar genomic findings across groups. Further work should be done to explore additional genomic and non-genomic factors to aid in patient selection for EGFR TKIs for uncommon findings.

Keywords: EGFR, genomic testing, biomarker



P1.12A METASTATIC NON-SMALL CELL LUNG CANCER - TARGETED THERAPY - EGFR
SUNDAY, SEPTEMBER 8, 2024 - 12:00 - 14:00

P1.12A.12 Liquid Biopsy Based Risk Stratification and Intensification of Treatment in EGFR Mutant Advanced NSCLC (L-BRITE) Preliminary Analysis

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Introduction: Documentation of ctDNA clearance at various time points after targeted therapy correlates with better progression free survival (PFS). Serial plasma ctDNA monitoring may provide risk stratification strategy by selecting the poor risk and a window of opportunity of treatment escalation which has not been formally tested. Patients of advanced NSCLC with EGFR mutations are treated with TKIs alone and Osimertinib is preferred over first generation TKIs. Recently, combination chemotherapy with TKIs have shown promising results. In this trial, we evaluated the role of combining chemotherapy in patients with residual ctDNA after gefitinib monotherapy for initial 9-12 weeks, in terms of 6 months PFS rates.

Methods: We conducted a phase II study at a single center on treatment-naïve metastatic NSCLC patients with EGFR mutations detected by liquid biopsy. Treatment consisted of gefitinib monotherapy for 9-12 weeks followed by the addition of 4 cycles of carboplatin and pemetrexed followed by pemetrexed maintenance in patients with residual ctDNA. Serial ctDNA monitoring using ddpCR was planned at 3 monthly intervals. The primary endpoint of the study was to evaluate 6-month Progression-free survival (PFS) rate by adding chemotherapy to gefitinib in patients with residual CtDNA after gefitinib monotherapy with the presumption that it would improve 6 month PFS rates in these patients from 40% to 65%. Secondary objectives include evaluating 6 month PFS in ctDNA cleared patients post gefitinib, overall survival, resistance mutation development, safety, and quality of life, employing Simon's two-stage design to reach a target sample size of 31.

Results: Between May 2022 and December 2023, 60 out of 84 screened patients were enrolled in the study, with 21 of them being included for primary efficacy analysis. The median participant age was 52, with the majority having Exon 19 EGFR mutations (71.6%). Most (over 83%) presented with multiple metastases(>1), commonly in bones (75%). At the start, 35% had brain metastases; 66.6% of these were symptomatic, with 76% completing WBRT. At 9-11 weeks of gefitinib treatment, 42% showed CtDNA clearance. Among the 56.1% non-responders, 3 had progressive disease, prompting treatment intensification for 26 patients. In the study, the median progression-free survival (PFS) in ITT population was 12 months, with a 6-month PFS rate of 76.9%. Molecular response influenced 6-month PFS rates following the start of gefitinib, with 75.7% in ctDNA positive vs 85.7% in ctDNA negative groups. This difference was not statistically significant (P=0.44), likely due to the effect of added chemotherapy. Addition of chemotherapy led to an 84.8% 6-month PFS rate, achieving its primary endpoint in residual ctDNA patients over 8.6 months of follow up.In the intervention group (26 patients), 21 completed 4 chemotherapy cycles, experiencing 9 grade 3 adverse events. Post-chemotherapy, 8 showed partial response, 12 stable disease, and 1 progressive disease. Reevaluation of ctDNA in 18 patients showed a 50% clearance rate.

Conclusions: In conclusion, initial results indicate the potential benefits of a liquid biopsy-based escalation strategy, though constrained by a small cohort and short follow-up. The trial is still ongoing to complete accrual, with current findings still considered preliminary.

Keywords: EGFR NSCLC, LIQUID BIOPSY, CTDNA

P1.12A METASTATIC NON-SMALL CELL LUNG CANCER - TARGETED THERAPY - EGFR
SUNDAY, SEPTEMBER 8, 2024 - 12:00 - 14:00

P1.12A.13 When Targeted Therapy Targets the Heart: Osimertinib-related Cardiotoxicity in EGFR Mutated Non-Small Cell Lung Cancer

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Introduction: Epidermal Growth Factor Receptor (EGFR) mutations are present in approximately 15% of lung adenocarcinomas in the United States. Osimertinib has proven efficacy for patients with lung cancer harboring certain EGFR mutations. Despite its efficacy, Osimertinib is associated with increased risk of cardiac adverse events, including heart failure (HF). This retrospective analysis examines the use of cardiac imaging in detecting HF among Osimertinib-treated patients.

Methods: The analysis investigated EGFR-positive non-small cell lung cancer patients prescribed Osimertinib from 01/01/2017 to 12/31/2022 within Kaiser Permanente Northern California, an integrated healthcare system with 21 community cancer centers serving 4.4 million patients. We assessed the use of cardiac imaging with transthoracic echocardiogram (TTE) or multigated acquisition scan (MUGA) and change in ejection fraction (EF) measured by TTE or MUGA between one year before treatment up to one year after treatment discontinuation. Patients were followed for HF-related admissions or ED visits from medication initiation until one-year post-discontinuation, death, health plan disenrollment, or study end (12/31/2023), whichever occurred earliest.

Results: This study evaluated 832 patients (median age: 76.4 years; 67.5% female; 50.5% Asian; 60.1% never smoked). The proportion of patients who underwent both baseline and follow-up cardiac imaging was 70.1%. Those in the EF reduction group commonly had a history of atrial fibrillation or already diminished EF (Table 1). During the research period, a total of 3,741 TTEs and 691 MUGA scans were conducted. The occurrence of HF-related ED visits or hospital admissions, which could be associated with Osimertinib therapy, was minimal, with only six cases identified. This translates to an incidence rate of 0.4 cases per 100 person-years, The median time from the latest cardiac imaging to HF related event was 24.5 days. All six patients for HF had existing cardiac comorbidities with the most common being atrial fib. All patients presented with clinical symptoms, including shortness of breath with bilateral pleural effusions.

Conclusions: Our retrospective analysis sheds light on the real-world application of cardiac imaging for patients with EGFR-positive NSCLC on Osimertinib. Findings point to a rare incidence of heart failure from Osimertinib. The expected benefit of outpatient cardiac imaging in averting heart failure related hospital visits was unsupported. These insights call for a re-evaluation of regular EF monitoring, which may be unnecessary for all patients and instead should be tailored for those at highest risk for developing heart failure complications or those with preexisting cardiac conditions.

Keywords: Osimertinib, Heart Failure, Cardio Oncology

Table 1: Demographic Distribution and Cardiac Monitoring Results in Osimertinib-Treated NSCLC Patients with EGFR Mutations

	Total (N=832)	No EF Measure (N=56)	EF Reduction (N=55)	No EF Reduction (N=520)	Baseline EF Only (N=119)	Follow-up EF Only (N=74)	P-value
Age, median (IQR)	69.0 (61.2-76.4)	67.0 (60.1-76.2)	70.3 (62.2-81.1)	69.3 (61.1-76.4)	69.0 (61.6-77.2)	67.2 (61.2-72.8)	0.35
Female Gender	562 (67.5)	36 (64.3)	26 (47.3)	**374 (70.8)***	76 (63.9)	50 (67.6)	**0.01***
Race/Ethnicity							0.60
Non-Hispanic White	287 (34.5)	21 (37.5)	18 (32.7)	179 (33.9)	40 (33.6)	29 (39.2)	
Non-Hispanic Black	30 (3.6)	1 (1.8)	0 (0.0)	23 (4.4)	4 (3.4)	2 (2.7)	
Asian	420 (50.5)	28 (50.0)	32 (58.2)	257 (48.7)	64 (53.8)	39 (52.7)	
Hispanic	66 (7.9)	6 (10.7)	3 (5.5)	45 (8.5)	9 (7.6)	3 (4.1)	
Multi-racial/Other/Unknown	29 (3.5)	0 (0.0)	2 (3.6)	24 (4.6)	2 (1.7)	1 (1.4)	
Smoking History							0.15
Current/Former	257 (30.9)	20 (35.7)	17 (30.9)	155 (29.4)	47 (39.5)	18 (24.3)	
Never/Unknown	575 (69.1)	36 (64.3)	38 (69.1)	373 (70.6)	72 (60.5)	56 (75.7)	
Baseline Reduced EF*	23 (2.8)	--	**5 (9.1)***	14 (2.7)	4 (3.4)	--	**0.04***
Elixhauser Comorbidity Index, Median (IQR)	4.0 (2.0-5.0)	4.0 (2.0-5.0)	4.0 (3.0-5.0)	4.0 (2.0-5.0)	4.0 (3.0-6.0)	4.0 (2.0-5.0)	0.73
Cardiac comorbidities							
Coronary artery disease	283 (34.0)	13 (23.2)	26 (47.3)	182 (34.5)	39 (32.8)	23 (31.1)	0.11
Chronic kidney disease	93 (11.2)	3 (5.4)	3 (5.5)	67 (12.7)	15 (12.6)	5 (6.8)	0.16
Diabetes	192 (23.1)	10 (17.9)	15 (27.3)	136 (25.8)	18 (15.1)	13 (17.6)	0.08
Atrial fibrillation	63 (7.6)	3 (5.4)	**10 (18.2)***	39 (7.4)	9 (7.6)	2 (2.7)	**0.02***
Hypertension	472 (56.7)	28 (50.0)	36 (65.5)	303 (57.4)	69 (58.0)	36 (48.6)	0.30
Dyslipidemia	437 (52.5)	25 (44.6)	31 (56.4)	290 (54.9)	57 (47.9)	34 (45.9)	0.26
Follow-up years, median (IQR)	1.7 (1.1-2.7)	1.2 (0.4-2.1)	2.0 (1.4-3.4)	2.0 (1.3-3.0)	0.8 (0.3-1.3)	1.7 (1.0-2.7)	< 001
ED/Hospitalizations for HF	6 (0.7)	0 (0.0)	4 (7.3)	1 (0.2)	0 (0.0)	1 (0.2)	

EF Reduction is defined as a change in EF greater than or equal to 10% and EF<53%
(*) denotes significant P-value <0.05
This table details the demographics and comorbidities of 832 patients, stratified by the extent and findings of cardiac monitoring, including no EF measurement, EF reduction, no EF reduction, baseline EF only, and follow-up EF only groups. EF reduction is defined by at least two comparable measurements, signifying active cardiac surveillance. The 'follow-up EF only' group represents patients monitored from Osimertinib initiation without a prior EF assessment, whereas 'baseline EF only' refers to patients with a single assessment within one year, with no subsequent monitoring during therapy. Differences in demographic and clinical characteristics were compared using chi-square tests for categorical variables and ANOVA for continuous variables. Heart-failure ED or hospitalizations were obtained through databases using ICD codes and validated by chart review to confirm if the event was Osimertinib-induced.

P1.12B METASTATIC NON-SMALL CELL LUNG CANCER - TARGETED THERAPY - FUSIONS: ALK / ROS1 / RET / NTRK
SUNDAY, SEPTEMBER 8, 2024 - 12:00 - 14:00

P1.12B.01 Intracranial Efficacy of Lorlatinib via RANO-BM in ALK-Fusion NSCLC with CNS Metastases: A Retrospective, Multicenter Study

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Introduction: Despite the remarkable systemic efficacy achieved with lorlatinib in first-line phase III CROWN study and the later-line phase II B7461024 study, intracranial efficacy of lorlatinib via RANO-BM criteria in ALK fusion NSCLC patients with brain metastases (BMs) or leptomeningeal metastases (LMs) still unknown.

Methods: Adults diagnosed with metastatic ALK-positive NSCLC who had baseline BMs and/or LMs before administration of lorlatinib were enrolled in the retrospective multicenter study. The evaluation of intracranial lesions was based on RANO-BM criteria. The primary endpoint was intracranial objective response rate (iORR). The secondary endpoints were median intracranial progression-free survival (miPFS), intracranial disease control rate (iDCR), median duration of treatment (mDOT), median overall survival (mOS), and safety.

Results: Between July 1, 2022 and July 1, 2023, 27 participants from 3 institutions were enrolled. At the data cutoff (December 24, 2023), median follow-up was 9.0 months. Among all patients, 18.5% were with LMs, median prior therapy lines were 3. The iORR was 44.4% in all patients including 11.1% with complete responses. The iORR was 36.4% in patients who progressed after second-generation ALK inhibitor(s). Among 19 patients with detectable baseline BMs, iORR was 57.9%, and 73.7% had brain lesions reduced. The iORR of patients with LMs was 20.0%. In all patients, the iDCR, miPFS, mOS, and mDOT were 66.7%, 8.6, 16.1, and 8.5 months while the iDCR, miPFS, and mOS for patients with LMs were 60.0%, 4.0, and 8.6 months, respectively. Common adverse events (≥10%) included hypercholesterolemia (85.2%), hypertriglyceridemia (60.3%), and edema (18.5%) were no greater than grade 2.

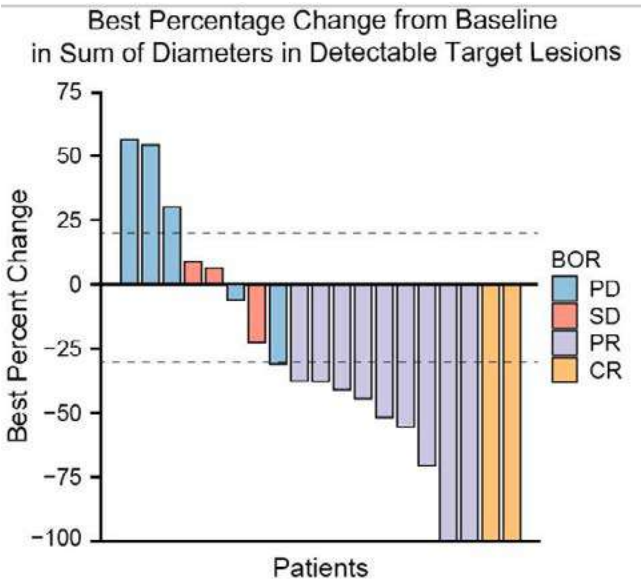
Conclusions: This is the first report shows the intracranial efficacy of lorlatinib in NSCLC patients with BMs and/or LMs assessed by RANO-BM criteria. Our study demonstrated that lorlatinib showed robust intracranial efficacy and manageable safety for patients with CNS metastases in the real-world setting.

Keywords: CNS metastases, RANO-BM criteria, lorlatinib

Characteristics of study cohort

Characteristic	Patient Cohort (N = 27)
Age, median years (IQR)	53.0(50.0-57.0)
Age, n (%)	
<65 years	2(7.4)
≥65 years	25(92.6)
Gender, n (%)	
Female	17(63.0)
Male	10(37.0)
Smoker, n (%)	
No	16(59.3)
Previous smoker	3(11.1)
Current smoker	1(3.7)
Unknown	7(25.9)
Brain or leptomeningeal metastasis at baseline, n (%)	
Brain metastasis	27(100)
Leptomeningeal metastasis	5(18.5)
Brain metastatic status, n (%)	
Single metastasis	6(22.2)
Multiple metastasis	21(77.8)

Other metastases, n (%)	
No	9(33.3)
Yes	18(66.7)
Histological type, n (%)	
ADC	24(88.9)
SCC	1(3.7)
Other types	2(7.4)
Treatment line, n (%)	
First-line	3(11.1)
Second-line	7(25.9)
Third-line and above	17(63.0)
Prior anticancer therapy, n (%)	
None	3(11.1)
Chemotherapy	1(3.7)
First generation ALK TKI	1(3.7)
Second generation±first generation ALK TKI(s)	22(81.5)
Previous Brain Radiotherapy, n (%)	
Yes	9(33.3)
No	18(66.7)
ECOG PS, n (%)	
0	4(14.8)
1	12(44.4)
2	9(33.3)
3	2(7.4)



P1.12B METASTATIC NON-SMALL CELL LUNG CANCER - TARGETED THERAPY - FUSIONS: ALK / ROS1 / RET / NTRK
SUNDAY, SEPTEMBER 8, 2024 - 12:00 - 14:00

P1.12B.02 Mechanisms of Resistance to First-Line vs Later-Line Alectinib in ALK Fusion-Positive Non-Small Cell Lung Cancer

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Introduction: Next-generation ALK tyrosine kinase inhibitors (TKI) such as alectinib have supplanted crizotinib as a standard first-line (1L) therapy for patients (pts) with ALK fusion-positive (ALK+) advanced/metastatic non-small cell lung cancer (mNSCLC). Post-progression biopsies can identify mechanisms of resistance and may guide therapy selection. Most studies on ALK resistance to date have evaluated pts who received alectinib as second- or later (2+) line therapy after prior crizotinib, with limited data on mechanisms of resistance when alectinib is used as 1L therapy.

Methods: This retrospective study included pts with ALK+ mNSCLC who received alectinib either as 1L therapy or 2L+ therapy after prior crizotinib. Tissue or plasma specimens obtained at progression (i.e., alectinib-resistant) were analyzed by next-generation sequencing (NGS). The frequency of detection of ALK resistance mutation(s), MET amplification, or histologic transformation was compared between the 1L and 2L+ cohorts.

Results: We identified 125 pts (median age, 54 years; 70.4% women) with ALK+ mNSCLC who received alectinib as 1L (n=66) or 2L+ (n=59) therapy and underwent post-alectinib biopsies. Median follow-up was 56.1 months. In total, 162 post-alectinib specimens underwent NGS (tissue: n=86 [81 pts]; plasma: n=76 [69 pts]); 21 (16.8%) pts had both tissue/plasma. Among 81 pts with post-alectinib tissue biopsies, 43 (53.1%) had ≥1 ALK resistance mutation detected, including ≥2 co-occurring ALK mutations in 2 (2.5%) pts. The most common ALK mutations among tissue biopsies were G1202R (n=17, 21.0%), I1171X (n=13, 16.0%), L1196X (n=7, 8.6%), and V1180L (n=6, 7.4%). When comparing the alectinib resistance landscape in 1L vs 2L+ cohorts, ALK resistance mutations were detected at a significantly lower frequency in the 1L vs the 2L+ tissue cohort (1L: 42.2% vs 2L+: 66.7%, p=0.029). ALK mutations were also detected at a numerically lower frequency in the 1L vs the 2L+ plasma cohort (1L: 35.9% vs 2L+: 58.6%, p=0.063), although this did not reach statistical significance. MET amplification had a trend towards more frequent detection in the 1L vs 2L+ tissue cohort (1L: 11.1% vs 2L+: 0%, p=0.062). Histologic transformation was identified in 4.4% (2/45) of 1L and 2.8% (1/36) of 2L+ post-alectinib tissue biopsies. We also compared the findings between plasma vs tissue post-alectinib biopsies. Plasma biopsy was more likely to detect ≥2 co-occurring ALK mutations than tissue in the 2L+ cohort (plasma: 20.7% vs tissue: 2.8%, p=0.039), though not in the 1L cohort (plasma: 7.7% vs tissue: 2.2%, p=0.33). There was a trend towards higher likelihood of detection of MET amplification by tissue than plasma in the 1L cohort (tissue: 11.1% vs plasma: 0%, p=0.058).

Conclusions: In this largest series of alectinib-resistant biopsies to date, on-target resistance (i.e., ALK resistance mutation) was significantly less common when alectinib was used as 1L vs 2L+ therapy, highlighting the importance of elucidating strategies to overcome off-target resistance to next-generation ALK TKI. Our findings additionally underscore the complementary role of tissue and plasma re-biopsies in delineating the resistance landscape, with tissue more likely to detect MET amplification and capable of identifying histologic transformation and plasma more likely to detect ≥2 co-occurring ALK mutations.

Keywords: ALK resistance mutations, Plasma and tissue biopsy, On- and off-target resistance

P1.12B METASTATIC NON-SMALL CELL LUNG CANCER - TARGETED THERAPY - FUSIONS: ALK / ROS1 / RET / NTRK
SUNDAY, SEPTEMBER 8, 2024 - 12:00 - 14:00

P1.12B.03 Real-World Outcomes of 2L ALK TKIs Following 1L Brigatinib for Patients with ALK+ NSCLC from the ALTA-1L Trial

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Introduction: In the phase III ALTA-1L trial, brigatinib showed superior efficacy vs. crizotinib in first line (1L) for anaplastic lymphoma kinase positive (ALK+) non-small cell lung cancer (NSCLC). A retrospective, non-interventional, multinational study reported real-world (rw) outcomes post-1L brigatinib1. This analysis assessed additional subgroups, including those stratified by response to 1L brigatinib.

Methods: Patients were previously enrolled in the brigatinib arm of ALTA-1L and discontinued 1L brigatinib during/after the trial. They were followed from last brigatinib dose until end of follow-up/death. Data were extracted from electronic case report forms. Second-line (2L) time-to-treatment discontinuation (TTD), 2L progression-free survival (PFS), and overall survival (OS) were estimated using Kaplan-Meier methods. Analyses evaluated patients who received any 2L ALK tyrosine kinase inhibitor (TKI), or 2L lorlatinib, or 2L alectinib. Patients receiving 2L ALK TKIs were also stratified as 1L brigatinib responders (best of complete or partial response by blinded independent review committee) or non-responders.

Results: As of October 18, 2023, 48 patients were enrolled (20 sites; 10 countries), and 40 (83.3%) received subsequent systemic anticancer therapies. Of these, 30 received a 2L ALK TKI (median follow-up, 17.0 months; median age, 57.5 years; White, 46.7%; Asian, 50.0%; female, 60.0%), including 16 (53.3%) on 2L lorlatinib and 8 (26.7%) on 2L alectinib. There were 23 (76.7%) 1L responders and 7 (23.3%) 1L non-responders, consistent with ALTA-1L results. For 2L ALK TKIs, rw objective response rate (rwORR) was 33.3% and disease control rate (rwDCR) was 70.8%. Median (95% CI) rwTTD was 34.7 (4.6, NR) months for 2L ALK TKIs, 37.2 (6.0, NR) months for 2L lorlatinib, and NR (1.1, NR) for 2L alectinib. Median (95% CI) rwPFS was 16.1 (4.4, NR) months for 2L ALK TKIs, 25.6 (3.8, NR) months for 2L lorlatinib, and 16.1 (1.1, NR) months for 2L alectinib. For 1L responders receiving 2L ALK TKIs, median (95% CI) rwTTD was 37.2 (3.6, NR) months and median (95% CI) rwPFS was 25.6 (3.8, NR) months. For 1L non-responders, median (95% CI) rwTTD was 11.6 (2.8, NR) months and median (95% CI) rwPFS was 13.0 (2.4, NR) months (Table).

Conclusions: This is the first long-term study evaluating rw outcomes post-1L brigatinib. Following 1L brigatinib discontinuation, most patients started another ALK TKI and had prolonged clinical benefit. 1L brigatinib responders appeared to have longer time on subsequent ALK TKI than 1L non-responders. This study was limited by small sample size. 1Delmonte A. Poster #38P ELCC 2024

Keywords: Brigatinib, ALK+ NSCLC, ALK TKI

Table. Real-world outcomes in patients receiving 2L ALK TKIs post 1L brigatinib

Outcome	2L ALK TKIs n=30	2L Lorlatinib n=16	2L Alectinib n=8	2L ALK TKIs - 1L responder n=23	2L ALK TKIs - 1L non-responder n=7
rwORR, %	33.3	30.8	57.1	33.3	33.3
rwDCR, %	70.8	76.9	85.7	66.7	83.3
Median rwTTD, mo (95% CI)	34.7 (4.6, NR)	37.2 (6.0, NR)	NR (1.1, NR)	37.2 (3.6, NR)	11.6 (2.8, NR)
Receiving 2L at 24 mo, % (95% CI)	53.1 (32.2, 70.2)	68.1 (35.4, 86.8)	50.0 (15.2, 77.5)	57.3 (32.1, 76.2)	42.9 (9.8, 73.4)
Median rwPFS, months (95% CI)	16.1 (4.4, NR)	25.6 (3.8, NR)	16.1 (1.1, NR)	25.6 (3.8, NR)	13.0 (2.4, NR)
24-mo PFS, % (95% CI)	47.0 (26.2, 65.3)	53.4 (23.9, 76.0)	43.8 (10.1, 74.2)	51.0 (26.4, 71.2)	34.3 (4.8, 68.5)
Median OS, months (95% CI)	74.7 (30.0, NR)	74.7 (30.0, NR)	NR (13.8, NR)	NR (30.0, NR)	74.7 (8.2, NR)
36-mo OS, % (95% CI)	66.7 (46.9, 80.5)	75.0 (46.3, 89.8)	75.0 (31.5, 93.1)	69.6 (46.6, 84.2)	57.1 (17.2, 83.7)

P1.12B METASTATIC NON-SMALL CELL LUNG CANCER - TARGETED THERAPY - FUSIONS: ALK / ROS1 / RET / NTRK
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P1.12B.04 Central Nervous System (CNS) Progression on CNS Penetrable ALK TKI: Real-World Practice Patterns and Patient Outcomes

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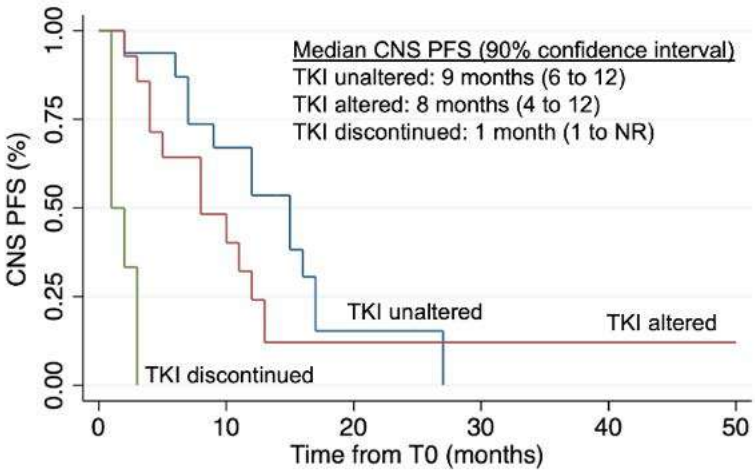
Introduction: Central nervous system (CNS) metastases are common in ALK-rearranged non-small cell lung cancer (NSCLC). The optimal treatment strategy for patients who develop CNS progression during treatment with CNS penetrable ALK tyrosine kinase inhibitors (TKIs) is unknown. Here, we characterize practice patterns and outcomes for patients who developed CNS progression during treatment with CNS penetrable ALK TKI.

Methods: Patients treated at Stanford Cancer Center who developed CNS progression (time 0, [T0]) on CNS penetrable ALK TKI (alectinib, brigatinib, ensartinib, lorlatinib) were identified. Patients were categorized according to TKI management (e.g., TKI unaltered, TKI altered [switched TKI or increased TKI dose], TKI discontinued) at T0. CNS progression-free survival (PFS) was evaluated using Kaplan-Meier and compared by log-rank test.

Results: We identified 36 patients (mean age 59) who developed CNS progression on CNS penetrable ALK TKI. Overall, 33 (92%) developed CNS parenchymal progression, 7 (19%) developed leptomeningeal progression and 18 (50%) developed concurrent systemic progression. At T0, 16 (44%) had TKI unaltered, 14 (39%) had TKI altered (8 switched TKI, 6 increased TKI dose), and 6 (17%) discontinued TKI (Table). Those patients who had their TKI altered tended to have a higher burden of disease at T0 progression (e.g., leptomeningeal disease, concurrent systemic progression). Radiation to the CNS was given concurrently at T0 in 14 (88%) of TKI unaltered and 3 (21%) of TKI altered patients. The median CNS PFS from T0 was not significantly different between these two groups (TKI altered versus unaltered; p=0.21) (Figure).

Conclusions: For patients with ALK-rearranged NSCLC with leptomeningeal progression and/or concurrent systemic progression, TKI change or dose increase was a feasible salvage strategy for CNS progression during treatment with CNS penetrable TKI. Our findings support continuing some form of TKI therapy among select patients with ALK-rearranged NSCLC who develop CNS progression on a CNS penetrable TKI.



Number at risk

TKI unaltered	16	10	2	0	0	0
TKI altered	14	6	1	1	1	1
TKI discontinued	6	0	0	0	0	0

Characteristic	Total Patients (N=36)n (%)	TKI unaltered (n=16)n (%)	TKI altered (switched TKI or increased TKI dose)(n=14)n (%)	TKI discontinued (n=6)n (%)	p-value
Baseline Characteristics					
Female	21 (58)	10 (63)	8 (57)	3 (50)	0.91
TKI at time of CNS progression (T0)					0.01
Alectinib	23 (64)	9 (56	12 (86)	2 (33)	
Brigatinib	4 (11)	0 (0)	2 (14)	2 (33)	
Ensartinib	6 (17)	5 (31)	0 (0)	1 (17)	
Number of prior systemic lung cancer treatments, including prior TKI					
0	7 (19)	5 (31)	1 (7.2)	1 (17)	**0.03**
1-2	16 (44)	7 (44)	9 (64)	0 (0)	
≥3	13 (36)	4 (25)	4 (29)	5 (83)	
Prior stereotactic radiosurgery	14 (39)	4 (25)	9 (64)	1 (17)	0.06
Prior whole brain radiation therapy	6 (17)	1 (6.3)	5 (36)	0 (0)	0.09
Disease Progression Characteristics					
Leptomeningeal progression	7 (19)	0 (0)	6 (43)	1 (17)	**0.01**
CNS parenchymal progression	33 (92)	16 (100)	11 (79)	6 (100)	0.12
Type of CNS parenchymal progression					0.26
No CNS parenchymal progression	3 (8.3)	0 (0)	3 (21)	0 (0)	
New CNS parenchymal lesion(s)	13 (36)	6 (37)	4 (29)	3 (50)	
Growth in baseline CNS	10 (28)	7 (44)	2 (14)	1 (17)	
parenchymal lesion(s)					
Both new and growth in baseline CNS parenchymal lesions	10 (28)	3 (19)	5 (36)	2 (33)	
Concurrent CNS and systemic progression	18 (50)	4 (25)	8 (57)	6 (100)	**0.01**

Abbreviations: ALK, anaplastic lymphoma kinase; CNS, central nervous system; NSCLC, non-small cell lung cancer; TKI, tyrosine kinase inhibitor

P1.12B METASTATIC NON-SMALL CELL LUNG CANCER - TARGETED THERAPY - FUSIONS: ALK / ROS1 / RET / NTRK
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P1.12B.05 Patient and Oncologist Preferences for ALK+ Advanced Non-Small Cell Lung Cancer Tyrosine Kinase Inhibitor Treatments

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Introduction: We aimed to understand the preferences of US patients and oncologists regarding key attributes associated with anaplastic lymphoma kinase positive (ALK+) tyrosine kinase inhibitors (TKIs) in the 1L setting and their willingness to tradeoff between benefits and risks.

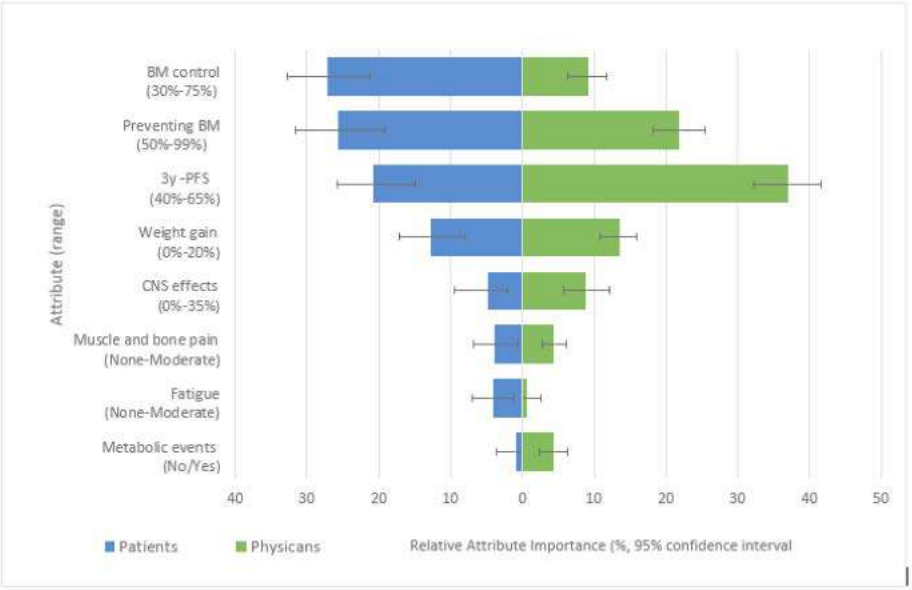
Methods: ALK+ advanced non-small cell lung cancer (aNSCLC) patients on TKIs and treating oncologists were recruited to participate in an online discrete choice experiment (DCE). The DCE was informed by a literature review of all 1L ALK TKIs, 30 qualitative interviews, and consultation with a steering committee including an oncologist and a patient advocate. The experiment comprised eight attributes: chance of lung cancer control at 3 years [3y-PFS], 3y stopping brain metastases (BM) development, 3y BM control, metabolic events, weight gain, central nervous system (CNS) effects, fatigue/asthenia, muscle and bone pain. DCE responses were analysed using a mixed logit model. Relative attribute importance (RAI) scores, which sum to 100%, were calculated to represent the relative impact of improving each attribute from the worst to the best level on overall treatment preference. The minimal benefit improvement in 3y-PFS that participants required to accept treatment-related risks was also calculated.

Results: 151 patients and 150 oncologists participated. Patients had mean age of 58.5 years (range 52-65), with most being male (65%). Over half (55%) had BM and were in 1L treatment (50%). Most oncologists practiced in academic (43%) or community hospitals (31%) and had been board-verified in oncology for over 5 years (89%). RAI scores (Figure 1) showed that the treatment benefits outweighed risks for both patients and oncologists, contributing to 84% of patient choices and 68% of physician choices. Preventing BM development was most important to patients (27%), while for oncologists PFS (37%) was most important. To compensate for the increased risk of moderate fatigue and moderate muscle and bone pain, patients required a treatment to increase 3y-PFS by 5.0% and 4.5% respectively, nearly four times more than required for risk of metabolic events or weight gain. Oncologists required at least a 3% improvement in 3y-PFS to accept a muscle or bone pain risk or metabolic events. Oncologists required a three-times greater increase in 3y-PFS than patients to accept increased risk of metabolic events.

Conclusions: Understanding trade-offs that oncologists and patients are willing to make between treatment attributes may facilitate shared decision-making in the 1L setting of ALK+ aNSCLC. Both patients and oncologists were willing to accept risks in exchange for treatment benefits.

Keywords: Preference, ALK, TKI

Figure 1. Relative attribute importance – patients and oncologists



P1.12B METASTATIC NON-SMALL CELL LUNG CANCER - TARGETED THERAPY - FUSIONS: ALK / ROS1 / RET / NTRK
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P1.12B.06 Deulorlatinib (TGRX-326)in Patients with ALK Fusion-Positive NSCLC: Update from the Phase 1 Trial

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Introduction: Deulorlatinib (TGRX-326), a deuterated derivative of lorlatinib, demonstrated desirable safety and durable activity in ALK-positive advanced NSCLC in a phase 1 trial (NCT05441956; data cutoff: 13 Jan 2023). Here we report the updated safety, efficacy and biomarker analysis of deulorlatinib from the phase 1 trial.

Methods: Patients with ALK-positive, advanced NSCLC received deulorlatinib 5-125mg once daily (qd) during dose-escalation stage, deulorlatinib 40, 60, or 80mg qd during dose-expansion, and deulorlatinib at recommended phase 2 dose (RP2D) during cohort-expansion stage. Cohort-expansion stage enrolled ALK-positive patients with disease progression after crizotinib with or without chemotherapy (EXP-A1), ALK-positive patients with disease progression after at least one second-generation ALK inhibitors (EXP-A2) and TKI-naïve ALK-positive patients (EXP-C). Primary objectives were safety and tolerability. Pharmacokinetics, clinical activity and potential biomarkers were also evaluated.

Results: A total of 198 patients were enrolled. At data cutoff (February 21, 2024), median (range) treatment duration in the primary efficacy cohorts was 19.2 (2.5-22.1) months in cohort A1 (n=14), 6.9 (0.9-23.0) months in cohort A2 (n=97) and 18.1 (1.2-22.1) months in cohort C (n=33). No new safety signals were detected with long-term treatment duration. Common TRAEs were hypercholesterolemia (77.8%), hypertriglyceridemia (74.2%) and weight gain (46.0%). TRAE-associated dose interruptions, reduction and discontinuation occurred in 8.6%, 2.5% and 1.5% of patients, respectively. Treatment-related CNS effects occurred in 7.6% of patients, with 0.5% (n=1) requiring dose modification. In cohort A1, confirmed ORR (cORR) was 71.4% (95% CI, 41.9-91.6); median (95% CI) DOR and PFS were NA (11.8-NA) months and NA (9.7-NA) months. In cohort A2, cORR was 39.2% (95% CI, 29.4-49.6); median (95% CI) DOR and PFS were 18.0 (15.1-NA) months and 9.0 (5.7-16.8) months. In cohort C, cORR was 87.9% (95% CI, 71.8-96.6); median (95% CI) DOR and PFS were both NA (NA-NA). The efficacy of the treatment is summarized in the table below. Responses were observed across ALK variants and mutations. 158 patients provided plasma samples for biomarker analysis. Detectable ALK alterations and concurrent mutations in DNA damage repair pathway at baseline predicted worse outcomes. ALK clearance at week 6 correlated with significantly prolonged progression-free survival and overall survival.

Conclusions: After long-term follow-up, deulorlatinib continues to demonstrate durable efficacy in patients with ALK-positive NSCLC regardless of prior therapies. Safety profile was manageable and consistent with previous report. Based on these findings, 2 pivotal studies (NCT05955391/NCT06082635) are currently ongoing.

Keywords: non-small cell lung cancer, ALK positive, Deulorlatinib

	Cohort A1n=14	Cohort A2n=97	Cohort Cn=33
ORR, % (95% CI)	71.4 (41.9-91.6)	39.2 (29.4-49.6)	87.9 (71.8-96.6)
DCR, % (95% CI)	100 (79.8-100)	82.5 (73.4-89.5)	97.0 (84.2-99.9)
Median DOR, months (95% CI)	NA (11.8-NA)	18.0 (15.1-NA)	NA (NA-NA)
12-month DOR estimate, % (95% CI)	90.0 (73.2-100)	73.3 (60.4-89.0)	88.9 (77.8-100)
Median PFS, months (95% CI)	NA (9.7-NA)	9.0 (5.7-16.8)	NA (NA-NA)
12-month PFS estimate, % (95% CI)	74.1 (51.3-99.5)	47.5 (38.1-59.1)	78.5 (65.5-94.0)
Median OS, months (95% CI)	NA (NA-NA)	NA (22.4-NA)	NA (NA-NA)
12-month OS estimate, % (95% CI)	85.7 (69.2-100)	80.4 (72.9-88.7)	90.9 (81.6-100)

P1.12B METASTATIC NON-SMALL CELL LUNG CANCER - TARGETED THERAPY - FUSIONS: ALK / ROS1 / RET / NTRK
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P1.12B.07 Iruplinalkib in Patients with ALK-Positive Crizotinib-Resistant NSCLC: Updated Efficacy and Safety Data from a Phase 2 Trial

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Introduction: Iruplinalkib, a highly-selective anaplastic lymphoma kinase (ALK)/c-ros oncogene 1 tyrosine kinase inhibitor (TKI), demonstrated favorable efficacy and manageable safety in patients with non-small cell lung cancer (NSCLC). Here we report the updated results with two years' additional follow-up of a phase 2 trial (INTELLECT) evaluating the efficacy and safety of iruplinalkib in ALK-positive crizotinib-resistant advanced NSCLC (NCT04641754).

Methods: INTELLECT recruited 146 patients with histopathologically- or cytologically-confirmed ALK-positive advanced NSCLC who had disease progression after continuous treatment with crizotinib of ≥12 weeks. After a 7-day lead-in phase of iruplinalkib at 60 mg once daily, patients were orally administered iruplinalkib at 180 mg once daily in a 21-day cycle. Efficacy evaluation was performed every 12 weeks until disease progression, loss of follow-up, start of other anti-tumor treatment, or death. Central nervous system (CNS) efficacy was evaluated according to the Response Assessment in Neuro-Oncology criteria. Adverse events were evaluated according to the Common Terminology Criteria for Adverse Events version 4.03.

Results: At the data cut-off date on December 29, 2023, median follow-up time was 42.41 months (range, 41.07 to 43.14). Per investigator, median duration of response, progression-free survival, and time to progression was 14.06 months (95% confidence interval [CI], 10.35 to 18.60), 14.55 months (95% CI, 11.73 to 19.91), and 14.55 months (95% CI, 11.73 to 19.98), respectively. In 146 patients, 72 (49.3%) died, and 16 (11.0%) were lost to follow-up. The median overall survival was 41.79 months (95% CI, 28.78 to not evaluable). Ninety-six (65.8%) patients received at least once anti-tumor therapy after discontinuation of iruplinalkib treatment. The most common subsequent anti-tumor therapy was ALK TKI (73 [50.0%]), of which alectinib accounted for the most (50 [34.2%]). Table 1 presents subgroup analysis per investigator in patients with measurable intracranial lesions and with CNS metastases. Treatment-related adverse events (TRAEs) occurred in 137/146 (93.8%) patients. The most common TRAEs were aspartate aminotransferase increased (66 [45.2%]), hypercholesterolemia (55 [37.7%]), alanine aminotransferase increased (54 [37.0%]), and creatine phosphokinase increased (52 [35.6%]). TRAE leading to treatment interruption and discontinuation occurred in 23 (15.8%) and five (3.4%) patients, respectively. Two patients (1.4%) died due to TRAE of multiple organ dysfunction syndrome and intracranial hemorrhage, respectively.

Conclusions: The long-term follow-up results of INTELLECT confirmed the robust efficacy and safety of iruplinalkib with promising survival prognosis and no new safety signal. The updated results provided new evidence for the use of iruplinalkib in patients with ALK-positive crizotinib-resistant advanced NSCLC.

I**Keywords:** Iruplinalkib, Non-small cell lung cancer, Crizotinib-resistant

Per investigator	Patients with measurable intracranial lesions (n=42)	Patients with central nervous system metastases (n=90)
Best of response, n (%)		
Complete response	3 (7.1%)	0
Partial response	24 (57.1%)	50 (55.6%)
Stable disease	13 (31.0%)	34 (37.8%)
Progressive disease	1 (2.4%)	4 (4.4%)
Not evaluable	1 (2.4%)	2 (2.2%)
Objective response rate, n (%)	27 (64.3%)	50 (55.6%)
95% confidence interval	48.0% to 78.4%	44.7% to 66.0%
Disease control rate, n (%)	40 (95.2%)	84 (93.3%)
95% confidence interval	83.8% to 99.4%	86.1% to 97.5%
Median duration of response, months	18.69	17.25
95% confidence interval	15.01 to 20.99	10.35 to 19.48

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P1.12B.08 Thrombotic Events at Diagnosis are Associated with Poorer First Line TKI Outcomes Among Metastatic ALK and ROS1 NSCLC Patients

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Introduction: ALK and ROS1 NSCLC have been associated with increased rates of thrombotic events at diagnosis. The relationship between thrombotic events (TEs) and clinical outcomes to first line TKIs among patients with ALK, ROS1, and EGFR mutant NSCLC is less well defined.

Methods: Retrospective review of patients with metastatic ALK, ROS1, or EGFR mutant NSCLC seen between 2014 - 2024 at the University of Colorado who received first line TKIs was performed. TEs were defined as deep venous thrombosis, pulmonary embolism, arterial embolism, or stroke occurring within 90 days of diagnosis. Clinicopathologic features, treatment outcomes, and genomic data were collected. Progression free survival (PFS) and overall survival (OS) were assessed using Kaplan Meier methods using both univariate and multivariate modeling.

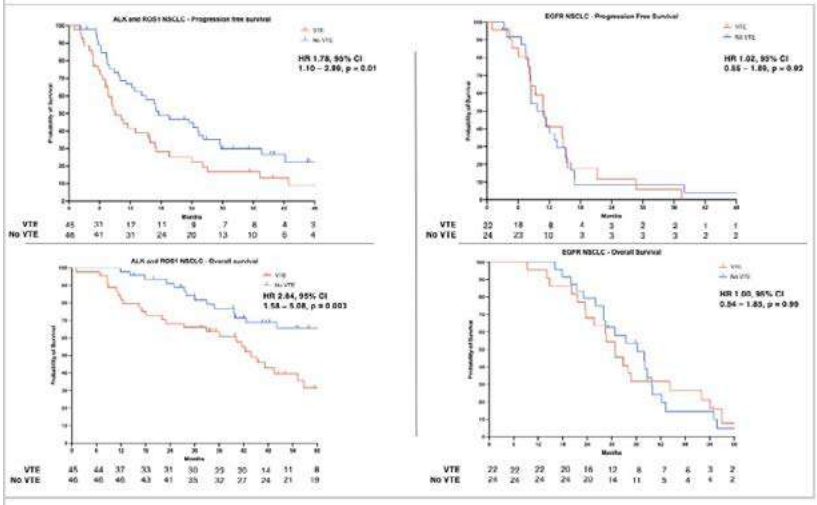
Results: Baseline characteristics of 135 patients are shown in Table 1. Univariate analysis of the entire dataset showed that patients with TEs had worse PFS (10 vs 14 months; HR 1.47, 95% CI 1.08 - 2.16, p=0.03) and OS (40 vs 43 months; HR 1.80, 95% CI 1.18 - 2.78, p = 0.01). When analyzed by oncogene, TEs at diagnosis were associated with worse PFS and OS for patients with ALK and ROS1 fusions, but not for patients with sensitizing EGFR mutations [Figure 1]. Multivariate modeling found no association with brain metastases (HR 0.77, 0.18 - 3.02, p=0.36), lines of therapy (HR 1.04, 0.52 - 2.09, p=0.92), CNS penetrance of TKI (HR 1.36, 0.80 - 2.33, p=0.25), or TP53 alterations (HR 1.20, 0.72 - 1.99, p=0.48) on PFS or OS.

Conclusions: Thrombotic events at diagnosis are independently associated with worse PFS and OS among patients with ALK and ROS1 fusions, but not among patients with EGFR mutations. Further studies exploring the nature of this relationship are warranted.

Keywords: ALK, thrombosis, TKI

Table 1: Clinical and Treatment Characteristics by Baseline Thrombotic Events

Characteristics	Thrombosis	No Thrombosis	Total	p-value
Total N (%)	67 (49.6)	68 (50.4)	135	
Age at diagnosis (years) Median [IQR]	57.0 (48.0 to 62.0)	57.0 (47.0 to 66.0)	57.0 (47.0 to 65.0)	0.862
Sex				0.345
Female	35 (52.2)	42 (61.8)	77 (57.0)	
Male	32 (47.8)	26 (38.2)	58 (43.0)	
Race				0.085
White	59 (88.1)	61 (89.7)	120 (88.9)	
Black	1 (1.5)	0 (0.0)	1 (0.7)	
Asian	3 (4.5)	7 (10.3)	10 (7.4)	
Other	4 (6.0)	0 (0.0)	4 (3.0)	
Smoking Status				0.190
Heavy smoker (≥ 10 pack years)	8 (12.1)	3 (4.4)	11 (8.2)	
Light smoker (< 10 pack years)	58 (87.9)	65 (95.6)	123 (91.8)	
NSCLC subtype				0.676
Adenocarcinoma	63 (94.0)	65 (97.0)	128 (95.5)	
Squamous	4 (6.0)	2 (3.0)	6 (4.5)	
Oncogene Driver				0.905
ALK or *ROS1*	45 (67.2)	44 (64.7)	89 (65.9)	
Sensitizing *EGFR* mutation	22 (32.8)	24 (35.3)	46 (34.1)	
TP53 alteration				0.654
Present	18 (48.6)	22 (56.4)	40 (52.6)	
Absent	19 (51.4)	17 (43.6)	36 (47.4)	
Unknown	30 (44.7)	29 (42.6)	59 (43.7)	
Brain metastasis				1.000
Yes	42 (62.1)	43 (63.2)	84 (62.7)	
No	25 (37.9)	25 (36.8)	50 (37.3)	
CNS penetrating TKI				0.863
Yes	35 (52.2)	34 (50.0)	70 (51.8)	
No	32 (47.8)	34 (50.0)	65 (48.1)	



P1.12B METASTATIC NON-SMALL CELL LUNG CANCER - TARGETED THERAPY - FUSIONS: ALK / ROS1 / RET / NTRK
SUNDAY, SEPTEMBER 8, 2024 - 12:00 - 14:00

P1.12B.09 Efficacy of Selpercatinib by RET Fusion Partner in RET+ NSCLC: Results from the LIBRETTO-001 and LIBRETTO-431 Trials

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Introduction: Selpercatinib is a highly selective and potent CNS active RET-inhibitor approved for treatment of advanced RET-driven cancers, including non-small-cell lung cancer (NSCLC). In the phase 1/2 LIBRETTO-001 (NCT03157128) and phase 3 LIBRETTO-431 (NCT04194944) studies, the clinical benefit of selpercatinib was demonstrated in patients with RET fusion-positive (RET+) NSCLC, regardless of fusion partner. Here, the relationship between selpercatinib efficacy and RET fusion partner was examined in a combined cohort of patients from both studies.

Methods: The primary analysis population included untreated and previously treated RET+ NSCLC patients who received selpercatinib in LIBRETTO-001 and LIBRETTO-431. LIBRETTO-431 patients were included in a separate controlled analysis of selpercatinib treatment versus platinum/pemetrexed chemotherapy +/- pembrolizumab (control), which was limited to KIF5B-RET due to low numbers of patients with other fusion partners. RET fusion partners were primarily identified in tumor tissue by NGS. Time-to-event efficacy outcomes were analyzed using the Kaplan-Meier method.

Results: Of the 415 patients who received selpercatinib, 263 (63.4%) were previously treated for advanced disease while 152 (36.6%) patients received no prior treatment. The most commonly identified RET fusion partners were KIF5B-RET (71.6%) or CCDC6-RET (21.2%). In patients with KIF5B-RET fusion, the median PFS was 19.4 months (95% CI: 17.1-22.7), while mPFS was not reached in patients with CCDC6-RET fusion. The ORR in patients with KIF5B-RET and CCDC6-RET was 65.3% (95% CI: 59.6-70.7) and 83.0% (95% CI: 73.4-90.1) respectively. Responses in patients with or without prior treatment by fusion partner are shown in Table 1. The median DOR was 20.3 months (95% CI: 17.5-23.9) in patients with KIF5B-RET, while not yet reached in patients with CCDC6-RET (Table 1). Among LIBRETTO-431 patients, 44.0% (70/159) patients in the selpercatinib group and 49.0% (50/102) patients in the control group had KIF5B-RET. In these patients with KIF5B-RET, the median PFS was 19.1 (95% CI: 13.9-24.8) months with selpercatinib compared to 7.4 months (95% CI: 4.9-11.2) with control.

Conclusions: In patients with RET+ NSCLC from LIBRETTO-001 and LIBRETTO-431, selpercatinib demonstrated robust and durable efficacy regardless of fusion partner. PFS in patients with KIF5B-RET from the LIBRETTO-431 control arm was consistent with prior reports of a poorer prognosis in this cohort regardless of treatment; however, clinical outcomes were improved with selpercatinib compared to chemotherapy +/- pembrolizumab. These data further support early and comprehensive genomic testing to identify RET fusions and use selpercatinib as the first-line therapy in patients with advanced RET+ NSCLC.

Keywords: NSCLC, RET, fusion partner

	Median PFS, months (95%CI)	ORR, [n/N] % (95% CI)	ORR, [n/N] % (95% CI)	ORR, [n/N] % (95% CI)	Median DOR, months (95%CI)
RET Fusion Partner	Overall (N=415)	Overall (N=415)	Prior Treatment (N=263)	Treatment Naïve (N=152)	Overall (N=415)
KIF5B-RET	19.4 (17.1-22.7)	[194/297] 65.3 (59.6-70.7)	[96/179] 53.6 (46.0-61.1)	[98/118] 83.1 (75.0-89.3)	20.3 (17.5-23.9)
CCDC6-RET	NE (33.0-NE)	[73/88] 83.0 (73.4-90.1)	[47/61] 77.0 (64.5-86.8)	[26/27] 96.3 (81.0-99.9)	NE (28.5-NE)
OTHER-RET	16.9 (7.5-NE)	[16/30] 53.3 (34.3-71.7)	[10/23] 43.5 (23.2-65.5)	[6/7] 85.7 (42.1-99.6)	17.6 (5.6-NE)

P1.12B METASTATIC NON-SMALL CELL LUNG CANCER - TARGETED THERAPY - FUSIONS: ALK / ROS1 / RET / NTRK
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P1.12B.10 Dose Adjustments and Exposure-Response Associated with Selpercatinib in Patients with Advanced NSCLC

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Introduction: Selpercatinib is a highly selective RET kinase inhibitor that has demonstrated improved progression-free survival (PFS) in patients with first-line RET fusion-positive non-small cell lung cancer (NSCLC). As with other targeted therapies for NSCLC, dose reductions are commonly used for managing selpercatinib toxicity. Given the potent and selective RET inhibition offered by selpercatinib, we hypothesize that outcomes would be maintained even with variable exposures resulting from dose adjustment.

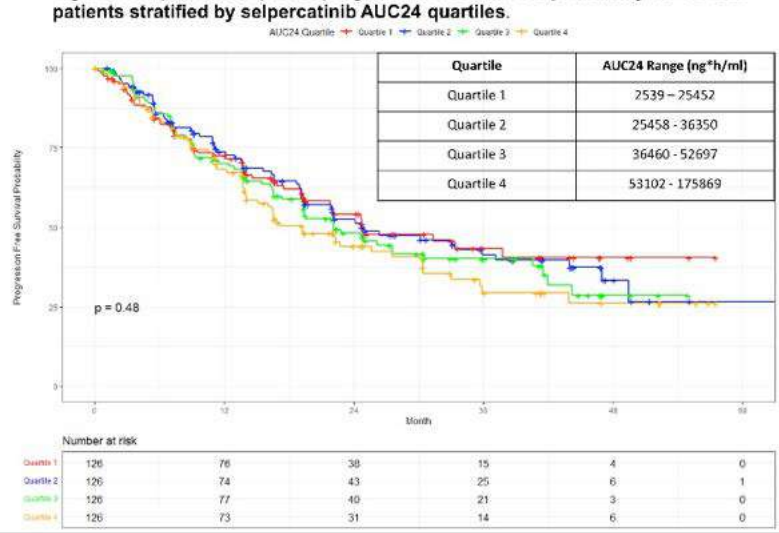
Methods: We studied patients with NSCLC treated with selpercatinib in 2 prospective trials (LIBRETTO-001 and LIBRETTO-431) where patients were started at 160 mg twice daily; dose reductions to 120 mg, 80 mg, and 40 mg twice daily were permitted. Exposure-response models were developed to characterize the relationship between selpercatinib at clinically relevant exposures and efficacy endpoints (overall response rate [ORR] and PFS). Steady-state exposure parameters selected for analysis (area under the plasma concentration-time curve over 24 hours at steady state [AUC24] and maximum and minimum selpercatinib concentrations) were representative of the average selpercatinib exposure over time. Additionally, average exposure over the last 10 doses was considered. Exposure-response analysis was conducted for ORR using a stepwise logistic regression. For PFS, Kaplan-Meier plots were created for each exposure parameter.

Results: Of 504 treated patients with NSCLC (LIBRETTO-431, n=150; LIBRETTO-001, n=354), 266 (53%) underwent dose reduction. Median time to first dose reduction was 2 months. Patients with dose reduction tended to be older (median age [range]: 61 [26-92] vs 59 [23-87] years) and had lower body weight (median weight [range]: 63 [39-148] vs 66 [42-131] kg) and longer time on therapy (median time on treatment [95% confidence interval]: 31.7 [26.2-37.9] vs 21.2 [17.3-25.3] months) versus patients without dose reduction. Aspartate and alanine aminotransferase elevation, QT prolongation, and hypertension were the most common adverse events leading to dose adjustments. Focusing on the 502 patients included in the ORR exposure-response analysis, the response rate was 69% (348 responders); a stepwise multivariate logistic regression showed that probability of response increased with increasing selpercatinib AUC24 (P<0.05). Exploratory analysis of PFS in 504 patients (254 events) by exposure metrics showed no significant relationship with PFS across exposure quartiles.

Conclusions: Our analyses did not find any correlation between drug exposure and PFS but did suggest that higher exposure was associated with better response rates. For patients experiencing toxicity on selpercatinib, dose adjustment to reduce exposure may allow ongoing clinical benefit without a decremental impact on PFS.

Keywords: Exposure-response, Dose adjustments, Selpercatinib

Figure 1: Kaplan-Meier plot of progression free survival probability for NSCLC patients stratified by selpercatinib AUC24 quartiles.



Quartile	AUC24 Range (ng*h/ml)
Quartile 1	2539 – 25452
Quartile 2	25458 - 36350
Quartile 3	36460 - 52697
Quartile 4	53102 - 175869

P1.12B METASTATIC NON-SMALL CELL LUNG CANCER - TARGETED THERAPY - FUSIONS: ALK / ROS1 / RET / NTRK
SUNDAY, SEPTEMBER 8, 2024 - 12:00 - 14:00

P1.12B.11 ALK Positive Lifestudy

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Introduction: Lung cancer remains the leading cause of cancer-related deaths worldwide. ALK-positive rearrangement, represents a distinct subset. The primary objective of this study is to comprehensively analyze the diagnostic journeys of patients with ALK-positive NSCLC using data from a global registry, focusing on symptomatic presentation of the lung cancer and the time intervals from initial symptom onset to the commencement of treatment.

Methods: A global registry for ALK-positive NSCLC patients was established by ALK Positive Inc, a patient-led advocacy organization to explore their diagnostic and treatment journeys. Our ongoing recruitment process includes direct outreach through various social media, email, and networking channels, along with IRB-approved informed consent procedures. An initial survey collected demographic data, and documented both pre-diagnosis and post-diagnosis phases, completed by patients or their caregivers. This survey covered the first symptoms presented at the clinic, diagnostic tests, referral to lung cancer specialists, time of diagnosis, and treatment initiation, using REDCap for data collection. This approach facilitated a broad spectrum of data collection, including demographics, medical history, specific treatment experiences, and importantly, pre-diagnostic timelines.

Results: As of February 2024, our cohort of 1147 ALK-positive lung cancer patients had a midlife average diagnosis age of 51.9 years, predominantly female (62.9%) and primarily white (76.9%). A substantial number of individuals hold higher education degrees, with 88.4% having attended at least some college. The most common symptoms at diagnosis were cough (56.6%) and shortness of breath (40.1%), followed by general fatigue (30%) and back pain (19.2%). The distribution of cancer stages at diagnosis among patients is as follows: early-stage cancer (Stages I/II) is present in 7% of the cases, with 5.8% at Stage IIIA, 6.4% at Stage IIIB, and 2.4% at Stage IIIC. The majority of the cases are Stage IV, accounting for 70.7%. The diagnostic and treatment timeline showed that from the first visit to the initial test (e.g., chest X-ray), the median time was 17 days, with an interquartile range (IQR) from 0 to 85 days. To see a lung specialist after the first visit, the median time was 31 days, with the IQR spanning 7 to 91 days. The median duration from the first visit to a lung cancer diagnosis was 41 days, with the IQR ranging between 13 and 120.25 days. For patients diagnosed at stage IIC or higher, the median initiation time starting TKI therapy post-diagnosis was 29 days, with an IQR of 16 to 75.9 days.These statistics, based on the largest ALK-positive real-world evidence dataset highlights the variability in patient journey times from initial symptoms to the commencement of TKI treatment.

Conclusions: The creation of a large global registry for ALK-positive lung cancer has allowed us to establish benchmarks for patient journeys from symptom onset to TKI treatment initiation. Utilizing these insights, our objective is to pinpoint critical intervention points to hone strategies that accelerate diagnosis and the delivery of personalized treatments. This ALK Life Study is providing longitudinal data that can enable crucial advances in patient care efficiency and improved clinical outcomes.

Keywords: ALK-positive NSCLC, Diagnostic pathways, Global patient registry

P1.13A SMALL CELL LUNG CANCER AND NEUROENDOCRINE TUMORS - CLINICAL TRIALS
SUNDAY, SEPTEMBER 8, 2024 - 12:00 - 14:00

P1.13A.01 DeLLphi-306 Trial: A Phase 3 Study of Tarlatamab after Concurrent Chemoradiotherapy in Limited-Stage Small Cell Lung Cancer

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Introduction: The current standard of care for limited-stage small cell lung cancer (LS-SCLC) is thoracic radiotherapy with concurrent platinum/etoposide chemotherapy. While most patients respond initially, relapse is common within months after treatment, indicating the need for additional therapies. Tarlatamab is a bispecific T-cell engager (BiTE®) immunotherapy that binds delta-like ligand 3 on the surface of SCLC cells and CD3 on T cells, facilitating T-cell-mediated cancer cell lysis. In phase 1 and phase 2 studies, tarlatamab demonstrated promising antitumor activity with a manageable safety profile in patients with previously treated SCLC. The DeLLphi-306 trial (NCT06117774) will compare the efficacy of tarlatamab versus placebo in patients with LS-SCLC who have not progressed following concurrent chemoradiotherapy.

Methods: DeLLphi-306 is a global, randomized, double-blinded, placebo-controlled phase 3 trial enrolling patients ≥ 18 years of age with histologically or cytologically confirmed SCLC and a diagnosis of LS-SCLC. Patients should have completed 3-4 cycles of platinum-based chemotherapy and concurrent radiation therapy, without progression per RECIST 1.1. Key exclusion criteria include a diagnosis of extensive-stage SCLC, non-small cell lung cancer that has transformed to SCLC, evidence of interstitial lung disease or active, non-infectious pneumonitis, and receipt of sequential (nonoverlapping) chemotherapy and thoracic radiotherapy during chemoradiation. Eligible subjects will undergo 1:1 randomization and receive either tarlatamab, 10 mg Q2W, (N ~ 200) or placebo (N ~ 200) until disease progression, unacceptable toxicity, withdrawal of consent, death, or for a maximum of 12 months (whichever occurs first). Randomization will be stratified by receipt of prophylactic cranial irradiation, disease stage, and the number of cycles of chemotherapy prior to enrollment. The primary endpoint is progression-free survival (PFS) by blinded independent central review (BICR) per RECIST 1.1. The key secondary endpoint is overall survival. Other secondary endpoints include investigator-assessed PFS, investigator and BICR-assessed objective response rate, disease control rate, duration of response, time to progression (all per RECIST 1.1), incidence of treatment-emergent and treatment-related adverse events, serum concentrations of tarlatamab, and incidence of anti-tarlatamab antibody formation. This trial is actively recruiting patients.

Keywords: Tarlatamab, limited-stage small cell lung cancer, phase 3

P1.13A SMALL CELL LUNG CANCER AND NEUROENDOCRINE TUMORS - CLINICAL TRIALS
SUNDAY, SEPTEMBER 8, 2024 - 12:00 - 14:00

P1.13A.02 Tarlatamab Plus Durvalumab as First-Line Maintenance in Extensive-Stage Small Cell Lung Cancer: DeLLphi-305 Phase 3 Trial

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Introduction: The current standard of care for first-line (1L) therapy for patients with extensive-stage small cell lung cancer (ES-SCLC) is induction with platinum-etoposide (EP) and a PD-L1 inhibitor, such as durvalumab or atezolizumab, followed by maintenance with a PD-L1 inhibitor. In the phase 3 CASPIAN trial, patients with treatment-naïve ES-SCLC were treated with EP plus durvalumab followed by durvalumab maintenance, resulting in a median overall survival (OS) of 12.9 months which was 2.4 months longer compared to EP alone (ESMO Open 2022;7:100408). Despite an improved OS, long-term survival remains poor with a 3-year OS rate of 17.6% in the CASPIAN trial (ESMO Open 2022;7:100408). There remains a need for additional therapies that can delay disease progression and further improve OS. Tarlatamab is a bispecific T-cell engager (BiTE®) immunotherapy that binds delta-like ligand 3 (DLL3) on the surface of SCLC cells and CD3 on T cells, facilitating T-cell-mediated cancer cell lysis. DLL3 expression is detectable by immunohistochemistry in ~85-96% of patients with SCLC. In the phase 2 DeLLphi-301 study, tarlatamab demonstrated durable objective responses with promising survival outcomes and a manageable safety profile in patients with previously treated SCLC (NEJM 2023;389:2063).

Methods: DeLLphi-305 (NCT06211036) is a randomized (1:1), global, open-label, phase 3 study examining tarlatamab (10 mg, Q2W) in combination with durvalumab versus durvalumab alone as maintenance following 1L treatment (EP with durvalumab) in approximately 550 planned patients with ES-SCLC. Key patient inclusion criteria are patients ≥ 18 years of age, histologically or cytologically confirmed ES-SCLC, completion of 3-4 cycles of 1L treatment prior to enrollment without disease progression, Eastern Cooperative Oncology Group performance status ≤ 1, and a minimum life expectancy > 12 weeks. Patients with treated brain metastases are eligible as per protocol. Key exclusion criteria are prior DLL3 pathway-selective inhibitor therapy, active or documented autoimmune or inflammatory disorders per protocol, known human immunodeficiency virus, hepatitis C and/or hepatitis B infections with exceptions according to the protocol, and a history of severe/life-threatening events from immune-mediated therapy. The primary endpoint is OS and key secondary endpoints include progression-free survival, objective response rate, disease control rate, duration of response, safety, and quality of life assessments.

Keywords: tarlatamab, extensive-stage small cell lung cancer, phase 3

P1.13A SMALL CELL LUNG CANCER AND NEUROENDOCRINE TUMORS - CLINICAL TRIALS
SUNDAY, SEPTEMBER 8, 2024 - 12:00 - 14:00

P1.13A.03 MOZART: Phase II Trial of Monalizumab, Durvalumab, and Platinum-based Chemotherapy for First-Line Treatment of Extensive Stage SCLC

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Introduction: Platinum-based chemotherapy in combination with PD-L1 inhibitor is the standard of care first-line treatment for extensive stage small cell lung cancer (SCLC) yielding median overall survival (OS) of slightly over a year. NKG2A/CD94 is an immune checkpoint that is selectively expressed on natural killer (NK) cells and CD8+ T cells in the tumor microenvironment. When engaging with its ligand, HLA-E, NKG2A transduces inhibitory signals that suppress immune-mediated cytotoxicity. Thus, NKG2A blockade enhances anti-tumor immunity by promoting both, NK and CD8+ T cell, effector functions. Monalizumab is a monoclonal antibody targeting NKG2A that enhances NK cell activity against tumor cells and rescues CD8+ T cell function in combination with PD-(L)1 axis blockade. Pre-clinical data have demonstrated that the absence of NK cells substantially enhances metastatic dissemination of SCLC tumor cells in vivo. NK cell function is modulated in response to DNA damage induced by platinum. Post-chemotherapy NK cells display higher expression of NKG2A and is associated with a reduced NK cell mediated anti-tumor activity. Hyperactivation of NK cell activity ameliorates SCLC metastases, an effect that is enhanced when combined with anti PD-1 therapy. Altogether, these data suggest that addition of monalizumab to standard of care first-line treatment may be associated with improved efficacy in patients with SCLC.

Methods: Patients with extensive-stage SCLC with ECOG performance status of 0-2 and adequate organ function are eligible for enrollment on this single-arm phase II study with an initial safety lead-in cohort of 6 patients. Patients may have received one prior cycle of platinum doublet with or without durvalumab and may have treated or untreated asymptomatic brain metastasis. Patients will receive platinum (cis or carbo), etoposide, durvalumab, and monalizumab every 3 weeks for 4 cycles followed by durvalumab and monalizumab every 4 weeks until disease progression or unacceptable toxicity. Primary endpoints include 1-year progression-free survival, safety, and tolerability. Secondary endpoints include objective response rate, 1-year overall survival, and intracranial progression-free survival. Exploratory objectives include analyzing association of treatment efficacy with minimal residual disease status, blood- and tissue-based genomic and transcriptomic signatures, tumor infiltrating immune cells, and peripheral blood NK cell and CD8+ T cell activity. The study has completed safety lead-in phase.

Keywords: Small cell lung cancer, Monalizumab, Extensive stage

P1.13A SMALL CELL LUNG CANCER AND NEUROENDOCRINE TUMORS - CLINICAL TRIALS
SUNDAY, SEPTEMBER 8, 2024 - 12:00 - 14:00

P1.13A.05 Preliminary Results of A Phase II Study of Camrelizumab Combined with Chemotherapy Followed by Concurrent Chemoradiotherapy for LD-SCLC

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Introduction: Immune checkpoint inhibitors combined with chemotherapy have significant clinical benefits in extensive-stage small cell lung cancer (SCLC). However, for patients with limited-disease SCLC (LD-SCLC), the data on immunotherapy combined with chemoradiotherapy is insufficient.

Methods: In this open-label, multi-center, phase 2 trial, we randomly 1:1 assigned patients with previously untreated LD-SCLC to receive camrelizumab combined with chemotherapy followed by concurrent chemoradiotherapy (CCRT) and camrelizumab consolidation therapy or standard chemoradiotherapy. Patients with ECOG performance status of 0 to 1, and adequate organ function were eligible. For thoracic radiation, 45 Gy in 3 weeks (1.5 Gy, BID) was given on the first day of the third cycle of chemotherapy. An etoposide plus platinum-based regimen was given 4 cycles in total. Patients who had a good response to initial treatment were offered prophylactic cranial irradiation. The primary endpoint was the 1-year progression-free survival rate. We assumed that the 1-year PFS rate in the experimental group was expected to reach 65% compared to chemoradiotherapy alone group 45%, and planned to enroll 112 patients with 56 in each group.

Results: Up to date, we have enrolled 40 patients. The median follow-up was 10.6 months. Safety was evaluated in all treated patients (Table 1). No Grade 5 adverse event was observed. Grade 3 or 4 treatment-related adverse events occurred in 58.8% of the patients in the camrelizumab plus chemoradiotherapy and in 52.9% of those in the chemoradiotherapy alone group. The most frequent grade 3 or 4 adverse events were hematologic toxicities (70.6% vs. 58.8%). Acute esophagitis and pneumonitis of grade 3 occurred in both groups were 1/17 (5.9%) and 1/17 (5.9%), respectively. In the experimental group, only one patient was developed grade 3 immune pneumonia 1/17 (5.9%). The 1-year PFS rate was 54.5% (95% confidence interval [CI] 19.5%-89.6%) with camrelizumab plus chemoradiotherapy and 44.4% (95% CI 3.9%-88.0%) with chemoradiotherapy alone. Among the 17 patients who received camrelizumab, the median PFS time was not reached, as compared with 14.35 (95% CI, 8.15-20.91) months among the 17 patients with chemoradiotherapy alone.

Conclusions: In patients with LD-SCLC, the addition of camrelizumab to chemoradiotherapy did not increase the incidence of adverse events. Camrelizumab plus chemoradiotherapy resulted in an encouraging 1-year PFS rate. Larger sample sizes and longer follow-up times are required to validate our preliminary results. Trial Registration:Chinese Clinical Trial Registry Identifier: ChiCTR2000032275

Keywords: limited-disease small cell lung cancer, immune checkpoint inhibitors, chemoradiotherapy

P1.13A SMALL CELL LUNG CANCER AND NEUROENDOCRINE TUMORS - CLINICAL TRIALS
SUNDAY, SEPTEMBER 8, 2024 - 12:00 - 14:00

P1.13A.06 Outcomes in LS SCLC Patients with Severe Acute Esophagitis During Chemotherapy and Concurrent Twice-Daily Thoracic Radiotherapy

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Introduction: Concurrent platinum/etoposide-chemotherapy and thoracic radiotherapy (TRT) is standard treatment of limited-stage (LS) small-cell lung cancer (SCLC). Twice-daily (BID) TRT is recommended but poorly implemented. 2/3 of patients relapse after chemoradiotherapy and it has been hypothesized that higher TRT-doses improve survival. Radiation induced esophagitis, typically presenting with chest pain and dysphagia after 2-3 weeks of TRT, is the most common radiotoxicity and considered main radiotherapy-dose-limiting toxicity, and major reason for poor implementation of BID TRT. It is, however, not known whether patients who experience severe esophagitis have worse treatment outcomes. We analyzed participants in our randomized phase II trial showing that BID TRT of 60 Gy/40 fractions significantly improved survival compared with the standard 45 Gy/30 fraction schedule (median OS 43.6 vs. 22.6 months; p=0.036) (n=170, NCT02041845) to investigate whether severe esophagitis was associated with more long-term sequelae or inferior PFS or OS.

Methods: Patients with untreated LS SCLC, ECOG PS 0-2, and measurable disease (RECIST 1.1) received four platinum/etoposide-courses and were randomized to receive BID TRT of 45 or 60 Gy. TRT target volumes were restricted to PET/CT positive lesions and modern radiotherapy- techniques (IMRT/VMAT) were allowed. Toxicity was assessed according to CTCAE v4.0. Patients were categorized as experiencing no (CTCAE-grade 0), mild (CTCAE-grade 1-2), or severe acute esophagitis (CTCAE-grade 3-4). Patients reported dysphagia on the EORTC QLQ-C30, a difference in mean scores of ≥10 points was defined as clinically relevant.

Results: 166 patients who commenced TRT were analyzed. Baseline characteristics, treatment, patient reports, long term sequelae and progression free-/overall survival data are listed in Table 1. More patients with severe esophagitis had stage III disease and weight-loss before inclusion. Other baseline characteristics and study-treatment completion rates were similar across esophagitis-categories. All patients had significant increase in dysphagia from baseline until TRT ended. None experienced grade 4-5 esophagitis. Patients with severe esophagitis reported slightly higher maximum and slightly higher mean scores the first 2 years, but proportions needing esophageal stent (3.2% vs. 0-1.4%; p=0.137) or having physician-reported long-term dysphagia (12.9% vs. 4.5-5.8%; p=0.29) were not significantly different. There were no significant differences in PFS (p=0.77) or OS (p=0.88) across esophagitis-groups, nor in multivariable analysis adjusting for sex/PS/disease stage/TRT-schedule (PFS: p=0.713, OS: p=0.882).

Conclusions: Using modern TRT-approaches, severe acute esophagitis was not associated with more long-term sequelae or worse treatment outcomes, indicating that concerns about such toxicity should not prevent LS SCLC patients from receiving BID TRT of 45-60 Gy.

Keywords: Chemoradiotherapy, Clinical impact, Toxicity

			All patients (n=166)		No acute esophagitis (CTCAE 0, n=69)		Mild acute esophagitis (CTCAE 1-2, n=66)		Severe acute esophagitis (CTCAE 3, n=31)	
			n	%	n	%	n	%	n	%
Baseline characteristics	Age	Median (range)	65 (36-81)		68 (36-79)		64 (48-81)		64 (46-80)	
	Sex	Male	70	42.2%	26	37.7%	33	50.0%	11	35.5%
		Female	96	57.8%	43	62.3%	33	50.0%	20	64.5%
	Performance status	0-1	148	89.2%	64	92.8%	55	83.3%	29	93.6%
		2	15	9.0%	4	5.8%	9	13.6%	2	6.5%
		Missing	3	1.8%	1	1.4%	2	3.0%	-	-
	TNM stage of disease	I-II	27	16.3%	16	23.2%	11	16.7%	-	-
		III	139	83.7%	53	76.8%	55	83.3%	31	100%
	Weight loss >5% prior to inclusion	Yes	33	19.9%	9	13.0%	12	18.2%	12	38.7%
		Missing	24	14.5%	11	15.9%	13	19.7%	-	-
Study treatment	Completed 4 chemo-courses	Yes	153	92.2%	61	88.4%	65	98.5%	27	87.1%
	TRT treatment group	45 Gy/30 fractions	77	46.4%	29	42.0%	34	51.5%	14	45.2%
		60 Gy/40 fractions	89	53.6%	40	58.0%	32	48.5%	17	54.8%

	Completed TRT	Yes	160	96.4%	66	95.7%	66	100%	28	90.3%
	Received PCI	Yes	138	83.1%	54	78.3%	59	89.4%	25	80.6%
		Missing	2	1.2%	2	2.9%	-	-	-	-
Patient reported dyspha gia	Baseline (Completed	Mean score	10 (6.5-13.5)		8 (3.0-13.3)		12 (5.5-17.6)		10 (2.0-17.5)	
	QLQs: n=117)	(95% CI)								
(EORTC QLQ-C30)	End of TRT (week 8) (QLQs: n=96)		48 (40.7-54.5)		43 (32.2-53.2)		48 (36.8-58.7)		57 (38.3-75.0)	
	4-5 weeks after TRT (week 12) (QLQs: n=123)		25 (19.1-30.8)		16 (9.7-22.9)		23 (14.1-32.1)		48 (29.5-66.2)	
	1 year after inclusion (QLQs: n=101)		8 (4.5-11.3)		4 (0.1-7.1)		7 (2.2-11.8)		17 (6.1-28.8)	
	2 years after inclusion (QLQs: n=64)		7 (3.5-11.1)		6 (0.2-10.9)		3 (0-6.5)		18 (6.0-29.6)	
	3 years after inclusion (QLQs: n=39)		6 (1.8-10.2)		5 (0-11.8)		6 (0-11.9)		10 (0-24.6)	
	4 years after inclusion (QLQs: n=25)		12 (4.2-19.8)		15 (0-33.4)		9 (0-19.6)		13 (0-36.0)	
	5 years after inclusion (QLQs: n=11)		3 (0-9.8)		8 (0-34.9)		0 (0.0- 0.0)		0 (0.0- 0.0)	
Long-term sequelae	Esophageal stent		2	1.2%	1	1.4%	-	-	1	3.2%
	Physician-reported long-term severe dysphagia		11	6.6%	4	5.8%	3	4.5%	4	12.9%
Survival	Progression free survival	Median (95% CI)	15.5 mos (10.7-20.2)		12.2 mos (6.8-17.7)		18.6 mos (4.2-33.0)		14.2 mos (7.9-20.6)	
	Overall survival		34.3 mos (27.6-41.0)		26.9 mos (10.2-43.6)		36.0 mos (25.4-46.6)		33.3 mos (20.9-45.8)	

P1.13A SMALL CELL LUNG CANCER AND NEUROENDOCRINE TUMORS - CLINICAL TRIALS
SUNDAY, SEPTEMBER 8, 2024 - 12:00 - 14:00

P1.13A.07 Real-World First-Line Serplulimab-Based Immunochemotherapy for Extensive-Stage Small Cell Lung Cancer: The Multicenter ASTRUM-005R Study

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Introduction: The phase III ASTRUM-005 study (NCT04063163) has demonstrated promising antitumor efficacy and well tolerability of first-line serplulimab combined with chemotherapy in patients with extensive-stage small cell lung cancer (ES-SCLC). However, due to the strict eligibility criteria of randomized controlled trials, the practical data of patients with more complex or specific diseases in the real world were lacking. To bridge this knowledge gap, we herein present a 2-year interim analysis drawn from the multicenter, real-world study ASTRUM-005R. This study aims to investigate and supplement the real-world efficacy and safety data of first-line immunochemotherapy regimens incorporating serplulimab with chemotherapy, specifically focusing on ES-SCLC patients in China.

Methods: This cohort study enrolled adult patients with ES-SCLC at 14 institutions in China from April 2022 to April 2024. These patients received at least two cycles of first-line serplulimab combined with chemotherapy and underwent at least one response assessment. The primary endpoint was the investigator-assessed real-world progression-free survival (rwPFS) according to RECIST version 1.1. Secondary endpoints included overall survival (OS), objective response rate (ORR), and safety profiles refer to CTCAE version 5.0.

Results: A total of 538 patients were enrolled and evaluated for both efficacy and safety. The participants had a median age of 63 years (range 57.00-68.75), with 467 (86.80%) being male and 406 (75.46%) having a history of smoking. Most patients (491, 91.26%) had an ECOG PS of 0 or 1. Comorbidities, excluding other primary tumors, were present in 44.05% (237 patients). Liver and brain metastases were observed in 33.09% (n=178) and 21.56% (n=116), respectively. The median number of immunochemotherapy cycles was 4 (range 4-6), with 41.26% (n=222) receiving more than four cycles. The median rwPFS was 9.1 months (95% CI 8.1-9.7), with a 1-year rwPFS rate of 34.6%, surpassing the 1-year PFS rate of 28.2% reported for the Asian in the ASTRUM-005 study. Besides, the 2-year rwPFS rate was shown to be 11.3%. The median rwPFS was 9.7 months (95% CI 8.8-12.8) in patients without liver metastasis, significantly longer than the 7.4 months (95% CI 6.2-8.9) in patients with liver metastasis (P < 0.0001). Patients who received >4 cycles of immunochemotherapy had a median rwPFS of 10.5 months (95% CI 9.3-13.3), which was significantly longer than the 6.7 months (95% CI 6.3-9.1) in patients who received ≤4 cycles (P < 0.0001). Patients without brain metastasis had longer PFS than patients with brain metastasis (9.6 [95% CI 8.9-10.8] vs. 7.3 [95% CI 6.3-8.6] months, p = 0.079), but the difference was not statistically significant. The OS was not yet mature, and the ORR was 71.29%. The occurrence frequency of adverse event of special interest (AESI) was 38.85% (421 events), in which grade ≥3 AESIs occupied 15.43%.

Conclusions: This cohort study reports the real-world survival outcomes of first-line serplulimab-containing immunochemotherapy regimen in patients with ES-SCLC, offering additional empirical evidence to substantiate the therapeutic value of such combinations while complementing the pivotal data to the ASTRUM-005 clinical trial.

Keywords: Extensive-stage small cell lung cancer, PD-1 inhibitor, Serplulimab

P1.13A SMALL CELL LUNG CANCER AND NEUROENDOCRINE TUMORS - CLINICAL TRIALS
SUNDAY, SEPTEMBER 8, 2024 - 12:00 - 14:00

P1.13A.08 Biomarker Analysis of Camrelizumab Plus Nab-paclitaxel and Carboplatin as First-Line Treatment for Extensive-Stage Small-Cell Lung Cancer

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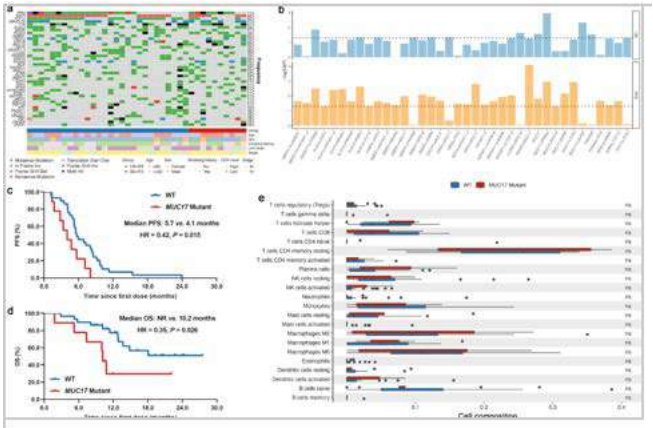
Introduction: This trial aimed to evaluate the efficacy, safety and predictive biomarkers of camrelizumab plus nab-paclitaxel and carboplatin as first-line treatment for extensive-stage small-cell lung cancer (ES-SCLC).

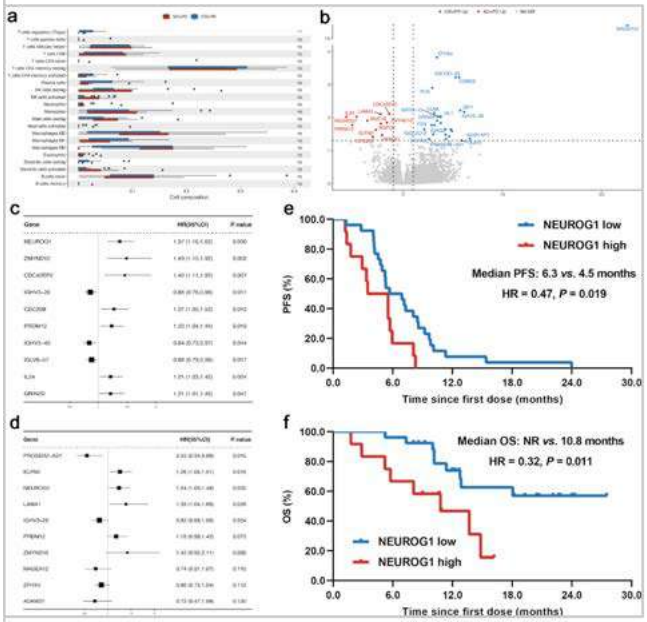
Methods: Camrelizumab plus nab-paclitaxel and carboplatin were administrated every three weeks for up to six cycles, followed by maintenance therapy with camrelizumab until disease progression or intolerable toxicity. The primary endpoint was 6-month progression-free survival (PFS) rate. Secondary endpoints included PFS, overall survival (OS), objective response rate (ORR), disease control rate (DCR) and safety. Integrated analysis of whole-exome and transcriptomic sequencing data were conducted.

Results: 60 patients were enrolled. Primary endpoint was met with 6-month PFS rate of 52.2%. The median PFS and OS was 7.1 and 18.1 months, respectively. The confirmed ORR was 73.3% and DCR was 93.3%. No unexpected adverse events were observed. Biomarker analysis showed that patients with MUC17 alterations or high NEUROG1 expression were associated with significantly shorter PFS and OS. Deeper investigation of transcriptomic data uncovers two subsets with distinct immune features and therapeutic vulnerabilities.

Conclusions: This study showed that camrelizumab plus nab-paclitaxel and carboplatin might be an alternative option of first-line regimens for ES-SCLC. MUC17 alterations or NEUROG1 expression would serve as potential biomarker for this combination.

Keywords: ES-SCLC, Immunotherapy, Biomarker





P1.13A SMALL CELL LUNG CANCER AND NEUROENDOCRINE TUMORS - CLINICAL TRIALS
SUNDAY, SEPTEMBER 8, 2024 - 12:00 - 14:00

P1.13A.09 RYZ101 (225Ac-DOTATATE) + Carboplatin + Etoposide + Atezolizumab in Somatostatin Receptor Expressing Extensive-Stage Small-Cell Lung Cancer

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Introduction: RYZ101 is a first-in-class, alpha-emitting radiopharmaceutical in development for somatostatin receptor expressing (SSTR2+) solid tumors. Alpha particles (emitted by 225Ac) have a higher linear energy transfer (80-100 keV/µm) and shorter path length (40-100 µm) than beta particles, potentially allowing for improved cancer cell kill rates while limiting off-tumor toxicity. Here we describe preliminary safety data from a single-arm, open-label, phase 1b dose-escalation and dose-expansion trial of RYZ101 in combination with standard of care (SoC) therapy in patients with treatment-naïve SSTR+ extensive-stage small-cell lung cancer (ES-SCLC; NCT05595460).

Methods: Adult patients with histologically/cytologically confirmed SSTR+ ES-SCLC, ECOG PS 0-1, life expectancy ≥12w, and sufficient renal, hepatic, and hematologic function are eligible. Patients are required to have ≥1 SSTR PET imaging-positive RECIST v1.1-measurable disease; ≥50% of measurable lesions must be SSTR2+. Patients may receive up to 1 cycle of SoC before/during screening. Patients with brain metastases are permitted but must be asymptomatic, adequately treated, and on stable/decreasing steroid doses. During dose-escalation, patients receive RYZ101 (IV q6w then q4w) starting at dose level 1 (DL1) of 6.5 MBq with escalation to 8.3 MBq (DL2) and 10.2 MBq (DL3) in the absence of any dose-limiting toxicities (DLTs). Patients also receive SoC: atezolizumab (Tecentriq®, 1200 mg IV d1 q21d, max 4×21-d cycles, then 1680 mg IV q28d); carboplatin (AUC 5-6 IV 60m d1 q21d, max 4×21-d cycles); etoposide (80-100 mg/mm2 IV 60m d1-3 q21d, max 4×21-d cycles). Primary endpoints: safety, maximum tolerated dose/recommended phase 2 dose. Secondary endpoints: efficacy, pharmacokinetics.

Results: As of 17 January 2024, 10 patients were screened and 4 were treated with RYZ101 at 6.5 MBq. Screen failure in all but 1 patient was due to not meeting criteria for SSTR2 PET positivity. Median age was 63y (range 49-79), 50% were female and had ECOG PS 0, all were former smokers with median 30 pack-yrs (range 9-42). All patients received 1 cycle of SoC before/during screening; median duration of treatment and number of RYZ101 doses was 2.6m (range 1.4-4.7m) and 1.5 (range 1-3). Of the 4 patients in DL1, 3 completed the DLT period (42d following first RYZ101 dose). There were no DLTs reported nor any G≥3 AEs related to RYZ101. AEs related to RYZ101 include G1 decreased appetite, G2 dehydration, G1 diarrhea, G1 fatigue, G2 influenza-like illness, G2 nausea, G2 neutrophil count decrease, and G1 vomiting. All SAEs were unrelated to RYZ101 and included pain (n=1), back pain (n=1), hyponatremia (n=1), and syncope (n=1). One patient had G4 neutropenia related to SoC following the 1st cycle of RYZ101, requiring RYZ101 dose reduction, which recovered with supportive care. Preliminary pharmacokinetic findings indicate clearance and half-life comparable to previous studies of RYZ101 and 177Lu-DOTATATE.

Conclusions: There were no DLTs reported at DL1 (6.5 MBq) and the dose of RYZ101 has been escalated to the next dose level. The study is actively enrolling patients to receive RYZ101 at DL2 (8.3 MBq) and additional safety data will be presented once mature.

Keywords: RYZ101, Somatostatin receptor-expressing, Extensive-stage small-cell lung cancer

P1.13A SMALL CELL LUNG CANCER AND NEUROENDOCRINE TUMORS - CLINICAL TRIALS
SUNDAY, SEPTEMBER 8, 2024 - 12:00 - 14:00

P1.13A.10 Efficacy and Safety of Lurbinectedin for Small Cell Lung Cancer in a Real-World Setting: Jazz EMERGE 402 Study

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Introduction: Lurbinectedin monotherapy is approved in many countries, including the United States (US) and Canada for adults with metastatic (US) or stage 3/metastatic (Canada) small cell lung cancer (SCLC) with disease progression on or after platinum-based chemotherapy. The Jazz EMERGE 402 phase 4 trial is assessing the real-world efficacy and safety of lurbinectedin for patients with extensive stage (ES)-SCLC. Preliminary safety data from this study were previously presented. For the first time, we report efficacy results along with updated safety data.

Methods: This observational, multicenter, single-arm study (NCT04894591) is enrolling patients with ESSCLC according to local approved labels, in the US and Canada.

Results: As of 02Jan2024, 171 patients had received ≥1 cycle of lurbinectedin; 13 (8%) had ongoing treatment and 158 (92%) discontinued with disease progression being the most common reason (n=104 [66%]). The median (range) age was 67 (29-89) years; 37 (22%) patients had an Eastern Cooperative Oncology Group performance status (ECOG PS) of ≥2; and 35 (20%) had central nervous system (CNS) involvement. Baseline characteristics were broadly similar between patients with a chemotherapy free interval (CTFI)<90 days vs ≥90 days. Ninety-two (54%) patients received lurbinectedin monotherapy as second-line (2L) and 59 (35%) as third-line. Median (range) number of lurbinectedin cycles was 4 (1-31) and duration of exposure was 105 (21-694) days. The objective response rate (ORR) in patients assessed by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 in 2L was 26.1% in the overall population; whereas ORR in 2L was 22.7% and 32.4%, respectively, in patients with CTFI <90 or CTFI ≥90 days (Table 1). Median progression-free survival (mPFS) and overall survival (mOS) in 2L were 3.5 and 7.6 months, respectively, in the overall population; whereas mPFS and mOS in 2L were 4.0 and 11.9 months for patients with CTFI ≥90 days. Similar ORR and mPFS were seen between RECIST and RECIST/non-RECIST evaluated patients. Treatment-related adverse events (AEs) occurred in 64 (37%) patients; AEs of special interest included grade ≥3 anemia (4.1%), neutropenia (6.5%), and thrombocytopenia (5.9%).

Conclusions: Jazz EMERGE 402 has enrolled a broader and sicker SCLC patient population than the phase 2 basket trial leading to lurbinectedin's approval. Patients with CTFI <90 or ≥90 days receiving lurbinectedin in 2L showed higher ORR, mPFS, and mOS than in later lines, and showed comparable mOS and mPFS as the basket trial. The real-world safety profile of lurbinectedin echoed previous reports, with no new safety signals.

Keywords: lurbinectedin, small cell lung cancer, real-world

Table 1. Efficacy outcomes

Efficacy data assessed per RECIST						
	Overall (N=115)		CTFI ≥90 days (n=61)		CTFI <90 days (n=33)	
	2L (n=69)	3L (n=46)	2L (n=37)	3L (n=24)	2L (n=22)	3L (n=11)
ORR, % (95% CI)	26.1 (16.2-38.1)	17.4 (7.8-31.4)	32.4 (18.0-49.8)	16.7 (4.7-37.4)	22.7 (7.8-45.4)	9.1 (0.2-41.3)
Median PFS, months (95% CI)	3.5 (2.1-4.7)	3.5 (2.5-4.9)	4.0 (2.1-5.3)	3.1 (2.4-4.7)	3.5 (1.8-6.0)	3.8 (0.4-8.2)
Median DoR, months (95% CI)	4.0 (2.7, 6.2)	3.5 (1.6, 10.9)	4.7 (2.3, NR)	3.5 (2.7, 3.5)	3.7 (2.3, 4.8)	1.6 (NR, NR)
DCR, % (95% CI)	43.5 (31.6-56.0)	41.3 (27.0-56.8)	51.4 (34.4-68.1)	37.5 (18.8-59.4)	45.5 (24.4-67.8)	45.5 (16.8-76.6)
Data assessed per RECIST and non-RECIST*						
	Overall (N=151)		CTFI ≥90 days (n=80)		CTFI <90 days (n=47)	
	2L (n=92)	3L (n=59)	2L (n=48)	3L (n=32)	2L (n=32)	3L (n=15)
Median OS*, months (95% CI)	7.6 (5.4, 11.9)	6.6 (4.7, 10.9)	11.9 (5.6, 13.8)	8.7 (3.2, 12.2)	5.8 (3.1, 7.2)	5.9 (3.4, 14.1)

*Includes patients who had at least 12 months of follow up by data cutoff date.

*RECIST was not consistently applied in real-world settings.

2L, second-line; 3L, third-line; CTFI, chemotherapy free interval; CI, confidence interval; DCR, disease control rate; DoR, duration of response; NR, not reached; ORR, objective response rate; OS, overall survival; PFS, progression free survival; RECIST, Response Evaluation Criteria in Solid Tumors version 1.1.

P1.13A SMALL CELL LUNG CANCER AND NEUROENDOCRINE TUMORS - CLINICAL TRIALS
SUNDAY, SEPTEMBER 8, 2024 - 12:00 - 14:00

P1.13A.11 Patterns of Disease Progression after Atezolizumab Plus Chemotherapy in ES-SCLC: Exploratory Analysis from IMfirst Study

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Introduction: The IMpower133 clinical trial showed that addition of atezolizumab to carboplatin + etoposide improved overall survival and progression-free survival in patients with extensive-stage small cell lung cancer (ES-SCLC). Despite this milestone in the management of ES-SCLC, most patients eventually experience progressive disease (PD). The understanding of how these tumours metastasize to specific organs in the era of immunotherapy is limited. Here, we carried out an exploratory analysis to delineate disease progression patterns in patients from the IMfirst study (EudraCT: 2019-002784-10), which includes a population that more closely resembles that of the real-world clinical practice in Spain.

Methods: The first reported PD and its corresponding site of progression, assessed by investigators according to Response Evaluation Criteria in Solid Tumours Version 1.1 (RECIST v1.1), was evaluated in the ITT population, as well as in patients with long-term benefit (LTB) or No-LTB. Patients were defined as LTB if they survived for at least 24 months post-randomization or No-LTB if they died within this time period. Percentages of PD are based on the total number of distinct sites (either new or existing). If a patient had multiple lesions at the same site, the site was counted only once.

Results: In total, 155 patients were enrolled in IMfirst study. Median follow-up was 28.4 months (data cut off: 14 December 2022). Of the 118 patients with PD, 115 had detailed reports of sites of progression and were included in the analysis: 85 (73.9%) had PD in existing lesions and 68 (59.1%) in new lesions. The most common sites of existing lesions (≥10% of patients) were lung, lymph nodes, liver, adrenal gland, bone and mediastinum, whereas the most frequent sites of new lesions were brain, liver, lung and lymph nodes. Of the 115 patients with PD included in the analysis, 14 were classified as LTB and 99, as No-LTB (2 patients with PD were censored before 24 months and were excluded from the analysis). PD in existing lesions was observed in 7 (50%) LTB and 77 (77.8%) No-LTB patients, while PD in new lesions was observed in 9 (64.3%) LTB and 57 (57.6%) No-LTB patients. The most common new or existing sites of progression (≥10% of patients) were similar between LTB and No-LTB patients. Regarding the distribution of PD sites, total new or existing lesions were restricted to 6 sites (lung, brain, lymph node, pleura, adrenal gland and liver) in LTB patients, while in No-LTB patients, progression was observed across a wider range of sites.

Conclusions: In this exploratory analysis from IMfirst, patterns of progression are in line with the results reported for IMpower133. These results suggest that No-LTB patients are more likely to experience PD in existing lesions and show a wider range of sites of progression compared to LTB patients. Given the limited sample size, these results should be further validated.

Keywords: Disease progression, IMfirst, exploratory analysis

P1.13A SMALL CELL LUNG CANCER AND NEUROENDOCRINE TUMORS - CLINICAL TRIALS
SUNDAY, SEPTEMBER 8, 2024 - 12:00 - 14:00

P1.13A.12 Exposure-Response Analyses to Support Ph3 Dose Selection for I-Dxd (Ifinatamab Deruxtecan) in Extensive Stage SCLC Patients

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Introduction: I-DXd (DS-7300), showed promising efficacy at ≥6.4 mg/kg in heavily pretreated extensive stage small cell lung cancer (ES-SCLC) patients in the ongoing Phase 1/2 study (IDeate-PT01, NCT04145622). Here, we report the exposure response (ER) analysis of I-DXd for safety and efficacy to support dose selection for Phase 3 development in ES-SCLC.

Methods: Interim data from ES-SCLC patients receiving I-DXd (8 or 12 mg/kg IV Q3W) in the dose optimization part of Phase 2 study (IDeate-L01, NCT05280470) and from patients with advanced solid tumors receiving I-DXd (0.8 to 16 mg/kg IV Q3W) in IDeate-PT01 were included in the analysis. Individual exposures for I-DXd and DXd (released payload) were derived based on a developed population pharmacokinetic (PK) model based on the same patients PK data. All patients were included in the exposure-safety (ES) analysis. Only ES-SCLC subjects were considered for exposure-efficacy (EE) analysis. ER analyses were conducted with selected efficacy and safety endpoints that have observed event rates >10% (8 out of 19 prespecified treatment emergent adverse events; TEAEs). Effects of other variables than exposure on the event probability were also evaluated. Modelling was performed using logistics regression analysis for binary endpoints.

Results: As of 25th July 2023, 256 patients were included in the ES analysis. ES analyses identified significant relationships between increased I-DXd exposure (C1 AUC) and any grade gastrointestinal (GI) disorders, and between DXd exposure (C1 or steady state AUC) and any grade and grade ≥3 anemia, any serious adverse event (SAE) and drug interruption. Positive ES relationships were also identified between DXd maximum concentration (C1 Cmax) and any adverse event (AE) grade ≥3 and any grade neutropenia. Geographical region, age, ECOG score, and cancer type were associated with some safety endpoint probability, but further evaluation is needed as the data become mature from these studies. Model projected median event rates at doses of interest, 8 mg/kg and 12 mg/kg were 60.6% and 74.8% for any grade GI disorders, 36.8% and 46.2% for any AE grade ≥3, 26.1% and 39.5% for any SAE, respectively. Difference between projected median event rates was <10% for all other safety endpoints. A total of 110 ES-SCLC patients were included in the EE analysis. EE analysis demonstrated significant relationships between all I-DXd exposure metrics and efficacy endpoints: objective response rate (ORR) and best tumor response. Model projected ORR median event rates at 8 mg/kg and 12 mg/kg were 30.7% and 51.7% respectively. Significant increase in tumor shrinkage is observed with increasing I-DXd exposure. Further EE analyses for progression free survival, duration of response, and overall survival are planned when data with longer follow-up are available. Overall, ER analyses predicted higher rates of efficacy with increasing I-DXd dose. However, frequency of TEAEs only marginally (<14%) increased, with both 8 mg/kg Q3W and 12 mg/kg Q3W showing manageable safety profiles.

Conclusions: Based on overall benefit-risk assessment and ER analyses, 12 mg/kg Q3W was selected as the recommended I-DXd dose for Phase 3 study (IDeate-L02; NCT06203210) and IDeate-L01 extension part for continued development in ES-SCLC.

Keywords: ER analysis, SCLC, antibody drug conjugate

P1.13A SMALL CELL LUNG CANCER AND NEUROENDOCRINE TUMORS - CLINICAL TRIALS
SUNDAY, SEPTEMBER 8, 2024 - 12:00 - 14:00

P1.13A.13 ALISertib in Patients with Extensive-Stage Small-Cell Lung Cancer: The Phase 2 ALISCA-Lung1 Study

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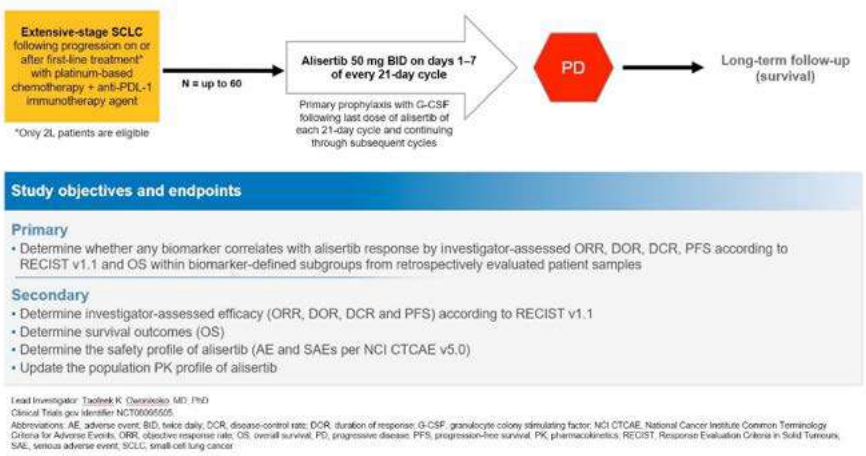
Introduction: Treatment options are limited for patients with small-cell lung cancer (SCLC) whose disease has progressed on or after platinum-based chemotherapy. Therefore, there is an urgent need for evaluation of novel agents in this setting. Aurora kinase A (AURKA) is a key regulator of mitosis and AURKA expression is associated with worse prognosis in multiple solid tumor types. Alisertib is a highly selective, reversible, ATP-competitive, orally administered, small-molecule AURKA inhibitor under investigation for SCLC. Phase 1/2 clinical trials of alisertib as either monotherapy or in combination with paclitaxel for relapsed/refractory solid tumors (including SCLC) reported response rates of 21-22%. The most common treatment-related grade ≥3 AEs were neutropenia, febrile neutropenia, and leukopenia. Preclinically, greater alisertib sensitivity has been reported in models with high c-Myc expression and/or loss of RB1 function. In a clinical study of alisertib + paclitaxel vs placebo + paclitaxel in SCLC, c-Myc expression or mutations in RB1, RBL1, RBL2, or CDK6 showed strong correlation with an improvement in both PFS and OS in the alisertib arm.

Methods: ALISCA-Lung1 (PUMA-ALI-4201, NCT06095505) is a phase 2 study to determine whether there is a biomarker-defined population of patients with extensive-stage SCLC that derives increased benefit from alisertib monotherapy. The study design is shown in Figure 1. Key inclusion criteria are: ≥18 years of age; progression on or after first-line treatment with platinum-based chemotherapy + anti-PD-L1 immunotherapy; ≥1 measurable lesion per RECIST v1.1; availability of tissue sample for retrospective biomarker evaluation. Key exclusion criteria: prior treatment with AURKA-specific or pan-Aurora-targeted agents; active infection; immunocompromise; unstable brain metastases; inability/unwillingness to swallow tablets. Primary objective: to determine whether any biomarker(s) correlate with increased benefit with alisertib monotherapy. Biomarkers will be assessed by next-generation sequencing, mRNA expression analysis, and immunohistochemistry. Candidate biomarkers include, but are not limited to, RB1 alteration, c-Myc expression, TP53 mutation, AURKA expression, and SCLC molecular subtype. Secondary objectives: to determine investigator-assessed efficacy, survival, safety, and population pharmacokinetics. Eligible patients will receive alisertib 50 mg orally BID d1–7 q21d (including primary prophylaxis with G-CSF) until disease progression, unacceptable toxicity, or withdrawal of consent. All patients will undergo sparse pharmacokinetic sampling. Recruitment is underway and up to 60 patients will be enrolled at approximately 20 centers in the USA. Findings are anticipated to identify a biomarker-defined population that derives the greatest clinical benefit from alisertib. Future development of alisertib in SCLC is anticipated to focus on this biomarker-defined population.

Keywords: Alisertib, Small-cell lung cancer, Aurora kinase A inhibitor

Figure 1. ALISCA-Lung1 study design



P1.13B SMALL CELL LUNG CANCER AND NEUROENDOCRINE TUMORS - RELAPSED/REFRACTORY ES-SCLC
SUNDAY, SEPTEMBER 8, 2024 - 12:00 - 14:00

P1.13B.01 Lurbinectedin vs. Platinum Rechallenge in Extensive Stage Small Cell Lung Cancer after Platinum Doublet, A Multicenter Retrospective Study

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Introduction: Although small cell lung cancer (SCLC) patients typically have a rapid and deep initial response to platinum doublet chemotherapy, relapse can occur quickly. Despite multiple available therapeutic options for patients with progressive disease after first-line therapy, outcomes remain poor and limited evidence exists indicating a preferred second-line treatment approach. Here we present findings from a multicenter retrospective cohort study comparing platinum doublet rechallenge and lurbinectedin in a real-world setting.

Methods: Patient records were identified from Vanderbilt Ingram Cancer Center and the University of Pennsylvania between 2000 and 2023. Study cohorts included extensive-stage (ES) SCLC patients treated with second line lurbinectedin or platinum rechallenge following initial platinum-based chemotherapy. Primary outcomes included overall survival (OS) and real-world progression-free survival (rwPFS).

Results: A total of 81 patients were included, with 45 receiving platinum rechallenge and 36 receiving lurbinectedin. Cohorts were similar for sex, race, comorbidities, and performance status. The platinum rechallenge group skewed younger and had shorter chemotherapy-free interval (CFTI) compared to lurbinectedin (median age 63 [58, 68] vs. 67 [63, 75] p=0.006, and CTFI 2.51 [1.20, 3.59] vs. 9.40 [5.25, 19.34] p<0.001). First line therapy included immunotherapy in 14 (31%) of platinum rechallenge and 28 (78%) of lurbinectedin patients. In the unadjusted dataset comparing platinum rechallenge and lurbinectedin, median rwPFS was 4.56 (1.64, 6.33) and 2.42 (1.36, 3.92) months (p = 0.003) and median OS was 11.14 (4.99, 15.64) and 4.81 (2.62, 7.40) months (p = 0.003), respectively. In a multivariate Cox proportional hazard analysis, OS and rwPFS hazard ratios for lurbinectedin compared to platinum rechallenge were 1.98 (1.15-3.38, p=0.012) and 1.57 (0.93-2.66) (p = 0.094) after controlling for CTFI and concomitant maintenance immunotherapy. CTFI was not independently associated with rwPFS (HR 0.98 (0.97-1.00)) or OS (HR 0.99 (0.97-1.00)) when adjusting for other covariates. When platinum rechallenge vs. lurbinectedin was examined within pre-specified CTFI levels (< 3 months, 3-6 months, or > 6 months) there was no significant difference in OS or rwPFS outcomes between the two strategies. In a secondary analysis of 57 patients from one site (36 platinum rechallenge, 21 lurbinectedin), there was no statistically significant difference in hospitalizations, neutropenic fever (22% platinum rechallenge vs. 5% lurbinectedin, p=0.13), anemia, or transaminitis between groups, although 7 (29%) of platinum rechallenge patients discontinued due to tolerability compared to 0 (0%) with lurbinectedin.

Conclusions: When comparing patients with similar CTFI prior to start of second-line therapy for ES-SCLC (< 3 months, 3-6 months, and > 6 months), there was no significant difference in median OS or rwPFS between platinum rechallenge and lurbinectedin. Drug-related safety events (evaluated in patients from one study site) were similar, although tolerability led to greater discontinuation with platinum-based chemotherapy. These multicenter findings support further research efforts within specific CTFI groupings to identify optimal therapeutic strategies for each patient subgroup in second-line treatment of ES-SCLC.

Keywords: SCLC, lurbinectedin, platinum-rechallenge

P1.13B SMALL CELL LUNG CANCER AND NEUROENDOCRINE TUMORS - RELAPSED/REFRACTORY ES-SCLC
SUNDAY, SEPTEMBER 8, 2024 - 12:00 - 14:00

P1.13B.02 Radiation Necrosis in Small Cell Lung Cancer Patients

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Introduction: Immunotherapy (IO) and new radiation therapy (RT) technics such as stereotactic radiosurgery (SRS), advanced the treatment of small cell lung cancer (SCLC) by improving quality of life and lengthening survival. However, attention should be paid to the treatment-related long-term secondary effects. Data from non-small cell lung cancer patients indicate a higher rate of radiation necrosis (RN) in patients treated with IO and cranial RT simultaneously. However, little is known regarding the prevalence of RN in SCLC patients treated with this combination.

Methods: This study focused on patients diagnosed with SCLC and treated in our medical center in the years 2019-2022.

Results: Out of 96 SCLC patients, 47 (49%) had brain metastasis, 34 (72.3%) of which received RT, with the majority (64.7%, n=22) receiving whole brain radiation therapy (WBRT) and the rest (35.3%, n=12) receiving SRS, with 20 patients (58.8%) treated with IO simultaneously or separately from RT. Surprisingly, patients treated with SRS had a shorter median survival of 100 days vs 140 days in the WBRT group. Eight out of 12 (66.6%) patients and 16 out of 22 (72.7%) patients in the SRS and WBRT groups, respectively, survived over 3 months, with only 4 (33.3%) and 8 (36.3%) patients surviving longer than 6 months, respectively. None of the patients was diagnosed with RN during the follow-up period, even with the combination of IO and RT.

Conclusions: These findings demonstrate that SRS is a safe treatment option in SCLC and does not increase the risk of RN, even in combination with IO, although a longer survival was observed in the WBRT cohort.

Keywords: Small cell lung cancer, Cranial radiation therapy, Radiation necrosis

P2.04A SCREENING AND EARLY DETECTION - CLINICAL TRIALS IN PROGRESS
SUNDAY, SEPTEMBER 8, 2024 - 18:15 - 19:45

P2.04A.01 FIRSTLUNG (L301): Cluster Randomized Trial Evaluating the Clinical Utility of DELFI's Blood-Based Lung Cancer Screening Test

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Introduction: To optimize the impact of lung cancer screening at the healthcare system level, additional tools are needed to increase the benefits of screening. While low-dose computed tomography (LDCT) has been shown to improve lung cancer detection and reduce mortality, it is not without its risks, such as radiation exposure, false-positive results, and unnecessary interventions often leading to complications. The additional complexity of lung cancer screening is the subpar adherence to LDCT for eligible individuals, which undermines the benefits of screening. Therefore, there is a need for alternative non-invasive methodologies that exploit our understanding of the biology of cancer pathogenesis. This clinical utility study aims to observe how a non-invasive blood-based test impacts physician behavior and LDCT utilization.

Methods: FIRSTLUNG 301 (NCT06145750) is a prospective, cluster randomized controlled trial (RCT) to observe the impact of the DELFI Lung cancer screening test on lung cancer screening utilization in primary care practices. Enrolled practices must meet the eligibility criteria of having a minimum of 50 actively engaged individuals in the practice eligible for lung cancer screening per the 2021 USPSTF criteria. These practices will be randomized 1:1:2 to Arm A1 (control), Arm A2 (control), or Arm B (intervention). Arm A practices will be randomized 1:1 into two groups (A1:A2) to observe the standard of care for lung cancer screening. Practices in A1 will be observed; practices in A2 will receive standard education on lung cancer screening for CME credit. Randomizing within Arms A1 and A2 aims to delineate the impact standard lung cancer screening education may have on utilization. Arm B (intervention) practices will receive education and have access to order the blood-based test for screen-eligible individuals that remained unscreened. The primary study endpoint is the proportion of practice-identified lung cancer screen-eligible individuals receiving a screening CT order and scan during the study period in the entirety of Arm A (control) versus Arm B (intervention). This RCT aims to understand the utilization and impact on lung cancer screening uptake after the DELFI blood-based test intended to inform clinical guidelines and policies focused on improving patient care and health outcomes. Progress: Study initiation on October 31, 2023, with practice randomization. As of April 2024, the study is open for enrollment with 13 practices randomized. The primary study completion date is estimated at December 2025.

Keywords: blood-based test, lung cancer screening, low-dose computed tomography (LDCT)

P2.04A SCREENING AND EARLY DETECTION - CLINICAL TRIALS IN PROGRESS, SUNDAY, SEPTEMBER 8, 2024 - 18:15 - 19:45

P2.04A.02 Using an AI Transformer Model to Identify Incidental Pulmonary Nodules (IPN) For Lung Cancer Early Detection

R.L. Myers1, W. Parker2, C. Bartolomeu3, A. Mojibian4, H. Lam3, R. Hung5, S. Lam6

1BC Cancer, Vancouver/BC/CA ,2Vancouver Coastal Health, Vancouver/BC/CA ,3BC Cancer Research Institute, Vancouver, Vancouver/BC/CA ,4Sapien Secure, Vancouver/BC/CA ,5Lunenfeld- Tanenbaum Research Institute, Sinai Health, Toronto/ON/CA ,6BC Cancer, Vancouver, Vancouver/BC/CA

Introduction: Outside a lung screening program, most lung nodules are incidentally found on imaging studies completed for other diagnostic purposes. An estimated 4.8 million Americans have at least one chest CT scan, and 1.57 million have a nodule identified; among these, ~4% received a new lung cancer diagnosis within two years. Chest imaging is increasingly used for various indications, such as cardiac disease detection. The detection of incidental pulmonary nodules (IPNs) will steadily increase. Growing data demonstrates most of the patients with IPNs receive no clinical follow-up, thus missing the opportunity for early cancer diagnosis. Developing an accurate automated IPN identification tool is imperative to ensure appropriate follow-up and ultimately, improve early diagnosis and treatment of lung cancer to complement current lung cancer screening programs.

Methods: As part of the Identifying Early Lung Cancer in A Diverse Population (IDEAL), study, a multi-centre national trial, - the Vancouver study site, is utilizing the Medical Named Entity Recognition Model (NER)- SapienNER v3a, as a screening tool for identifying pulmonary nodules in reports of all lung-in-view CT scans that were done in the Greater Vancouver area. NER is a custom developed, RoBERTa-based transformer model tailored for interpreting unstructured medical reports. All lung-in-view CT imaging studies performed between November 2023 to March 2024 were identified using a list of inclusion and exclusion criteria, based on the specific lexicon of terms used to describe pulmonary nodules in CT reports. The scans were categorized by age ≥ 50 to 74 years, and nodules ≥6 mm. The reports were reviewed by the clinical staff to ensure the nodules were truly incidental.

Results: During a 5-month time period, a total of 14,154 lung-in-view scans were identified in the PACS system. 4363 scans were classified as having a pulmonary nodule, and 1436 of these scans had a nodule size ≥6 mm. Of those, 1072 scans occurred in individuals ages 50-74 yrs. Following clinical review, 131 scans were confirmed to have a truly incidental nodule ≥6mm. Scan type included 44% cardiac (51% with contrast), 45% chest (81% with contrast), 7% CT abdomen, and 3% Head and neck. The majority of scans that were removed from further follow-up were scans that were ordered specifically to track a nodule from a prior imaging study, or for surveillance of lung metastasis in patients with cancer. 74% of patients identified with IPN agreed to be followed-up.

Conclusions: Our study showed a Natural Language Processing (NLP) system can be easily deployed in a large healthcare organization, to reliably and efficiently identify patients with clinically significant IPNs. Our study also identified areas that need further improvement such as comparison with prior imaging studies and extraction of relevant medical history. Implementing a Large Language Model will address these issues and reduce clinician time investment to identify patients with IPN who require follow-up. Advancing our NLP system with LLM capabilities may be the crucial future step required for the complete automation and optimization of follow-up protocols to bolster early lung cancer detection and compliment screening programs.

Keywords: Incidental Pulmonary Nodule, Lung Cancer, Natural Language Processing

P2.04A SCREENING AND EARLY DETECTION - CLINICAL TRIALS IN PROGRESS, SUNDAY, SEPTEMBER 8, 2024 - 18:15 - 19:45

P2.04A.03 Enhancing Participation in Flemish Lung Cancer Screening: Strategies for Engaging the Hard-To-Reach

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Introduction: Lung cancer remains one of the most prevalent and deadly cancers worldwide, with late-stage diagnosis significantly contributing to poor prognosis and survival rates. While large randomized screening trials with Low-Dose Computed Tomography (LDCT) have demonstrated effectiveness in reducing lung cancer-specific mortality (NELSON/NLST), reaching and engaging populations at high risk, the “hard-to-reach”, remains challenging. The Council of the European Union, recognizing lung cancer screenings vital role in mortality reduction, recommended in 2022 to explore the feasibility and effectiveness of LDCT for high-risk individuals. This recommendation underscores the necessity to tackle the screening challenges and develop tailored strategies to ensure equity. While lung cancer screening offers significant benefits, it also faces a number of challenges, including stigma, how to address incidental findings, overdiagnosis, false-positive results, workload/capacity issues... One of the most important challenges is the difficulty in reaching and engaging hard-to-reach participants.

Methods: The ZORALCS-study aims to address these challenges through a comprehensive, multidisciplinary approach with a special focus on socioeconomic factors, health literacy, digital literacy and educational factors, involving a wide range of healthcare professionals from various sectors with emphasis on multidisciplinary collaborations (pharmacists, general practitioners, tabaccologists, nurses, occupational therapists, centre for general well-being, public centre for social welfare...). Our study explores and focuses on three key trajectories:

1. Education of healthcare providers and the public: our study emphasizes educating healthcare providers on lung cancer screenings’ benefits and risks, incorporating motivational techniques for active engagement. Addressing lung cancer stigma and providing comprehensive education materials for participants are also central, utilizing mediums like leaflets, radio, TV, and posters in public spaces.

2. Invitation strategy assessment: by examining psychological drivers influencing participation, we assess different invitation methods

to identify the most effective one. Evaluating and scoring these invitations by an external citizens' committee ensures that the most compelling one is utilized.

3. Developing effective recruiting strategies: leveraging the insights from invitation strategy research, we assess various recruiting strategies to identify the most effective for the Flanders region. From community outreach initiatives to leveraging digital platforms, we seek to identify and implement strategies that facilitate access to screening services for hard-to-reach populations.

In conclusion, our implementation study in Flanders highlights the critical need for specific strategies to overcome barriers and enhance participation in lung cancer screening among hard-to-reach populations. By addressing screening challenges and implementing research-backed interventions, our goal is to boost early detection rates and ultimately reduce lung cancer's impact in our community.

Keywords: Lung Cancer Screening, Targeting hard-to-reach, Recruitment strategies

P2.04A SCREENING AND EARLY DETECTION - CLINICAL TRIALS IN PROGRESS, SUNDAY, SEPTEMBER 8, 2024 - 18:15 - 19:45

P2.04A.04 The Lung Health Check Pilot: Ireland's Flagship Lung Cancer Screening Trial

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Introduction: The use of low-dose chest CT (LDCT) has demonstrated the ability to detect early stage lung cancer (LC), and improve disease-specific mortality in high-risk individuals. Use of LC risk scores (Prostate, Lung, Colorectal, Ovarian Model; PlCO2012/Liverpool Lung Project; LLPv2) improves the sensitivity, specificity and positive predictive value for LC screening. However, the screen-eligible population remains at 2-4%, and uptake rates are low in existing national programs, particularly in the socially disadvantaged who may benefit most from LC screening. These programs have identified that primary care participation, patient engagement, and improved accessibility may optimize the success of LC screening; as well as provide an opportunity to collect biospecimens from participants, to optimize LC early detection through next-generation biomarker discovery. Currently, there is no national LC screening program in the Republic of Ireland. In the first pilot study of LC screening in Ireland we will: i) investigate the feasibility of a lung cancer screening in a socially disadvantaged area, based on primary care-based participant identification and patient engagement methods, and mobile CT-scanning and ii) investigate novel blood/breath biomarkers in high-risk individuals who participate in the LC screening trial, to identify biologic parameters that may supplement existing risk scores, to maximise LC early detection.

Methods: In a pilot feasibility clinical trial, we will invite 13,933 high-risk participants to a 'Lung Health Check'. This will involve a respiratory disease assessment, baseline spirometry, smoking cessation, a low-dose chest CT, and blood/breath biospecimen collection. Participants will be invited via their primary care practitioner with remote assessment of PLCO2012/LLPv2 scores and eligibility. Eligible participants will be invited to an in-person lung health check at a mobile unit. The primary endpoint is the percentage of high-risk eligible participants who attend (of those invited for the lung health check). A total of 13,933 participants who have ever smoked will be invited to estimate the uptake in the underlying population (Republic of Ireland) with a precision of 1% (i.e. assuming a 95% confidence level ± 1%). Allowing for drop-out, we estimate a sample size of 2183 participants for a baseline lung health check (T0). Participants will attend for a follow-up CT scan at 1 year (T1) if there are no significant findings at T0, while those with lung nodules will be assessed 3 months after T0. Blood and breath samples will be investigated for genomic, proteomic and immunological features associated with a diagnosis of lung cancer, compared with controls (Participants enrolled who are not diagnosed with nodules/LC).

Results:

Conclusions: In this pilot feasibility trial, we will investigate the uptake of lung cancer screening utilising a community-based strategy amongst high-risk participants with additional work focusing on blood/breath biomarkers associated with lung cancer.

Keywords: Lung Cancer, Low dose CT, Lung cancer screening

P2.04A SCREENING AND EARLY DETECTION - CLINICAL TRIALS IN PROGRESS, SUNDAY, SEPTEMBER 8, 2024 - 18:15 - 19:45

P2.04A.05 Providing Tobacco Treatment to Patients Undergoing Lung Cancer Screening at a Large U.S. Health System: A Randomized Trial

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Introduction: Providing tobacco treatment in conjunction with lung cancer screening is estimated to substantially reduce lung cancer

deaths and increase life-years gained, compared to conducting lung cancer screening alone. Although many organizations recommend that individuals who are currently smoking cigarettes and are undergoing lung cancer screening be offered cessation treatment, there are multiple barriers to treatment delivery. We are conducting a health system-level, pragmatic, randomized trial to compare the effectiveness of two evidence-based treatments for cigarette smoking at MedStar Health, the largest and most diverse health system in the U.S. Mid-Atlantic region. The trial addresses known barriers to tobacco treatment in the healthcare setting, using 'opt out' procedures to contact all eligible patients for enrollment and using centralized delivery of the cessation interventions to address inequities in receipt of cessation treatment.

The goals of this ongoing trial (R01 CA274716) are to improve the evidence-base of cessation treatment for lung screening patients, to improve the systematic uptake of cessation treatment into routine practice, to address barriers to reach and engagement among diverse populations, and to maximize generalizability to other health systems. An economic analysis will evaluate costs, average and incremental cost per quit, and the budget impact of the intervention from the health system's perspective.

Methods: All patients who are currently smoking cigarettes and have received an order for a low-dose CT scan at MedStar Health are identified via the EHR, contacted for trial enrollment using an opt-out approach, and randomized to: 1) E-referral to the Tobacco Quitline (N=594) via the integrated closed-loop system between the EHR and the quitline. The quitline protocol includes proactive outreach and standard phone-based counseling + nicotine replacement; vs. 2) the MedStar Health System (N=594) arm, a centralized, phone-based + nicotine replacement intervention delivered by tobacco treatment specialists (TTS) trained to use motivational interviewing techniques to assist participants in their efforts to reduce or stop cigarette smoking. Using an adaptive design, those who are not abstinent at the 3-month assessment will be randomized a second time, to receive either continued treatment from the TTS vs. a more intensive intervention delivered by a registered nurse and nurse practitioner in which varenicline or bupropion can be prescribed as clinically appropriate. The primary trial outcome is bioverified abstinence from cigarettes at 6-months following randomization. Secondary trial outcomes include self-reported smoking status, quit attempts, and sustained abstinence.

Strengths include testing the effectiveness and economic outcomes of two cessation interventions while simultaneously laying the groundwork for sustainability and future implementation within this and other diverse health systems. Our innovative approach capitalizes on the EHR for recruitment, is focused on accruing diverse populations, and accounts for intervention context to inform future care delivery. Integrating cost effective and broad reaching tobacco treatment interventions into health care systems will maximize the benefits of lung cancer screening.

Keywords: smoking cessation, lung cancer screening, tobacco treatment

P2.04A SCREENING AND EARLY DETECTION - CLINICAL TRIALS IN PROGRESS, SUNDAY, SEPTEMBER 8, 2024 - 18:15 - 19:45

P2.04A.06 A Multilevel Approach to Address Disparities in Lung Cancer Screening: The PREP Trial

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Introduction: Lung cancer is the leading cause of cancer-related mortality in the US, with more than 120,000 deaths expected in 2024. Based on the National Lung Screening Trial, which showed that low-dose computed tomography (lung cancer screening) vs. chest X-ray reduced mortality from lung cancer by 20%, the US Preventive Services Task Force recommends annual lung cancer screening for asymptomatic high-risk individuals. Despite this recommendation, utilization is poor (3%-20%). Lung cancer screening may be particularly beneficial for African Americans (AA) because they are more likely to have advanced disease, lower survival, and lower screening rates compared to White individuals. The causes of low uptake of lung cancer screening are multifactorial and consistent with evidence from other cancer screening disparities, pointing to the need for multilevel interventions that simultaneously address multiple barriers to increase screening rates and decrease lung cancer morbidity and mortality in minoritized populations. Guided by NIH's Health Disparities Research Framework, the ongoing study (NCI R00CA256515) is targeting provider and patient behaviors, two key levels of influence in the healthcare setting, to address disparities between AA and Whites in lung cancer screening awareness and utilization.

Methods: We are conducting a quasi-experimental study (pretest-posttest, with a nonequivalent control group) in partnership with four primary care clinics within the MedStar Health system. Sites are matched on CT scanner on site (yes/no) and minority representation (> 40% AA). Individuals eligible for lung cancer screening, defined as 50-80 years old, 20+ pack-years, currently smoking or quit <15 years ago, no history of lung cancer, and who are non-adherent to screening (never screened or > 13 months since last screen), identified via the electronic health record (EHR), are contacted and enrolled (N = 184 in the intervention clinics, N = 184 in the control clinics; total N = 368). Provider participants (N = 21) include those practicing at the partner clinics. To increase provider-prompted discussions about lung cancer screening, an EHR pre-visit planning message will be sent to primary care providers 48 hours prior to scheduled visits with screening-eligible patients. To target patient-level knowledge and promote patient activation about lung cancer screening, an in-reach specialist will educate the patients about screening prior to their visit. Patient participants will be assessed at baseline and 1-week post-visit to measure provider-patient discussion about lung cancer screening, screening intentions, and knowledge. Screening referrals and screening completion rates will be assessed via the EHR 6 months post visit. At the time of this submission, recruitment is ongoing. This multilevel intervention targets important barriers to lung cancer screening. The study will inform future work designed to measure the independent and overlapping contributions of the multilevel implementation strategies to advance equity in lung cancer screening rates.

Keywords: lung cancer screening, health disparities, multilevel trials

P2.04A SCREENING AND EARLY DETECTION - CLINICAL TRIALS IN PROGRESS, SUNDAY, SEPTEMBER 8, 2024 - 18:15 - 19:45

P2.04A.07 Improving IPN Management Through CAD and Virtual Nodule Clinics: A Prospective, Observational Multicenter Study (PINPOINT)

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Introduction: Early detection of lung cancer plays a pivotal role in improving lung cancer survival. Besides screening a high-risk population, detection and follow-up of incidental pulmonary nodules (IPN) is a complementary pathway to detect lung cancer in earlier stages . However, IPN are frequently missed, while follow-up of IPN is regularly absent or non-standardized (1,2). Computer-Aided Detection (CAD) has the potential to increase a radiologists' capability to detect IPN on chest CT scans and aid in identifying patients that need follow-up procedures . Adherence to these follow-up procedures can be improved by implementing a Virtual Nodule Clinic (VNC). In this study, we hypothesize that implementation of CAD and VNC improves clinical management of IPN and therefore induces a stage shift towards earlier lung cancer diagnosis.

Methods: This study is a prospective, observational multicenter study to determine the impact of CAD together with a VNC on IPN detection, follow-up and lung cancer diagnosis. The CAD software supports clinicians in detecting IPN and identify patients that need follow-up procedures according to guidelines of the British Thoracic Society (BTS). A dedicated health care professional will manage the VNC as 'navigator' to ensure all patients adhere to the scheduled referrals and follow-up procedures. Primary outcome is the rate of patients diagnosed with stage I/II lung cancer with curative intent treatment. Secondary outcomes include cost-effectiveness of the program, clinical management with patient outcomes, adherence to guidelines, psychological burden and eligibility for lung cancer screening. Based on an increase in the rate of stage I/II lung cancer diagnosis from 25% in current clinical practice to 60%, one thousand IPN patients have to be recruited in the 8 hospitals across Europe. In addition, we will perform a retrospective study in each participating hospital to further determine the impact of CAD. In this historical cohort generated by Natural Language Processing (NLP), we will re-analyze all chest CT scans with CAD to determine the difference in IPN detection rate and lung cancer diagnosis (Figure 1).

Keywords: Incidental Pulmonary Nodule, Early Detection, Artificial Intelligence

P2.04A SCREENING AND EARLY DETECTION - CLINICAL TRIALS IN PROGRESS, SUNDAY, SEPTEMBER 8, 2024 - 18:15 - 19:45

P2.04A.08 Feasibility of Cell-Free DNA Liquid Biopsy in Screening High-Risk Patients for Lung Cancer

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Introduction: Lung cancer screening (LCS) with low dose computed tomography (LDCT) significantly reduces death from lung cancer but is severely underutilized. Despite many U.S. guidelines recommending LDCT for LCS, fewer than 5% of eligible adults are screened. LDCT utilization is even lower for minoritized and low-income populations. Barriers to LCS access and completion are numerous, complex, and multi-level. Innovative strategies that bring LCS to individuals, rather than require travel to health care facilities, are therefore urgently needed. DELFI cell-free DNA (cfDNA) liquid biopsy, which is a low-cost platform and can be collected at home or as point-of-care testing, is a promising LCS-specific blood-based tool that may improve participation in LCS among individuals who face barriers to screening. This study aims to determine the feasibility and acceptability of the DELFI cfDNA test that can be collected at-home or during a community-based healthcare encounter, with a focus on under-resourced populations.

Methods: Feasibility of Cell-Free DNA Liquid Biopsy in Screening High-Risk Patients for Lung Cancer (NCT: NCT05384769) is an investigator-initiated research (IIR) study designed to evaluate the adoption of lung cancer screening when a choice in modality is offered (blood-based test versus LDCT). We plan to recruit 100 participants over a 12-month period through an urban Federally Qualified Health Center (FQHC), a rural LCS program, and a mobile cancer screening clinic in a medically underserved and remote region north of Los Angeles. Participants are eligible to participate if they meet the 2021 USPSTF LCS criteria and are English or Spanish-speaking. After LCS shared-decision making, eligible participants will choose to undergo either a blood-based test (BBT) at home or as point-of-care testing, or standard of care LDCT. Participants undergoing BBT may undergo LDCT at any time after their results are returned. Participants in

both cohorts will complete a baseline and a six-month follow-up survey. The baseline survey will include questions regarding socio-demographics, smoking history, cancer screening history, the LCS Health Beliefs survey, and the Cancer Worry Scale. The six-month follow-up survey will include questions regarding patient satisfaction, the Cancer Worry Scale, cancer diagnosis, and screening follow-up with LDCT. The primary study endpoint is the proportion of participants who agree to undergo lung cancer screening using the BBT versus LDCT, with a feasibility threshold of at least 30% preferring the blood test. Secondary endpoints include the proportion of participants with either Elevated or Not Elevated results subsequently undergo LDCT, and the LCS barriers and sociodemographic characteristics that are associated with the choice to undergo BBT vs. LDCT. Focus groups also will be conducted to assess LB feasibility and implementation. This IIR study will provide insight into the utilization and impact of a blood-based test for lung cancer screening and will inform a larger clinical trial designed to assess the role of this test in improving the early detection of lung cancer in under-resourced communities.

Progress: The study was open to enrollment on March 25, 2024 with an estimated primary study completion date of December 31, 2025.

Keywords: Lung cancer screening, Liquid biopsy, Barriers to screening

P2.04B SCREENING AND EARLY DETECTION - SCREENING IMPLEMENTATION AROUND THE WORLD, SUNDAY, SEPTEMBER 8, 2024 - 18:15 - 19:45

P2.04B.01 Argentine Lung Cancer Screening Programes Collaborative Registry: The LuCaS.Ar Project

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Introduction: Despite the growing body of high-quality evidence on the effectiveness of the Lung Cancer Screening (LCS) with low dose computed tomography (LDCT) in reducing lung lancer (LC) mortality in high-risk populations,barriers have been reported at both the health provider and target population level4 and low adherence rates. These challenges can be even greater in low-income countries. Several academic associations in Latin America have published recommendations about LCS and promising results in terms of early lung cancer detection and diagnostic accuracy have been described. In this context, we present the first experience of a collaborative registry of LCS in Argentina: LUng CAncer Screening (LuCaS) Project.

Methods: We aim to describe the characteristics of the Argentine LCS Collaborative registry and its participants institutions, with particular reference to adherence to LCS national consensus recommendations at baseline. The LuCaS Project has been designed as an analytical, observational, ambispective, follow-up study on a cohort of individuals with a history of heavy smoking undergoing LCS with LDCT. All institutions that have LCS pilot programs in the country were invited to participate. Individuals are being recruited by each center, all variables are recorded in a common web-based management system. Patient enrolment criteria are current 30 pack-year smokers, or former smokers for a maximum of 15 years, aged between 55 and 74 years. The institutions were questioned about their baseline program characteristics according to the recommendations of the latest LCS national consensus.

Results: Twenty one Argentine institutions have already joined the LuCaS project.Seven of them are funded by the government. Among the 14 private institutions, one has also a government grant (Fig1). Ten programs take place in the city of Buenos Aires. At baseline 20/21 LCS programmes have a multidisciplinary team; 19/21 offer a smoking cessation plan integrated with the LCS programme; 20/21 have pre-established protocols for clinical decision-making about lung nodule management; 15/21 ensure the distribution of educational materials about the benefits and risks of LCS; 19/21 offer cardiovascular risk evaluation; and all have strategies for symptomatic patients care.

Conclusions: LuCas Project is the first Argentine LCS Collaborative registry. Participating institutions have a relatively heterogeneous medical care profile, mostly developed in large urban centers and privately financed. Challenges will remain on how to equate the features of the programs according to the LCS consensus recomendations, recruit more participating institutions, as well as improving the access to LCS to more patients throughout the country.

Keywords: lung cancer screening, early detection, national registry

P2.04B SCREENING AND EARLY DETECTION - SCREENING IMPLEMENTATION AROUND THE WORLD, SUNDAY, SEPTEMBER 8, 2024 - 18:15 - 19:45

P2.04B.02 Eight Year Outcomes of a Multidisciplinary Lung Cancer Screening Program at a Large Community Centre in Canada

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Introduction: Low-dose chest CT scan (LDCT) lung screening programs reduce lung cancer mortality for high-risk patients. In 2012, William Osler Health System, Canada, a large community centre implemented the longest running multidisciplinary lung cancer screening program in Canada outside of a research/pilot study. We present the real world outcomes of this program.

Methods: Retrospective chart review of screened patients with LDCT (Siemens 120kV, 20 quality reference mAs, Caredose) from February 2012 to December 2019 with follow up to April 2023. Patients were referred by family physicians or specialists. Patients were eligible for annual screening while they met the following criteria: age 55 to 77, minimum of 30-pack-year history of cigarette smoking, no prior lung cancer, no CT scan within 12 months of initial LDCT and former smokers must have quit within the previous 15 years. This multidisciplinary program had standardized radiologist reporting of high risk LDCT. Prior to 2014, a nodule was deemed positive if solid or subsolid and greater than 6 mm in mean diameter on initial study or growing. In 2014. we started transitioning to ACR Lung Rads protocol. All Lung Rads 4 cases were referred to thoracic surgery and seen in a Solitary Pulmonary Nodule clinic.

Results: During the study period, 5460 unique patients were enrolled, with 14,048 high risk LDCT completed (average LDCT/patient was 2.6). Average of 683 new patients entered the program/year, with average annual growth of 27.6%. Median age at program entry was 63 and 61% were males. Of patients screened, 287 (5.3%) had a biopsy by CT guided +/- EBUS/Mediastinoscopy (n=208) or EBUS/Mediastinoscopy alone (n=79). A total of 225 CT guided biopsies were completed of which 118 (52.4%) were malignant, 26 (11.6%) were atypical/suspicious for cancer, 49 (21.8%) were benign, and 32 (14.2%) were non diagnostic. Overall detection rate of cancer including 8 cases of non lung cancer was 4.2% (n=229), and 4.0% (n=221) for lung cancer. Clinical or surgical stage of lung cancers detected was primarily early stage with the following distribution: stage I (61.5%), II (11.8%), III (17.2%) and IV (9.5%). There were 198 surgical resections for 187 unique patients in which the cancer detection rate was 88.8% if they had a pre-surgical biopsy versus 76% if they did not. The pathology of resected cases was lung cancer (85.4%), non lung malignancy (3%) and benign/atypia (11.6%). Majority of surgeries were lobectomies +/- wedge (62.1%), or segmentectomy/wedge (34.8%) with low rates of bilobectomy (1.5%) and pneumonectomy (1.5%). In patients with lung cancer, 60 did not have surgery for various reasons, and patients with surgical resection the stage was as follows: stage I (78.3%), II (13.7%), and III (13.7%).

Conclusions: We report outcomes of the longest running multidisciplinary lung cancer screening program in Canada outside a research protocol with over 5000 patients screened. The collaboration between radiology and thoracic surgery resulted in detection and management of early stage lung cancers which compared favourably to pivotal trials. Our experience provides further evidence supporting lung cancer screening and feasibility of such programs at community centres.

Keywords: lung cancer screening, real world data, early detection

P2.04B SCREENING AND EARLY DETECTION - SCREENING IMPLEMENTATION AROUND THE WORLD, SUNDAY, SEPTEMBER 8, 2024 - 18:15 - 19:45

P2.04B.03 Low Cost Low Dose CT Scan for Lung Cancer Screening - Seven Year Experience at a Sub-urban Community Hospital.

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Introduction: Lung cancer is the largest cause of cancer-related death in U.S. USPSTF recommends annual low dose CT (LDCT) scans for lung cancer screening in high risk population within 50 and 80 years of age, 20 pack years history of smoking and who are either currently smoking or have quit within 15 years. Due to the cost and lack of awareness, most patients are not able to afford LDCT scans and this recommendation has not been widely implemented leading to less than 7% of eligible patients going through the required screening.

Methods: We describe a low-cost approach adopted by Columbus Regional Hospital in conjunction with a multi-specialty physician collaborative. We offered a highly subsidized LDCT screen to high risk patients followed by a multi-disciplinary evaluation for those with Lung rad 3 or 4 findings. The care model utilized evidence-based standards to direct further management including further imaging with LDCT, PET scan or biopsy. We also focused on incorporating the primary care physicians on record to assist with patient follow-up. Aggressive use of patient navigators facilitated care coordination and open communication between providers, patients and family. We hypothesized the cost of initial screens is the most significant barrier and were able to overcome that by offering LDCT at a low price of $25 which at times was further subsidized to $10 and also offered free to 200 patients every year during Lung cancer awareness month. We also hypothesized that Lung cancer was under-diagnosed in our community and convenience and care coordination with a multi-disciplinary care team standardizes the decision making process, promotes primary care and families' inclusivity and shortens the time to treatment. We intensified our efforts to educate the community to promote self directed referrals to obtain LDCT by spreading awareness through many modalities including traditional and social media.

Results: We screened 3095 new patients over seven years. 6646 annual and baseline LDCTs were performed in total. 1180 scans were identified with findings consistent with Lung RADS 3 or 4 requiring further work up. A total of 162 new cancers were identified, of these 135 were lung and 27 were non-lung cancers. 64% of all lung cancers were identified at Stage 1 or 2. We calculated incidence of lung cancer in our population at 4.36% and for all cancers at 5.23%. The incidence dropped to 2.03% and 2.43% for lung cancer and all cancers respectively when adjusted for patient years but still remained significantly higher than the incidence reported in National Lung Cancer Screening Trial.

Conclusions: Low cost screening CT and Multi-Disciplinary approach to report and follow up on findings resulted in more effective screening of the high risk population resulting in more than twice the number of cancers identified compared to traditional lung cancer screening programs. We believe this to be a result of improved implementation of screening program within a high risk rural population due

to low cost, rigorous direct to patient educational efforts and and a multi-disciplinary approach in form of Lung Nodule Review Board.

Keywords: Lung Cancer, Screening, Multi-Disciplinary

P2.04B SCREENING AND EARLY DETECTION - SCREENING IMPLEMENTATION AROUND THE WORLD, SUNDAY, SEPTEMBER 8, 2024 - 18:15 - 19:45

P2.04B.04 Harnessing EHR/IT to Accelerate Lung Cancer Screening - An American Cancer Society National Lung Cancer Roundtable Initiative

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Introduction: Uptake of lung cancer screening (LCS) in the U.S. is low, with approximately 20% of eligible adults reporting recent screening. Following the American Cancer Society National Lung Cancer Roundtable (ACS NLCRT) 2022 Summit, Accelerating Uptake of Lung Cancer Screening, a workshop was held to develop/prioritize tactics to enhance EHR/IT usability and functionality towards increasing screening uptake.

Methods: Eighty individuals (clinicians/researchers/patient advocates) from 58 organizations (professional societies/advocacy organizations/health systems/industry/EHR/IT vendors) attended the workshop to develop recommendations addressing current challenges in using EHR/IT tools to accelerate high-quality LCS uptake. After presentations to create common understanding (LCS workflows, EHR/IT lessons from American College of Radiology LCS Learning Collaborative, intersection of EHR/IT with LCS programs/patients/primary care, and operational and clinical outcomes metrics), nine EHR/IT vendors discussed their current tools. Workshop participants were divided into breakout groups facilitated by two subject matter expert moderators and ACS NLCRT staff: 1) Identifying Individuals Eligible for LCS; 2) Patient Tracking After LCS; 3) Education for Patients, Including Shared Decision Making; and 4) Key Performance Indicators and Quality Measures. Each group reviewed the strategies identified by the 2022 LCS Summit EHR/IT breakout group aligned with their topic and devised tactics that were presented to workshop participants for feedback. The same groups met again, refining tactics and assessing feasibility, after which they re-presented to all participants. Lastly, all attendees ranked their top three priorities anonymously.

Results: Fifteen tactics were ranked (see table). The top 5 tactics were to: 1) Use EHR portals that are standardized and targeted to educate patients about LCS; 2) Develop a national LCS EHR module; 3) Incorporate unstructured data from EHR with natural language processing to improve data capture; 4) Establish a centralized program with IT and navigation to track patients and findings from the point of entry into the LCS program; and 5) Partner with major EHR vendors to make data needed for risk stratification available through a standard data interface. An executive summary details the work: NLCRT-EHR-IT-Executive-Summary_FINAL.pdf

Conclusions: ACS NLCRT developed and prioritized actionable EHR/IT tactics for accelerating screening uptake. Active work underway after the workshop includes: multidisciplinary brain trust launch by one EHR vendor to inform their work; ACS NLCRT-facilitated work with EHR vendors to address the risk factor standard data interface; and ACS NLCRT and American Lung Association funding to develop LCS HEDIS and tobacco history documentation quality measures by the National Committee for Quality Assurance, which are measured through EHR interfaces.

Keywords: lung cancer screening, electronic health record, information technology

P2.04B SCREENING AND EARLY DETECTION - SCREENING IMPLEMENTATION AROUND THE WORLD, SUNDAY, SEPTEMBER 8, 2024 - 18:15 - 19:45

P2.04B.05 Engaging Culturally and Linguistically Diverse Communities to Prepare for Lung Cancer Screening Implementation in Australia.

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Introduction: Lung cancer is the number one cause of cancer death worldwide, including in Australia, where more than 14,000 cases will be diagnosed in 2024. The Australian Population Based Screening Framework stipulates that new screening programs must be: 1)

acceptable to the population, 2) clinically, socially, legally, ethically acceptable to health professionals, consumers and the Australian public and 3) promote equity and access in target groups. Very little Australian research has engaged culturally and linguistically diverse (CALD) communities about lung cancer screening (LCS) to gauge readiness for implementation. In Australia's existing cancer screening programs, unique barriers to participation have been documented amongst some CALD groups. The Australian National Lung Cancer Screening Program (NLCSP) will commence from July 2025. This study was conducted prior to a NLCSP funding announcement. The aims were to identify barriers and enablers to LCS implementation and determine views about LCS acceptability and feasibility.

Methods: This qualitative focus group study used community-based participatory research principles to collaboratively engage CALD stakeholders. The research team worked with highly-experienced program managers, multicultural health workers and bilingual facilitators/translators ('leaders') who provide support and education to Arabic, Macedonian, Italian and Vietnamese communities. The leaders used culturally-appropriate methods to recruit participants, and organised and delivered focus groups with support from the research team. All research study materials were translated into community languages. Participant orientation to lung cancer screening was enabled through a moderator guide to ensure coverage of core topics and a National Health Service England video (used with permission) that featured 'voice-over' translations into community languages. All participants gave written consent. Focus groups were recorded and translated into English by nationally accredited translation services. Thematic analysis is underway to code data to themes.

Results: Nine focus groups were conducted either face to face (n=5) or on Zoom (n=4) with 69 participants across New South Wales, Australia. Six groups were delivered in community languages. Preliminary analysis identified that LCS was perceived as acceptable across all focus groups. Identified barriers included concerns about eligibility criteria exclusions of tobacco use in formats preferred to cigarettes (e.g. shisha) and people who have never used tobacco. Other barriers were significant concerns about the stigma and fear associated with cancer, medical procedures and scans; screening costs and reliance on family or community members to act as interpreters. Participants expressed a preference for recruitment via General Practitioners (GPs) but raised concerns about missing people without a regular GP. Enablers included co-designing complex strategies with communities to disseminate promotion and awareness materials that extend beyond mass media and invitation letters. Community champions were strongly endorsed as a strategy to enhance uptake. Participants reiterated that key program messages must be locally tailored and presented in community languages.

Conclusions: This qualitative study provides crucial foundational evidence from four culturally diverse Australian communities about barriers and enablers prior to NLCSP implementation. The findings are highly informative for other jurisdictions who may be preparing for LCS implementation or need to modify programs to attract more culturally diverse populations to engage in screening.

Keywords: screening, qualitative, diversity

P2.04B SCREENING AND EARLY DETECTION - SCREENING IMPLEMENTATION AROUND THE WORLD, SUNDAY, SEPTEMBER 8, 2024 - 18:15 - 19:45

P2.04B.06 Lung Cancer Screening Program in Serbia: A 3-year- Results and Challenges

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Introduction: Lung cancer screening aim is to detect high risk subjects and subjects in early stage. The implementation of a lung cancer screening program is very complex. Objective of this study was to present the results and challenges in implementing lung cancer screening program.

Methods: Subjects aged 50-74 years, with a smoking history of 30 pack-years or more and/or 20 pack-years with additional risks (COPD, prior pneumonia, other malignancy, lung cancer hereditary history or exposure to environmental carcinogens) undergone low-dose CT evaluation. Radiological assessment and further evaluation was done per Lung RADS score. Screening was performed at Institute for Pulmonary Diseases of Vojvodina in Sremska Kamenica, and observed period was from October 2020 to December 2023.

Results: Total of 5404 LDCT scans were performed on 2892 screened subjects. The majority were females (58.9%). Females compared to males were often active smokers (87.0% vs 77.8%, p<0.001) with frequently reported positive family history of lung cancer4 (7.3% vs 3.2%, p<0.001), and positive personal history of other solid tumor (7.3% vs 3.2%, p<0.001). Compared to risk perception for lung cancer, male significantly often were not worry at all or were rarely worry about their risk compared to females (82.9% vs. 77.5%, p<0.001). Emphysema was reported in 31.2% (902/2892), with significant differences between males and females (34.2% vs. 29.1%, p=0.004). Lung RADS score positive screens were found in 9.4% (273/2892). The invasive diagnostic was performed in 3.7% (107/2892) of participants, while 0.7% (20/2892) refused invasive procedures. The rate of false positive findings was 1.14% (32/2892). The lung cancer detection rate was 2.3% (67/2892). From total detected lung cancer subjects 87.0% were NCSLC (adenocarcinoma 56.0%, squamous 24.0% and NOS 6.0%) and 11.0% were SCLC. Almost 55.0 % of lung cancer subjects were detected in stage I and II. Significant differences were observed between baseline and follow-up lung cancer stages (32.6 % vs. 52.6% in I, and 36.8% vs. 15.8% in IV stage).The screening respond rate to control LDCT after 12 months (Lung RADS 1 and 2) was 73.9% (1757/2375).

Conclusions: More than 50% of lung cancer subjects detected in screening were in early stages of disease. Innovative approaches, education and a more recognizable campaign are necessary to increase the responds rate among participants with negative baseline LDCT.

Keywords: Lung Cancer, Screening, LDCT

P2.04B SCREENING AND EARLY DETECTION - SCREENING IMPLEMENTATION AROUND THE WORLD, SUNDAY, SEPTEMBER 8, 2024 - 18:15 - 19:45

P2.04B.07 Impact of Primary Care Initiated Lung Cancer Screening Program: The VANCHCS Experience

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Introduction: Despite the known benefits of low dose CT scan (LDCT) in improving the survival of lung cancer patients through early diagnosis, screening rates remain low across the United States. Only 5.8% of eligible Americans were screened for lung cancer in 2021. California and Nevada had the lowest screening rates at 1.0% and 1.3%, respectively. The VA Northern California Health Care System (VANCHCS) serves the 7th largest catchment area in the country with over 385,000 Veterans who reside in 21 different counties. To address the need for improved lung cancer screening (LCS), a primary care-based LCS program was initiated around 2017. We conducted this retrospective study to evaluate the impact of LCS program on the stage of lung cancer diagnosis between 2012 and 2022.

Methods: Eligible Veterans were screened by primary care providers who ordered LDCT scans. A dedicated LCS coordinator reviewed the Lung-RAD reports and coordinated diagnostic workups with relevant specialists. Demographics and stage at lung cancer diagnosis were obtained through the tumor registry. The Chi-square test was conducted to assess the difference in screening rates across all and different race groups.

Results: Between 2012 and 2022, 1073 Veterans were diagnosed with lung cancer at VANCHCS. The distribution of lung cancer stages was as follows: 31.2% stage 1, 8.2% stage 2, 20.6% stage 3, and 40.0% stage 4. While the total number of lung cancer cases diagnosed per year remained stable, there was a notable increase in the proportion of patients diagnosed at stage I and a decrease in stage IV over time.Before 2017, the average percentages of patients diagnosed at stage 1 and stage 4 were 23.6% and 44.1% respectively. However, from 2018 to 2022, the average percentages increased to 38.3% for stage 1 and decreased to 34.8% for stage 4. As of 12/1/2023, 86.9% of 4151 eligible Veterans accepted LCS. Among those who accepted LCS, 71% had been screened with LDCT scan within 1 year. Black and Hispanic Veterans had significantly lower screening rates compared to other ethnicities.

Conclusions: The primary care provider-initiated LCS program at VANCHCS has enhanced the clinical implementation of lung cancer screening.Since 2018, more Veterans have been diagnosed at stage I lung cancer, allowing for potentially curative treatment. Further studies are needed to address the disparities in screening rates, particularly among Black and Hispanic Veterans, and to evaluate the impact of this LCS program on cancer-specific mortality at VANCHCS.

Keywords: Lung cancer screening, VANCHCS, multidisciplinary

P2.04B SCREENING AND EARLY DETECTION - SCREENING IMPLEMENTATION AROUND THE WORLD, SUNDAY, SEPTEMBER 8, 2024 - 18:15 - 19:45

P2.04B.08 Terminology in Lung Cancer Screening and Early Detection - IASLC Early Detection and Screening Committee Recommendations

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Introduction: To facilitate global implementation of lung cancer (LC) screening and early detection in a quality assured and consistent manner, common terminology is needed. A lexicon with definitions should be used by the entire multidisciplinary team, including primary care physicians, radiologists, respiratory physicians, thoracic surgeons, as well as pathologists, epidemiologists and biostatisticians, and also health care managers and funders, which patients, screening participants and family can understand. Currently, researchers and clinicians within different specialties and professional societies may use the same terms but with different meanings, or different terms for the same intended meanings.

Methods: I n this study, the Diagnostics Working Group of the International Association for the Study of Lung Cancer Early Detection and Screening Committee has analyzed and intensively discussed relevant terms used on a regular basis and suggests recommendations for consensus definitions of terminology applicable in this setting. These recommendations take into account that thoracic imaging includes not only the lungs and airways, but adjacent mediastinal organs including cardiovascular structures, the chest wall and adjacent portions of the lower neck and upper abdomen. The findings should be considered in the context of not only LC but also other potential diseases and comorbidities. Our goal was to understand the basis for differences in definitions and what the impact of these differences might be. We explored how we might reach consensus to define the most common relevant and unambiguous terminology for use by health care

providers, researchers, patients, screening participants and family. Discussions among members were held during regular monthly calls and final recommendations were approved by all members.

Results: Analyzed terms and definitions in use for epidemiological and health-economical purposes included: Standardized incidence and mortality rates, LC specific survival, long-term survival and cure rates, and overdiagnosis, overtreatment, undertreatment. Analyzed terms and definitions in use for defining screening results/findings included: Positive, false positive, negative, false negative and indeterminate screening findings and additional findings and incidental findings. Analyzed terms and definitions in use for describing programme parameters in screening programmes included: Opportunistic vs programmatic LC screening, Screening rounds, interval / interim diagnoses, invasive and minimally invasive procedures. Analyzed terms and definitions in use for shared decision making included: LC screening - possible harms and risks and LC risk (probability of event per defined time) and modifiers prior and posterior to a measure.

Conclusions: Screening programs have been developed in the context of specific health systems and various interdisciplinary settings. Depending on the specific interest, terminology from the fields of epidemiology, health economics and radiology have primarily been used. These terms have their value in the specific discipline and may be necessary for communication in these fields but may have a different meaning in other settings which can cause confusion and may impede the implementation of screening and early detection globally. Therefore, a common set of terminology with standard definitions is recommended when describing clinical LC screening programs to facilitate program uptake, and the discussion about effectiveness and outcomes. The use of the terms should be clearly defined and explained.

Keywords: Lung Cancer, Early detection and screening, Terminology recommendations

P2.04B SCREENING AND EARLY DETECTION - SCREENING IMPLEMENTATION AROUND THE WORLD, SUNDAY, SEPTEMBER 8, 2024 - 18:15 - 19:45

P2.04B.09 A Qualitative Evaluation of the Critical Role of Lung Cancer Screening Program Navigators

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Introduction: Lung cancer screening with low dose computed tomography (LDCT) entails a complex operational process and often relies on navigators who have been shown to improve LDCT utilization and patient experience. Factors influencing these navigators' roles, responsibilities, and ability to impact program outcomes remain incompletely understood. We explored the perspectives of a diverse, national population of Veterans Health Administration (VHA) healthcare team members regarding influences of lung cancer screening program navigators' roles and responsibilities.

Methods: We conducted a cross-sectional qualitative study with healthcare team members involved in lung cancer screening at 10 Veterans Affairs Medical Centers. Semi-structured telephone interviews were conducted from December 2020 to September 2021 with radiologists, pulmonologists, primary care providers, oncologists, surgeons, advanced practice providers, nurses, CT technicians, and administrators. We utilized the Consolidated Framework for Implementation Research for study development and data coding and the Health Systems Science Framework for thematic analysis. The qualitative data was analyzed through an inductive and deductive approach to identify emerging themes.

Results: A total of 30 interviews were conducted and included in the final analytic sample. Participants described the critical role of the navigator in several steps of the lung cancer screening process. Participants described the individual navigator characteristics such as professional background, attending navigator training, dedicated program percent effort and foundational skills as traits that can influence a navigator's impact on the overall program outcomes. Foundational interpersonal skills including teaming, leadership, and commitment to the program were identified as traits that can have profound impact on improving program enrollment and outcomes. Healthcare team interview participants also indicated that VHA organizational structures including adequate program staffing, location of program activities (including virtual and in person and where LDCT examinations are performed), available technology, and financial support for program activities and personnel can be influential in the navigator roles and influence over program activities and outcomes. Sample supporting quotations can be seen in Figure 1.

Conclusions: Lung cancer screening program navigators positively impact lung cancer screening program outcomes. Individual characteristics such as leadership, teaming, training and professional background, and commitment likely influence this impact. This study offers insight into how both healthcare system structure and individual navigator characteristics influence a navigator's impact. As VHA continues to expand lung cancer screening, these data can inform strategies aiming to improve lung cancer screening for Veterans.

Keywords: lung cancer screening, navigator, Health Systems Science Framework

P2.04B SCREENING AND EARLY DETECTION - SCREENING IMPLEMENTATION AROUND THE WORLD, SUNDAY, SEPTEMBER 8, 2024 - 18:15

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P2.04B.10 Leveraging High Mammography Screening Prevalence to Increase Lung Cancer Screening Among Women - A Geospatial Perspective

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American Cancer Society, American Cancer Society/GA/USA

Introduction: Although lung cancer is a leading cause of mortality among women, screening is still low, below 20% for men and women nationwide. In comparison, national estimates of biennial screening mammography among women 50-74 exceed 70%. That discrepancy, combined with some overlap in the age of eligibility between screening for lung and breast cancer, provides an opportunity to increase awareness, check for eligibility, and schedule or screen women for lung cancer when going for their mammogram. This project focuses on the geographic feasibility and impact of such an approach.

Methods: A geographic approach was developed to assess proximity of lung cancer screening facilities (American College of Radiology lung cancer screening registry facilities) to mammography facilities identified by the FDA MQSA program. Although we examined facilities within growing distances, up to 1 mile, we focused on locations within 0 mile (a.k.a. close proximity, facilities residing within the same plaza/health center). Rural and urban designations were also factored into the analysis. While limited by data availability, we wanted to further estimate the number of women that may be impacted and utilized geospatial analysis of population data (gender and age) as well as estimates of prevalence of mammography.

Results: Most lung cancer and mammography facilities that are in close proximity, are located in urban settings where most women aged 50-74 reside, as well as where most women report having had a mammogram in the past 2-years. There are more facilities in close proximity in the east. Counties with facilities in close proximity are mainly in urban geographies and account for over 30M women aged 50-74 (out of almost 50M women of that age group nationwide). Further analysis utilizing the prevalence of mammography facilities shows a significant number of women who can be identified to discuss lung cancer screening eligibility and then as needed refer to a nearby lung cancer screening facility. Integration of geographic layers of screening facilities within close proximity, lung cancer mortality, and mammography prevalence was done to identify priority locations for interventions.

Conclusions: While limited by data availability, our analysis nonetheless reveals an opportunity to identify women eligible for lung cancer screening when electronic health records and busy primary care providers have been challenged to do so.

Keywords: Lung cancer, Mammography, Screening

P2.04B SCREENING AND EARLY DETECTION - SCREENING IMPLEMENTATION AROUND THE WORLD, SUNDAY, SEPTEMBER 8, 2024 - 18:15 - 19:45

P2.04B.11 Factors Associated with Early-Stage Lung Cancer Diagnosis (ESLCD) In Brazil - 2013 - 2019: A Multivariable Analysis.

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Introduction: Lung cancer has the highest mortality rate among the leading deadly cancers worldwide. Despite improvements in tobacco cessation and treatment over the years, disparities in access to care, timely diagnosis, and proper treatment remain prevalent. This study aims to identify the factors associated (FA) with Early-Stage Lung Cancer Diagnosis (ESLCD) in Brazil.

Methods: This retrospective cohort study includes individuals diagnosed with lung cancer from January 2013 to December 2019, registered in the Brazilian hospital-based Cancer Registry (HBCR). Descriptive and bivariate analysis was performed, and T-tests and Chi-square were used to compare early vs late-stage groups. Multivariable backward stepwise logistic regression identified FA with ESLCD at a 95% confidence interval (CI).

Results: The study was conducted with data on 86,558 individuals registered in the HBCR; 56.6% were men, 64 years old on average, and 54.8% were white. We found a high percentage of patients without education information (23.9%), and 70% had completed high school. As for behavioral characteristics, only 20% of the patients had never smoked; the others were current smokers (40%) or former smokers (40%). Almost half of the patients were from the Southeast region of Brazil (44.6%), 27% from the South, 19.9% from the Northeast, 3.9% from the North and 3.9% from the Midwest. The vast majority of the individuals were diagnosed at a late stage (85.6%), while 14.4% were ESLCD. In the bivariate analysis, being less than 65 years old, being female, white, never smoking, having a college degree, and living in the south or southeast regions were associated with ESLCD. In the final multivariable model, the Factors Associated with ESLCD were having less than 65 years (OR=1.28 [95% CI: 1.22-1.34]), of the female gender (OR=1.26 [95% CI: 1.22-1.32]), having education greater than a college degree (OR=1.49 [95% CI: 1.38-1.61]), and living on the southeast (OR=1.22 [95% CI: 1.15-1.30]); and in the south region (OR=1.21 [95% CI: 1.18-1.32]); which are the wealthiest regions in the country.

Conclusions: The education level was the most decisive factor associated with ESLCD. Geographic location played an important role in ESLCD, indicating issues related to wealth and access to health services. Improving access to lung cancer diagnosis, especially for vulnerable populations, can reduce disparities in the rates of early-stage diagnosis and improve overall survival.

P2.04B SCREENING AND EARLY DETECTION - SCREENING IMPLEMENTATION AROUND THE WORLD, SUNDAY, SEPTEMBER 8, 2024 - 18:15 - 19:45

P2.04B.12 Respiratory Function as a Prognostic Factor for Lung Cancer in Screening and General Populations

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Introduction: The role of respiratory function as a prognostic factor among lung cancer patients remains unclear. The objective of this study was to investigate lung function as a prognostic factor for overall survival (OS) in lung cancer patients from a general population-based cohort (UK Biobank, UKB) and a high-risk screening eligible population (National Lung Screening Trial, NLST).

Methods: Patients with an incident lung cancer diagnosis and spirometry-assessed lung function were included. Lung function was measured as the forced expiratory volume in 1-second (FEV1), forced vital capacity (FVC), ratio of FEV1/FVC, and relative FEV1 (observed FEV1 relative to predicted FEV1). OS is time from lung cancer diagnosis to death from any cause or censoring. Multivariable Cox proportional hazards models, adjusted for known prognostic factors selected a priori, were fitted to estimate the effect of lung function on OS in lung cancer patients from populations with different baseline lung cancer risks. We report hazard ratios (HR) and 95% confidence intervals (CI).

Results: 2,690 and 609 lung cancer patients were included in the analysis from the UKB and the NLST, respectively. In the UKB, a higher relative FEV1 and a higher FEV1/FVC ratio were associated with better overall survival after a lung cancer diagnosis with adjusted HR of 0.98 (95% CI: 0.95-1.00, per 10% increase) and 0.95 (95% CI: 0.90-1.00, per 10% increase), respectively. Contour plots illustrate the decreased probability of OS predicted for individuals with decreased lung function. No statistically significant results were found when assessing the NLST data.

Conclusions: Impaired lung function was associated with poorer survival for lung cancer patients diagnosed in a general population, but not in the high-risk screening-eligible population. This highlights the potential clinical importance of respiratory function as a prognostic factor in lung cancer in the general population and presents a possibility for personalized cancer management.

Keywords: Spirometry, Survival, Prognostic factor

P2.04B SCREENING AND EARLY DETECTION - SCREENING IMPLEMENTATION AROUND THE WORLD, SUNDAY, SEPTEMBER 8, 2024 - 18:15 - 19:45

P2.04B.13 Time to Benefit: A Systematic Review and Meta-Analysis of Lung Cancer Screening Trials

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Introduction: Lung cancer screening with annual low-dose computed tomography (CT) reduces lung cancer mortality in the long-term but can lead to immediate harms. Guidelines recommend targeting cancer screening to those persons whose life expectancy exceeds the screening test's time to benefit. Therefore, we aimed to estimate the time to benefit from lung cancer screening using low-dose CT to prevent mortality from lung cancer by conducting a systematic review and survival meta-analysis of randomized controlled trials of lung cancer screening.

Methods: We identified randomized controlled trials of lung cancer screening with low-dose CT based on two systematic reviews. We extended one review's search terms/approach to 12/3/2023. We focused on studies that reported lung cancer and all-cause mortality over years of follow-up. For each eligible study, we fit independent Weibull survival curves and generated Markov chain Monte Carlo simulations to estimate the absolute risk reduction at different time points. We determined time to benefit as the time at which specific absolute risk reduction thresholds (ARR=0.0005, 0.001, 0.002) were crossed. We pooled these estimates using random-effects meta-analysis model.

Results: A total of eight randomized controlled trials comprising 88,526 participants were included in the meta-analysis. Enrollment age ranged from 50s to 70s in most studies. Follow-up duration ranged from 7.3 to 12.3 years. For every 500 people screened with low-dose CT, 5.3 years (95% confidence interval 3.9-8.7) passed before one death from lung cancer was prevented (ARR=0.002). The time to prevent one lung cancer death per 1000 persons screened (ARR=0.001) was 3.4 years (95%CI: 2.2-5.1); per 2000 persons screened (ARR=0.0005), 2.2 years (1.4-3.4 years).

Conclusions: Our findings suggest that lung cancer screening with low-dose CT is most appropriate for those with life expectancy greater

than approximately 5.3 years.

Keywords: Lung Cancer Screening, Time to Benefit, Meta-analysis

P2.04B SCREENING AND EARLY DETECTION - SCREENING IMPLEMENTATION AROUND THE WORLD, SUNDAY, SEPTEMBER 8, 2024 - 18:15 - 19:45

P2.04B.14 Barriers to Maximal Screening Impact in Persons Diagnosed with Lung Cancer in a Prospective Cohort.

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Introduction: Lung cancer screening (LCS) reduces mortality, but implementation barriers reduce benefit. For maximal benefit, all persons truly at risk should participate in LCS throughout their years of eligibility; persons who smoke should quit. We mapped barriers to maximal benefit of LCS.

Methods: We categorized all persons diagnosed with lung cancer from 2015 to 2023 in three prospective institutional databases (Cohort 1), those who: met USPSTF 2021 LCS eligibility criteria (Cohort 2); had at least one LCS episode (Cohort 3); quit smoking before LCS (Cohort 4); had multiple LCS episodes (Cohort 5). We plotted K-M overall survival for Cohorts 2 to 5. Using Cohort 5 for reference, we compared hazard ratios (adjusted for age, sex, race, insurance and Charlson morbidity score) among LCS-ineligible (Cohort 1 minus Cohort 2), unscreened eligible (Cohort 2 minus Cohort 3), single-episode LCS (Cohort 3 minus Cohort 5), LCS patients who had quit (Cohort 4) versus not quit smoking (Cohort 3 minus Cohort 4).

Results: Of 3,074 patients, 1,686 (55%) were eligible for LCS; 420 (14%) had any LCS; 109 (4%) had LCS after quitting smoking; 131 (4%) had multiple LCS episodes (Figure 1). The survival of patients across Cohorts 2 to 5 differed (Figure 2). With Cohort 5 (screening adherent) as reference, aHR was 2.45(1.62 - 3.70, p< 0.0001) for LCS-ineligible; 2.66(1.76 - 4.00, p < 0.0001) for unscreened eligible; 1.88(1.19 - 2.97, p = 0.0072) for single-episode LCS; and 1.31(0.70 - 2.44, p = 0.3983) for persons who had quit and 2.14(1.68 - 3.44, p = 0.0016) for persons who had not quit smoking before LCS.

Conclusions: Eligibility criteria limitation was the largest barrier to LCS, access for eligible persons was the next largest barrier. Survival was significantly worse in screened patients who actively smoked. Patients with multiple LCS episodes had the best survival.

Keywords: lung cancer screening, Barriers, Tobacco Cessation

P2.04B SCREENING AND EARLY DETECTION - SCREENING IMPLEMENTATION AROUND THE WORLD, SUNDAY, SEPTEMBER 8, 2024 - 18:15 - 19:45

P2.04B.15 Co-Design of Decision Support Tools for Lung Cancer Screening in Australia

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Introduction: Lung cancer is the highest cause of cancer death in both men and women, with five-year survival rates 23% in Australia. Mortality rates are substantially higher in regional and remote Australia, in lower socioeconomic groups, culturally and linguistically diverse communities, and among Aboriginal and Torres Strait Islander communities (First Nations). Australia's National Lung Cancer Screening (LCS) Program will commence from July 2025, targeted at people with high risk of lung cancer based on age and smoking history criteria. This study aimed to co-design evidence-based tools to support shared decision-making for LCS by collaborating, including and designing with people that will use these tools.

Methods: Co-design workshops were conducted with potential end-users of decision support tools for LCS: culturally and linguistically diverse consumers (3 workshops; n=21), First Nations communities (4 workshops; n=30) and experts/clinicians (2 workshops; n=9). Workshops included presentations and activities to elicit the most important, convenient, desirable and/or actionable functional

requirements for each group for decision support tools. Cognitive interviews (n=15) were conducted with an independent group of end-users. The resources were designed to align with International Patient Decision Aid Standards and revised iteratively.

Results: The workshop outputs were three decision support tools including a two-page tool, a longer, more detailed decision-aid and a video. Workshop participants outlined key priorities to include in the decision tools as being information about the screening process including the appointment, location of screening services, what treatment might be, screening benefits, the importance of cultural safety, and managing stigma. Consumers wanted a visual representation of the LCS process, testimonials from previous participants of LCS, and found icon arrays to be too statistics focussed. First Nations communities expressed the desire for personalised videos of community members and local health workers, education sessions about LCS, as well as culturally designed t-shirts to help 'get the word out'. Consumers and experts/clinicians were passionate about "getting people in the door" for LCS. Process driven questions were a priority for experts/clinicians, including what the screening involves. Reframing of potential harms of screening as 'other things to consider' was important for both consumers and clinicians. Cognitive interview participants highlighted refinements for each tool regarding comprehension and some design elements. End users found all tools easy to read and understand, and saw the benefit of the different tools for different purposes and audiences.

Conclusions: Co-design workshops identified specific components for shared decision-making tools in LCS appropriate for a range of different communities, including First Nations. These tools have been developed prior to implementation of the National Lung Cancer Screening Program to support those eligible for LCS in making their decision about taking part in screening. Further personalisation and localisation of resources, or information sessions may be beneficial to reach these priority groups. These findings will be highly relevant to other jurisdictions implementing LCS and to inform the development and co-design of these tools with their communities, particularly those with First Nations communities.

Keywords: Shared decision-making, Lung cancer screening, Co-design

P2.04B SCREENING AND EARLY DETECTION - SCREENING IMPLEMENTATION AROUND THE WORLD, SUNDAY, SEPTEMBER 8, 2024 - 18:15 - 19:45

P2.04B.16 Real-World First Round Results from a Charity Lung Cancer Screening Program in East Asia

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Introduction: Screening with Low Dose Computed Tomography (LDCT) has been proven to potentially reduce the rate of mortality of lung cancer. Lack of real-world data outside of protocolized trials has been cited as an impediment to its more widespread implementation, especially in Asia.

Methods: A single round of LDCT was provided through a community-based charity program in Hong Kong to asymptomatic adults with a family history of lung cancer and/or smoking history. Anonymized data from this program was analyzed.

Results: LDCT was performed for 99 participants, including 98 (99%) who had one or more family members with history of lung cancer, and 70 (71%) who were never-smokers. After a single round of screening, a positive LDCT was noted in 47 participants (47%). A sister with a history of lung cancer (28% versus 8%, p = 0.01) and a multiplex family (47% versus 23%, p = 0.02) were factors associated with a positive LDCT. Lung cancer (all adenocarcinoma) was diagnosed as a direct consequence of positive LDCT findings in 6 participants (6%), of whom 4 had stage I disease and 5 received surgery with curative intent. In the 47 participants with a positive LDCT, having a sister with a history of lung cancer increased the risk of a lung cancer diagnosis (relative risk = 5.23, 95% confidence interval: 1.09 - 25.21). Detected lesions categorized as Lung-RADS 3 or above (odds ratio = 12.08, 95% confidence interval: 1.27 - 114.64) or deemed by an experienced specialist to be suspicious (odds ratio = 63.33, 95% confidence interval: 5.48 - 732.29) weresignificantly more likely to turn out to be a lung cancer.

Conclusions: This real-world data demonstrates that a single round of LDCT screening at a community level in East Asia can detect potentially curable lung cancer at a rate comparable to those reported by protocolized trials. When considering future LDCT screening programs in East Asia, a family history of lung cancer may be a key factor indicating a person for screening, and how features of a LDCT-detected lesion should trigger further intervention warrant further definition.

Keywords: Lung Cancer Screening, Family History of Lung Cancer, Low-Dose Computed Tomography

P2.05A PULMONOLOGY AND STAGING - CLINICAL COURSE, SUNDAY, SEPTEMBER 8, 2024 - 18:15 - 19:45

P2.05A.01 Clinical Presentation, Outcomes, and Anticoagulant Strategies in Patients with Lung Cancer-Associated Isolated Distal Deep Vein Thrombosis

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Introduction: The prognosis and anticoagulation strategies for isolated distal deep vein thrombosis (iDDVT) remain controversial. Currently, no studies have analyzed lung cancer-associated iDDVT (LC-iDDVT) in different subtypes, namely axial venous thrombosis (AVT) and muscular venous thrombosis (MVT).

Methods: The study included 593 patients with LC-iDDVT and 260 patients with lung cancer-associated proximal DVT (LC-Proximal DVT). LC-iDDVT was further classified into AVT (112 patients) and MVT (481 patients). Short-term (90-day) outcomes were assessed using logistic regression (odds ratio [OR]; 95% confidence interval [CI]), and long-term (1-year) outcomes were evaluated using survival analysis (hazard ratio [HR; 95% CI]).

Results: At the 90-day follow-up, patients with MVT had a lower adjusted risk of pulmonary embolism (PE; OR=0.18 [0.07-0.52], P=0.001) or venous thromboembolism (VTE) recurrence (OR=0.51 [0.30-0.85], P=0.010) than patients with LC-Proximal DVT. Similar results were observed at the 1-year follow-up. However, there was no significant difference in the 90-day and 1-year adjusted risk of PE (OR=0.75 [0.27-2.13], P=0.594; HR=0.87 [0.42-1.78], P=0.700) and VTE recurrence (OR=0.97 [0.51-1.87], P=0.935; HR=0.99 [0.63-1.56], P=0.970) between patients with AVT and those with LC-Proximal DVT. Among patients with LC-iDDVT, those receiving anticoagulation had a lower risk of VTE recurrence (HR=0.57 [0.35-0.95], P=0.030) and DVT deterioration (HR=0.28 [0.13-0.60], P=0.001) compared to those without anticoagulation. Moreover, patients with AVT receiving >3 months of anticoagulation had a lower risk of VTE recurrence compared to those with ≤3 months of anticoagulation (HR=0.23 [0.03-0.92], P=0.038).

Conclusions: Unlike patients with MVT, patients with AVT have a prognosis similar to that of patients with LC-Proximal DVT. Furthermore, patients with LC-iDDVT should receive anticoagulation therapy, and anticoagulation strategies should be optimized in patients with AVT.

Keywords: isolated distal deep vein thrombosis, lung cancer, anticoagulation

P2.05A PULMONOLOGY AND STAGING - CLINICAL COURSE, SUNDAY, SEPTEMBER 8, 2024 - 18:15 - 19:45

P2.05A.02 Incidence of Pneumonitis in Asian Patients with Non-Small Cell Lung Cancer: A Systematic Literature Review and Meta-Analysis

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Introduction: Pneumonitis is a well-documented adverse event (AE) of certain treatments for non-small cell lung cancer (NSCLC), including PD-1/PD-L1 inhibitors and thoracic radiation. However, it remains unclear whether there are racial/ethnic differences in the risk of pneumonitis. Several recent studies, such as the PACIFIC study, have reported a higher rate of post-chemoradiation pneumonitis in Asian compared with non-Asian patients with NSCLC, therefore, understanding the unique susceptibility and risk of pneumonitis in Asian patients is crucial for optimizing therapeutic efficacy and safety in this population. The objective of this study was to quantify the incidence of pneumonitis in patients treated for NSCLC in East and Southeast Asian countries.

Methods: A systematic literature review and meta-analysis was performed and reported in accordance with PRISMA guidelines. MEDLINE, Embase, Cochrane Central Register, and five local language databases in Chinese, Japanese, and Korean were searched from 1/1/2014-8/2/2023. Records were screened for eligible randomized-controlled trials (RCTs), single-arm trials, and non-randomized trials evaluating pharmacological or radiation therapy in lung cancer patients. Trials were included if conducted in East or Southeast Asian countries, or if their results were stratified by these regions. Random-effects meta-analyses were performed to assess the incidence of all-grade (grade 1-5), grade 1-2, and grade 3-5 pneumonitis using generalized linear mixed models in R 4.3.3.

Results: Among 4,280 records identified from the search, 202 studies on Asian patients with NSCLC met the inclusion criteria. A total of 189 studies (23,173 patients) were included in the meta-analysis, comprising 108 single-arm trials, 76 RCTs, and 5 non-randomized trials. Most studies were conducted within a single country, with Japan (n=89), China (n=72), and South Korea (n=12) being the most frequently reported study sites. While there was variation across studies in NSCLC subtype, line of treatment, outcome reporting, and follow-up duration (median range: 8.2-81 months), this variation was deemed acceptable. Targeted therapy (n=81), chemotherapy (n=41), and chemoradiation (n=37) were the most extensively studied treatments among the included trials. Across all types of treatments, the pooled incidence of all-grade, grade 1-2, and grade 3-5 pneumonitis in Asian patients was 5.42% [95% confidence interval (CI): 4.25-6.89], 3.58% [95% CI: 2.54-5.03], and 1.34% [95% CI: 1.06-1.70], respectively. Among patients that received radiation-containing treatments, the pooled incidence of pneumonitis was estimated to be 34.12% [95% CI: 25.11-44.45] for grade 1-2 events and 2.96% [95% CI: 2.12-4.12] for grade 3-5 events, whereas among patients that did not receive radiation-containing treatments, the pooled incidence of grade 1-2 and 3-5 pneumonitis was 1.74% [95% CI: 1.33-2.27] and 1.00% [95% CI: 0.76-1.32], respectively.

Conclusions: This study quantifies the background risk of pneumonitis among East and Southeast Asian patients receiving any treatment for NSCLC. Pneumonitis incidence markedly increases in Asian patients receiving radiation-containing treatments, , primarily in grade 1-2 pneumonitis. This increase in radiation-induced pneumonitis among Asian patients is much larger than what is reported in the literature for non-Asian populations (22-24%). Results from this study help to contextualize the safety data from trials combining other therapies with thoracic radiation.

Keywords: Pneumonitis, Non-small cell lung cancer, Asia

P2.05A PULMONOLOGY AND STAGING - CLINICAL COURSE, SUNDAY, SEPTEMBER 8, 2024 - 18:15 - 19:45

P2.05A.03 Regional Disparities in Distant Metastatic Lung Cancer Patients and Overall Survival in Norway. A Nationwide Population Study

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Introduction: The incidence of lung cancer with distant metastases (stage IV) in Norway has remained stable at 40% since 2013 and varies between 32% and 56% in different health trusts. The aim of this project was to examine the situation of lung cancer patients in the two health trusts with the highest proportion, Vestfold and Førde, were formerly heavily industrialized places. Nevertheless, the proportion of daily smokers and the incidence of lung cancer were at the national average.

Methods: We included 16 953 patients diagnosed with non-small cell lung cancer (NSCLC) or small cell lung cancer (SCLC) in Norway between 2018 and 2022. Data from the Cancer Registry of Norway were analyzed. Descriptive statistics on age, sex, stage, performance status (ECOG) and morphological distribution were performed. Relative survival was estimated using the Pohar-Perme estimator, and a health trust specific lifetable stratified by age, sex and calendar period.

Results: Lung cancer characteristics in Førde and Vestfold matched the national average for age and morphological distribution. However, Vestfold patients exhibited poorer health, and functional status (Figure 1). More lung cancer patients in Førde and Vestfold than in the rest of the country were diagnosed based on severe symptoms (Figure 2). Fewer incidental findings were noted in Førde and Vestfold for local stage disease. Norway's overall survival rate from 2018-2022 was 28%, with regional disparities ranging from 23.6% to 35.9%. Førde demonstrated a comparatively higher survival rate of 32%, whereas Vestfold reported a slightly lower rate of 27%.

Conclusions: Lung cancer patients in Vestfold and Førde, health trusts with the highest proportion of advanced disease in Norway, experienced delayed access to specialized healthcare with severe symptoms, compared to those elsewhere. Besides cancer stage, factors like comorbidity and functional status also affect survival.

Keywords: survival, regional disparities, distant metastatic lung cancer

P2.05A PULMONOLOGY AND STAGING - CLINICAL COURSE, SUNDAY, SEPTEMBER 8, 2024 - 18:15 - 19:45

P2.05A.04 Does the Treating Physician's Specialty-Oncology or Pulmonology-Affect Clinical Outcomes and Survival in Lung Cancer Patients?

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Introduction: Up to 75% of lung cancer patients at the time of diagnosis or relapse have advanced disease with distant metastasis (stage IV) and need palliative treatment, which is a systemic life-prolonging treatment involving radiotherapy, chemotherapy, immune checkpoint inhibitors or targeted therapy, sometimes in combination with radiotherapy.Lung cancer patients with stage III or IV disease who require palliative treatment are treated by either oncologists or pulmonologists, depending on the practices used in different countries. There is still a lack of information on how physician specialty affects clinical outcomes and survival and whether there are any differences; professional discussions are ongoing on this subject.The aim of this study was to investigate whether there are any differences in lung cancer outcomes between treatments administered by oncologists and pulmonologists.

Methods: All lung cancer patients with a stage IV registered at the Cancer Registry of Norway in the period 2018-2022 were included. Based on the patients' place of residence, and the clinical specialty available, each health trust was categorized as either 'oncologist' or 'pulmonologist'. Time from date of diagnosis to treatment with either palliative radiotherapy or immunotherapy, and one-year overall survival were assessed according to specialty categories

Results: A total of 6,724 patients were included, 51.4% of whom were treated by pulmonologists and 48.6% by oncologists. No significant differences were observed between the groups in relation to age, sex, histology, stage, palliative radiotherapy, or PD-L1 expression.There was no difference in the proportion of patients who received palliative radiotherapy (34.6% [pulmonologists] vs 35.5% [oncologist], p=0.41). Patients treated by an oncologist came to palliative radiotherapy sooner after the time of diagnosis than patients treated by a pulmonologist (35 vs. 41 days, p= 0.10). Significantly more patients treated by a pulmonologist received immunotherapy than patients treated by an oncologist (45.6 and 38.3%, p<0.01), (Figure 1). The wait time to start immunotherapy was significantly shorter for pulmonologist-treated patients, median 21 vs. 28 days (p=0.04), (Figure 2). The 1-year overall survival was slightly longer among patients treated by a pulmonologist compared to those treated by an oncologist (30.8% [28.7%-31.8%] and 27.8% [26.2%-29.4%]).

Conclusions: Our results suggest that more patients treated by pulmonologists received immunotherapy with shorter wait time and had a tendency of improved survival than patients treated by oncologists. A likely reason for this is that the transition between departments is time-consuming and delay the treatment onset.

Keywords: survival, oncologist, pulmonologist

P2.05B PULMONOLOGY AND STAGING - IMAGING, SUNDAY, SEPTEMBER 8, 2024 - 18:15 - 19:45

P2.05B.01 How Reliable Is PET/CT in T1A and T1B Non-Small Cell Lung Cancer for Mediastinal Staging?

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Introduction: TNM staging is used in non-small cell lung carcinomas.For preoperative clinical mediastinal staging, PET/CT is utilized; for pathological mediastinal staging, EBUS, mediastinoscopy, and VAMLA are employed.Staging also benefits from systematic lymph node dissection following lung resection.In our study, we aimed to evaluate accuracy of PET-CT in T1a and T1b NSCLC non-small cell lung cancer patients.

Methods: Those who received lung resection, systematic lymph node dissection, and videomediastinoscopy or video-assisted mediastinoscopic lymphadenectomy(VAMLA) for non-small cell lung cancer in our clinic between January 2002 and January 2022 were included.Tumors with a tumor diameter larger than 2 cm were excluded from the study.A total of 224 patients were included.Clinical mediastinal staging status and pathological staging status were noted.The groups were evaluated in terms of demographic characteristics, biochemical parameters, tumor characteristics and survival.

Results: Of the 196 patients with clinical(c) T1A-BN0 underwent VAMLA, 173 were pathologically found to have N0(88.2%), whereas occult N1 rate was 7.1%.Occult N2 rate was 4.7%. Of 17 patients with cT1aN2 NSCLC, 10 (58.8%) and 4 (23.5%) were found to have pN2 and pN1 disease whereas only 3 patients (17.7%) were found to have pN2.The sensitivity of PET/CT in the evaluation of N0 and N1-2 was 91%, specificity was 32.3%, and accuracy was 82.1%.The sensitivity of PET/CT in the evaluation of N0-1 and N2 was 98.4%, specificity was 78.5%, and accuracy was 88.8%.The area under the curve(AUC) for the prediction of N0, N1 and N2 by PET-CT were 0.639(95% CI: 0.517-0.761) 0.614 (95% CI: 0.425-0.803) and 0.641 (95% CI: 0.488-0.794) respectively(Figure 1-3).

Conclusions: The low accuracy observed when PET/CT indicates N0 for mediastinal staging of non-small cell lung carcinomas smaller than 2 cm should not be overlooked. Therefore, it is advisable that comprehensive mediastinal staging is essential to accurately detect N1-2 involvement.VAMLA could be considered the reference staging procedure for staging cT1A-BN0-2 NSCLC.

Keywords: Non-Small Cell Lung Cancer, Mediastinal Staging, T1 Staging

P2.05B PULMONOLOGY AND STAGING - IMAGING, SUNDAY, SEPTEMBER 8, 2024 - 18:15 - 19:45

P2.05B.02 Automated Extraction of Key Entities from Thorax CT Reports Using NER with Prompt Engineering

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Introduction: Medical records have undergone dramatic transformations over the past decades. Traditionally, patient information was documented and stored in paper files, posing challenges in terms of accessibility, organization, and analysis. The advent of Electronic Medical Records (EMRs) revolutionized healthcare data management, enabling efficient storage, retrieval, and sharing of patient information. However, EMRs often contain vast amounts of unstructured data, particularly within radiology reports, making it difficult to efficiently extract and utilize key clinical findings. This is where Artificial Intelligence (AI) comes into play. AI-powered tools, such as Natural Language Processing (NLP) and Named Entity Recognition (NER), can automatically analyze and extract relevant information from unstructured medical texts. This has the potential to significantly improve workflow efficiency for healthcare professionals, facilitate large-scale data analysis for research, and ultimately contribute to better clinical decision-making and patient care. Medical NLP models are mainly available in English, with limited options for other languages.

Methods: In this study, we explore the use of NER with chat prompts to automatically extract key entities from anonymized thorax CT reports, demonstrating the potential of AI in transforming how we interact with and utilize medical data. This study investigates the feasibility of using Named Entity Recognition (NER) with chat prompts to automatically extract key entities from anonymized thorax CT reports, ensuring patient privacy is protected in accordance with HIPAA regulations. We trained and tested the model on a dataset of 53 and 50 reports respectively, focusing on six entities: anatomy (ANAT), impression (IMP), outsider words (O), and observation presence (OBS-P), absence (OBS-A), and uncertainty (OBS-U).

Results: Evaluation on the test set yielded promising results, with an overall accuracy of 97% and macro-averaged F1 score of 0.96. Notably, ANAT and OBS-A achieved F1 scores of 0.99, demonstrating high precision and recall in identifying anatomical structures and absent observations (Table-1). The model also performed well in recognizing other entities, with F1 scores exceeding 0.91 for IMP, O, and OBS-U.

Conclusions: These findings suggest that NER with chat prompts can be a valuable tool to extract key information from thorax CT reports.

This approach can potentially improve workflow efficiency for radiologists, facilitate data analysis and research, and ultimately contribute to enhanced patient care. Further research will explore the model's performance on larger datasets and investigate its generalizability to other types of radiology reports. We aim to refine the chat prompt design and explore different NER models to potentially improve performance further.

F1 scores, calculated by python language, sklearn.metrics library, classification_report fuction cal

Entity

Presicion

recall

f1-score

support

ANAT

0.99

0.99

0.99

1459

IMP

0.93

0.88

0.91

189

O(Outsiders)

0.96

0.94

0.95

932

OBS-A

0.99

0.98

0.99

351

OBS-P

0.95

0.99

0.97

1141

OBS-U

0.94

0.91

0.93

56

Accuracy

0.97

4128

Macro avg

0.96

0.95

0.96

4128

weighted avg

0.97

0.97

0.97

4128

Keywords: natural language processing, Machine learning, radiology reports

P2.05B PULMONOLOGY AND STAGING - IMAGING, SUNDAY, SEPTEMBER 8, 2024 - 18:15 - 19:45

P2.05B.03 A Novel Lung Nodule Localize Method: Topographic Map Dyeing Model for Target Vessel Watershed Boundary

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Introduction: Blind spots quite often occurred in the surgical localization of pulmonary nodules, and complex process and various complications makes nodules localization difficult. We found that segment boundary during Expansion and collapse method or ICG dyeing after target vessel blocked or stumped is irregular, If the boundary texture can be accurately simulated before surgery, it can be used as an optional localization method

Methods: Retrospective collection of cases of lung segment, subpulmonary segment, or watershed wedge resection with indocyanine green boundary display as a training cohort, including preoperative thin-layer chest CT collection and intraoperative use of 3D fluorescence endoscopic recording. Preoperative CT was delineated manually and delivered to deep learning to establish an automated AI 3D reconstruction model. Use fluid thermal diffusion algorithm to delineate the target area of reconstructed blood vessels, and perform constant correction by comparing the real staining boundaries inside the endoscope through machine learning, iterating to obtain the most suitable parameter formula. Prospective watershed staining validation was conducted in three medical centers in China.

Results: For 1/3 of peripheral pulmonary nodules, the accuracy of drainage wedge resection was 95%, AUC0.914 95% (0.875-0.953), and the accuracy of puncture localization wedge resection was 95%, AUC0.857 95% (0.804-0.910), p=0.0898; For 2/3 of pulmonary nodules, the accuracy of watershed wedge resection is 91%, AUC0.841 95% (0.779-0.903), watershed wedge resection accuracy is 95%, AUC0.620 95% (0.524-0.716) P=0.0001;

Conclusions: The watershed method has no significant difference in efficacy and puncture localization of 1/3 peripheral pulmonary nodules, and can be used as an alternative solution; For internal 2/3 nodules, it is significantly better than traditional segmental resection surgery. It is feasible to use artificial intelligence to automatically reconstruct the boundaries of pulmonary blood vessels and target blood vessels, and simulate staining, which is highly consistent with the contour of staining boundaries in real endoscopes. These findings have the potential to further develop preoperative planning and intraoperative navigation system technology, enabling real-time non-invasive localization and precise resection of pulmonary nodules during the surgical process.

Keywords: Watershed boundary, artificial intelligence, early stage

P2.05B PULMONOLOGY AND STAGING - IMAGING, SUNDAY, SEPTEMBER 8, 2024 - 18:15 - 19:45

P2.05B.04 Development of a CT Image-Based Virtual Atelectasis Simulation Model and Noninvasive Lung Nodule Localization System

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Introduction: This study aimed to develop a computed tomography-based virtual atelectasis simulation system for noninvasive lung nodule localization to improve the precision of presurgical planning for pulmonary nodule resections.

Methods: Contrast-enhanced computed tomography images of the lungs of 20 patients diagnosed with pulmonary nodules at Korea University Ansan Hospital between June 2021 and February 2024 were acquired, and image data were converted into three-dimensional models using 3D slicer. The mesh points extracted from these lung models were then manipulated to simulate the effects of gravity, by adjusting the lung shapes and nodule positions to align with the respective surgical postures. Subsequently, we assessed the similarity of the simulation by comparing the resulting deformed lung shape and nodule locations with the corresponding perspectives observed in the surgical videos.

Results: Overall, the average volume of the entire lung was 2,226 cm3 (±588) and the lung shrinkage rate was 48.6% (±12.9). Evaluations of an average of 15 pairs of images per case revealed significant conformity between atelectasis simulation images and surgical video snapshots, with average Dice and Jaccard similarity coefficient values of 90.28 and 88.25, respectively. Furthermore, the alignment of nodule positions between the simulations and surgical anticipation demonstrated notable accuracy, with an average Hausdorff distance of 6.39mm.

Table

Patient Number

Age

Sex

Size (mm)

Location

Localization

1

53

M

12

RUL

Hook-wire

2

44

F

14

LUL

CT-based

3

56

M

14

RUL

Hook-wire

4

83

F
26
LLL
CT-based
5
72
M
12
RLL
CT-based
6
57
F
13
LLL
CT-based
7
76
F
12
LLL
CT-based
8
64
F
21
RLL
CT-based
9
46
F
6
LUL
CT-based
10
50
M
16
LUL
CT-based
11
68

F
23
RUL
CT-based
12
55
F
15
RLL
Hook-wire
13
62
M
12
LUL
Hook-wire
14
70
M
20
RUL
Hook-wire
15
61
M
9
LLL
CT-based
16
65
F
12
RUL
CT-based
17
62
M
13
RLL
CT-based
18
51

F

19

RLL

CT-based

19

58

F

10

RML

CT-based

20

65

M

17

RUL

Hook-wire

Conclusions: We developed a simulation of lung atelectasis based on preoperative computed tomography scans. The integration is anticipated to enhance the accuracy of locating nodules contributing to efficient and precise surgical planning.

Figure. a.DICOM data from 20 patients were used to create a 3D model. The model was adjusted accordingly. The chest cavity shape was captured using the drape function, and mesh points were adjusted to match the concave sternum. Texture was applied for realism, and the model was presented in real-time. Evaluation involved comparing the simulated lung shape with images from the surgical video.

Keywords: 3D atelectasis simulation, Video-assisted thoracic surgery, Image similarity evaluation

P2.05C PULMONOLOGY AND STAGING - PATHOLOGY ASSESSMENT, SUNDAY, SEPTEMBER 8, 2024 - 18:15 - 19:45

P2.05C.01 Pathologic Nodal Staging Reporting Quality: A Multi-Center Assessment of NSCLC Trends Over Time & Key Reporting Parameters

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Introduction: Non-small cell lung cancer (NSCLC) staging, treatment and survival data are collated nationally to draw conclusions about optimal management. Nodal staging quality is associated with improved NSCLC survival, but there is significant variability in pathologic reporting. This multi-center retrospective study evaluates the quality of pathologists' nodal staging in early-stage NSCLC patients, assessing key reporting parameters and trends over time.

Methods: We evaluated adult patients with clinical stage I-II NSCLC who underwent upfront resection between 2009-2019 whose surgical pathology report indicated a negative (N0) or unclear (Nx or unreported) nodal stage. Patient characteristics, treatment variables and key pathologic reporting parameters, including presence of nodal tissue in specimens, pathologist-reported nodal number and stage, and surgical lymph node adequacy (>3N2 & 1N1) were ascertained through chart review. Key outcomes were the appropriateness of pathologist-designated N0 or Nx stage. Tumor specimens staged N0 with incomplete nodal specimens (<3N2 & 1N1) were designated "i-N0," while those completely lacking nodal tissue that were inappropriately staged N0 were designated "X-N0." Specimens with complete nodal specimens (>3N2 & 1N1 nodes) inappropriately staged as Nx were designated "X-Nx." Associations between patient characteristics, treatment variables and pathologic reporting parameters were evaluated using Kruskal-Wallis, Chi-square and Fisher's exact tests. Staging trends over time were analyzed using a Wilcoxon-type rank-sum test and key outcomes were analyzed with multivariate logistic regression.

Results: Among 2356 patients, N stage was unreported in 103 (4.4%), Nx in 120 (5.1%) and N0 in 2133 (90.5%). There was a clear trend in pathologist-designated N stage by reporting year (p<0.0001) with a decrease in unreported N stage after 2011. 15.6% (n=348) of pathology reports with lymph nodes lacked a node count and most of these (67.0%, n=233) involved nodal fragments. Among 2133 N0-designated specimens, 59.9% (n=1278) were "i-N0" and 0.8% (n=17) were "X-N0." Each additional year predicted decreased odds of "i-N0" (OR 0.94 [95% CI: 0.09-0.97]), as did pre-operative receipt of invasive mediastinal staging (OR 0.71 [95% CI: 0.53-0.95]). Care in Region D (vs. A, B, or C) predicted increased odds of "i-N0" (OR 2.34 [95% CI: 1.58-3.45]). Similarly, each subsequent surgery year, anatomic resection (vs. wedge), and care in Region B were associated with decreased odds of "X-N0" (OR 0.61 [95% CI: 0.45-0.84]; OR 0.06 [95% CI: 0.01-0.28]; OR 0.05 [95% CI: 0.004-0.43], respectively). Among 120 Nx-designated specimens, 17.5% (n=21) were "X-Nx." No factors with associated with "X-Nx."

Conclusions: Data quality limits our ability to identify optimal treatment and survival patterns. Standardized reporting template uptake has propelled significant advances in pathologic reporting, but room for improvement remains with notable variability between centers. A pathologic-reporting indicator for an "incomplete" surgical nodal harvest and a standardized approach to quantifying lymph node fragments may be warranted to improve pathologic data quality.

Keywords: Pathologic nodal staging, Staging quality, N0 or Nx

P2.05C PULMONOLOGY AND STAGING - PATHOLOGY ASSESSMENT, SUNDAY, SEPTEMBER 8, 2024 - 18:15 - 19:45

P2.05C.02 Does the Proposed 9th TNM Offer Improved Prognostic Accuracy after Lung Carcinoma Resection? Preliminary Analysis Results

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Introduction: The proposed 9th TNM for lung carcinoma provides for the division of the N2 category into subgroup N2a and N2b - according to number of positive nodal stations. Following the changes in the N2, a revision of the TNM IIA-IIIB stage groups was proposed.

The aim of this study was to compare overall survival (OS) and disease-free survival (DFS) in stage groups defined according to the 8th and proposed 9th TNM in the real population.

Methods: For this retrospective study, a group of patients who underwent lung resection for primary lung carcinoma between 2012 and 2013 were selected. Information about disease, treatment and follow-up was obtained from the institutional databases of two hospitals. The stage was determined according to the 8th and proposed 9th TNM. The number and stations of resected lymph nodes were recorded. The date of death was obtained from the Central Informatics Center Data Sharing Team in Poland. OS and DFS were determined according to Kaplan-Meier survival analyses.

Results: So far, of the 944 patients identified in the databases, the medical histories and histopathology reports of first 200 patients operated on in 2012 have been analyzed in detail. This group included 132 men (66%) and 68 women (34%), aged 34 to 85 years (median 64). The majority of patients had adenocarcinoma (47.5%) and squamous cell carcinoma (36%), mostly in stages IB, IIB and IIIA. In 96% of patients the R0 resection was achieved, in 8 patients the surgical margin was positive (R1: 7; 4% and R2: 1, 0.5%). Adjuvant radiotherapy or chemotherapy was used in 41 patients (21%). Thirty-eight patients (19%) were lost to follow-up after surgery. In 59 patients, disease recurrence was registered between 0 and 138 months (median 20) from the date of surgery. By the date of the study, 130 patients had died (65%) between 0 and 143 (median 66) months after surgery; the exact cause of death could not be determined in most cases. Reclassification from the 8th to the proposed 9th TNM resulted in a change of staging group in 17 cases (9%).OS for stages IIA, IIB, IIIA and IIIB determined according to the 8th vs. proposed 9th TNM showed no statistically significant differences (P = 0.73; 0.93; 0.81; 0.49, respectively). Similarly, there were no significant differences in DFS between the groups (IIA: P=0.41; IIB: P=0.59 IIIA: P=0.51; IIIB: P=0.18).

Stratification of staging groups determined according to the 8th TNM showed difference for OS (P = 0.0066) and for DFS (P = 0.0031). Stratification of staging groups determined according to the proposed 9th TNM showed weak difference for OS (P = 0.0391) and no difference for DFS (P = 0.09).

Conclusions: Preliminary analysis showed that in our group of patients with surgically treated lung carcinoma, the 8th TNM more clearly separated the prognostic staging groups for OS and DFS than the proposed 9th edition. This may be related to the small number of cases analyzed and the need for multivariate analysis. The study will continue.

Keywords: 9th TNM, Overall Survival, Disease Free Survival

P2.07A EARLY-STAGE NON-SMALL CELL LUNG CANCER - DEVELOPMENTS IN EGFR MUTATED EARLY STAGE NSCLC, SUNDAY, SEPTEMBER 8, 2024 - 18:15 - 19:45

P2.07A.01 Clinicopathological vs. Molecular Models in Predicting Adjuvant EGFR-TKI Benefit in Stage I NSCLC

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Introduction: Adjuvant EGFR-TKIs show promising outcomes in early-stage NSCLC with EGFR mutations, but accurately identifying patients who would derive the greatest benefit remains a clinical challenge. We compared the predictive performance of clinicopathological factors and the 14-gene assay to assess postoperative prognosis and predict the potential benefit of adjuvant EGFR-TKIs in stage I NSCLC.

Methods: From March 2013 to February 2019, patients with completely resected stage I NSCLC (8th TNM staging) and EGFR mutation were included. The 14-gene assay, assessed through quantitative PCR, was developed and subsequently validated across diverse international cohorts. Clinicopathological high-risk factors include any feature indicating a higher risk of recurrence based on NCCN guidelines. The primary endpoint of this study was the 5-year disease-free survival (DFS) rate.

Results: Diagnostic values were evaluated in 180 stage I NSCLC patients. The 14-gene assay demonstrated superior performance compared to clinicopathological factors in predicting recurrence events, with a larger AUROC (C-index of 0.73 vs. 0.57; P<0.001). Patients with molecular high-risk, rather than clinicopathological high-risk factors, showed a more favorable response in predicting the benefit of adjuvant EGFR-TKIs. Specifically, adjuvant EGFR-TKIs benefited molecular high-risk patients over not using EGFR-TKIs, regardless of clinicopathological high-risk (DFS rate increased from 65.9% to 95.0%, P=0.016) or low-risk subgroups (80.0% to 100%, P=0.044). Patients with molecular low risk did not show any benefit from EGFR-TKIs, regardless of clinicopathological high-risk (DFS rate increased from 95.5% to 100%, P=0.460) or low-risk subgroups (94.1% to 100%, P=0.630).

Conclusions: The 14-gene assay proved to be superior to clinicopathological factors, offering valuable guidance for adjuvant EGFR-TKIs decisions in stage I NSCLC.

Keywords: Adjuvant EGFR-TKI, Stage I, Risk stratification

P2.07A EARLY-STAGE NON-SMALL CELL LUNG CANCER - DEVELOPMENTS IN EGFR MUTATED EARLY STAGE NSCLC, SUNDAY, SEPTEMBER 8, 2024 - 18:15 - 19:45

P2.07A.02 The Effect of EGFR Mutation on Adjuvant Tegafur/Uracil for Patients with Non-Lymph Node Metastatic NSCLC (> 2 Cm)

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Introduction: The use of adjuvant osimertinib for epidermal growth factor receptor (EGFR) mutants is expected to expand to earlier stage I in the future, potentially competing with the current standard of care, oral tegafur/uracil (UFT), in Japan. However, the effect of EGFR mutation status on the therapeutic effect of UFT remains unclear. This study was conducted as an exploratory analysis of a retrospective observational study that investigated the real-world data of postoperative adjuvant chemotherapy in Japan (CSPOR-LC03).

Methods: Between 2008 and 2013, 1812 patients with completely resected adenocarcinoma diagnosed as pathologic stage I (T1 > 2 cm, TNM classification sixth edition) were included. This study exclusively enrolled physically low-risk patients—namely, those who have maintained organ function, and no history of other cancers. Additional gene analysis was performed using surgical specimens for patients whose EGFR mutation statuses were unknown. The primary endpoint was the 5-year disease-free survival (DFS) rate, and the secondary endpoint was the 5-year overall survival (OS) rate. We compared these survival rates between four groups classified based on the administration of adjuvant UFT and EGFR mutation status. We performed univariable and multivariable analyses using a Cox proportional hazards model to identify prognostic factors for recurrence and death using clinicopathological factors including the administration of adjuvant UFT and EGFR mutation status.

Results: The median duration of follow-up of participants was 5.8 years (interquartile range [IQR]: 5.0–7.1 years). Of the 1812 patients, 831 (46%) were men, and the median preoperative age was 67 years (IQR: 61–72 years). Of the 933 (51%) patients with EGFR mutations, 394 underwent adjuvant UFT therapy. Of the 879 (49%) patients without EGFR mutations, 393 underwent adjuvant UFT therapy. The 5-year DFS of UFT+/ EGFR+ and UFT-/EGFR+ patients were 82.0% and 87.1%, respectively, and those of UFT+/ EGFR- and UFT-/EGFR- patients were 80.0% and 86.9%, respectively. DFS was significantly worse in the UFT+ group than in the UFT- group (P = 0.015). In OS analysis, no significant difference was observed between the four groups (P = 0.125). In the multivariable analysis for DFS, male sex (HR, 1.333; P = 0.014), pleural invasion positive (HR, 1.538; P = 0.004), lymphatic permeation positive (HR, 1.371; P = 0.017), vascular invasion positive (HR, 2.173; P < 0.0001), and nodule with GGO (HR, 0.570; P < 0.0001) were significant, however, adjuvant UFT therapy was not an independent prognostic factor for DFS. Univariable and multivariable analyses restricted to the higher-risk subgroups, without GGO and tumor diameter >3 cm, also showed no effect of UFT, regardless of EGFR mutation. In OS, EGFR mutation-positive was significant predictive factors in the univariable analysis (HR, 0.716: P = 0.024), however, the significance disappeared in the multivariable analysis.

Conclusions: In pathologic stage I (>2 cm) lung adenocarcinomas with EGFR mutation, the survival benefit of adjuvant chemotherapy using UFT was not observed.

Keywords: adjuvant chemotherapy, tegafur/uracil, epidermal growth factor receptor

P2.07A EARLY-STAGE NON-SMALL CELL LUNG CANCER - DEVELOPMENTS IN EGFR MUTATED EARLY STAGE NSCLC, SUNDAY, SEPTEMBER 8, 2024 - 18:15 - 19:45

P2.07A.03 Prognostic Analysis of Completely Resected Lung Adenocarcinoma with Uncommon EGFR Mutations: CReGYT-01 EGFR Study

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Introduction: Despite the established evidence regarding the epidermal growth factor receptor (EGFR) mutation status as a biomarker for EGFR tyrosine kinase inhibitor (EGFR-TKI) treatment in patients with advanced lung adenocarcinoma (LUAD), the prognostic implications of EGFR mutation status in surgically resected LUAD remain unclear, especially concerning uncommon EGFR mutations (UCM). This study aims to clarify the prognostic differences between UCM and common EGFR mutations (CM) in completely resected LUAD patients.

Methods: A multicenter retrospective observational study was conducted at 21 centers in Japan, involving 4,181 LUAD patients who underwent pulmonary resection between 2015 and 2018. Patients with EGFR mutation negativity or unavailability, wedge resection, and incomplete resection were excluded, resulting in the evaluation of clinicopathological and prognostic characteristics of 1,636 patients with CM and UCM.

Results: Among eligible patients, 1,441 (88.1%) had CM and 195 (11.9%) had UCM. Clinicopathological features were similar between the two groups, except for a higher prevalence of smoking history and lower incidence of nodules with ground glass opacity on CT findings in patients with UCM, who also underwent mediastinal lymph node dissection more frequently compared to those with CM. Recurrence-free survival (RFS) did not exhibit significant differences between CM and UCM groups (Figure 1A). However, overall survival (OS) was notably shorter in patients with UCM compared to those with CM. In a multivariable analysis of OS, UCM independently predicted poor prognosis (hazard ratio [HR] 1.538, 95% confidence interval [CI] 1.003-2.359) (Figure 1B). Furthermore, this association was notably pronounced when focusing on patients with pathological stage II-III disease (HR 2.007, 95% CI 1.195-3.370). Median survival after recurrences was significantly shorter in patients with UCM compared to CM (46.7 vs 59.0 months, P= 0.001). Although the administration rate of first-line treatment after recurrences was comparable between UCM and CM groups (73.2% and 78.4%, respectively), the use of EGFR-TKIs was significantly lower in UCM compared to CM (44.1% vs 76.6%).

Conclusions: Patients with surgically resected EGFR-mutated LUAD harboring CM and UCM demonstrated similar recurrence risk; however, those with UCM exhibited significantly shorter OS compared to CM. Further advancement of post-recurrent and perioperative management for patients with UCM is imperative.

Keywords: uncommon EGFR mutation, surgery, prognosis

P2.07A EARLY-STAGE NON-SMALL CELL LUNG CANCER - DEVELOPMENTS IN EGFR MUTATED EARLY STAGE NSCLC, SUNDAY, SEPTEMBER 8, 2024 - 18:15 - 19:45

P2.07A.04 Clinical Relevance of PD-L1 Expression Levels in Surgically Resected EGFR-Mutant Lung Adenocarcinoma Patients (CReGYT-01 Study)

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Introduction: In the perioperative treatment for lung adenocarcinoma (LUAD), biomarkers like programmed cell death-ligand 1 (PD-L1) expression and epidermal growth factor receptor (EGFR) mutation are utilized. However, the clinical relevance of PD-L1 expression in surgically resected EGFR-mutant LUAD remains uncertain.

Methods: We made a real-world dataset collecting LUAD patients who underwent surgical resection across 21 centers in Japan from 2015 to 2018. We explored the relationship between PD-L1 expression, EGFR mutations, and prognosis.

Results: In total, 4,181 LUAD patients were registered. Of them, we excluded the patients who underwent wedge resection (N=391) or R1 resection (N=29) and the patients with unknown PD-L1 expression (N=2,914). Eventually, 847 LUAD patients were included in the analysis. Among them, 429 patients (51%) had negative PD-L1 expression (tumor proportion score [TPS]<1%) and 418 patients (49%) had positive PD-L1 expression (275 and 143 patients with weakly positive [TPS=1-49%] and strongly positive [TPS≥50%], respectively). EGFR mutations were detected in 331 (39%) LUADs. High PD-L1 expression correlated with unfavorable recurrence-free survival (RFS) in both EGFR-mutant (N=330, P=0.0001) and EGFR-wild (N=515, P=0.0001) LUADs (Figure 1). Additional analysis according to the type of EGFR mutation showed that high PD-L1 expression showed an association or a trend with poor RFS in exon 19 deletion (N=135, P=0.0024) or exon 21 L858R mutation (N=148, P=0.0516), respectively (Figure 2). In contrast, high PD-L1 expression correlated with poor OS only in EGFR-wild LUADs (P=0.0293) but not in EGFR-mutant LUADs (P=0.2535). Multivariable analysis elucidated that high PD-L1 expression was an independent factor of unfavorable RFS but not OS.

Conclusions: High PD-L1 expression could predict poor RFS independent of EGFR mutation status or type of EGFRmutation. Further investigation is warranted to elucidate whether EGFR-mutant LUAD patients expressing high levels of PD-L1 require an additional adjuvant strategy to prevent disease recurrence.

Keywords: EGFR mutation, PD-L1, Surgery

P2.07A EARLY-STAGE NON-SMALL CELL LUNG CANCER - DEVELOPMENTS IN EGFR MUTATED EARLY STAGE NSCLC, SUNDAY, SEPTEMBER 8, 2024 - 18:15 - 19:45

P2.07A.05 Synchronous Super Multiple Primary Lung Cancers Prefer High-Frequency BRAF and Low-Frequency EGFR Mutations in MAPK Pathway

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Introduction: Recently, the detection rates of multiple primary lung cancer (MPLC) are increasing. In clinical practice, we found some patients with a large number of lesions. Continuing our series of research published in 2020 and 2022, we defined lung cancer with five or more confirmed primary lesions as super MPLCs. Elucidating the genomic characterization of the special MPLC subtype can help reduce disease burden and understand tumor evolution.

Methods: We removed and identified most of the potentially malignant lesions in 18 patients with super MPLCs. Whole-exome sequencing was performed on the 130 resected malignant specimens.

Results: In our cohort of synchronous super early-stage MPLCs (PUMCH-ssesMPLC), we found that BRAF mutations, rather than EGFR mutations, predominate in super MPLCs. The mutations of super MPLCs were enriched in PI3k-Akt and MAPK signaling pathways. By comparing with a total of 11 control cohorts for 3 types, we found that in the MAPK pathway, super MPLCs have a significantly higher BRAF mutation frequency (31.5%) than MPLCs with fewer lesions and early-stage single-lesion lung cancer, while the EGFR mutation frequency (13.8%) is significantly lower. Combined with our previous research, we found that as the mean lesion number of MPLCs increases, BRAF mutations gradually become dominant. Class II mutation (48.8%) is the predominant BRAF mutation subtype. Also, with lesion invasiveness increasing, the mutation pattern more inclines to the classic pattern of super MPLCs. Follow-up also confirms that super-MPLC patients who underwent surgery only have a good prognosis.

Conclusions: In the study, we provided a comprehensive genomic landscape of super MPLCs. High-frequency BRAF mutations, especially class II BRAF mutations, and low-frequency EGFR mutations determine the limited effectiveness of targeted therapy in super-MPLC patients. Combined with follow-up, the importance of surgery is further emphasized.

Comparing mutation rates of key driver genes in our PUMCH-ssesMPLC cohort with other public datasets

Dataset

Mean of lesion number

EGFR mutation %

Significance

BRAF mutation %

Significance

KRAS mutation %

Significance

TP53 mutation %

Significance

PUMCH-ssesMPLC

7.22

13.8% (18/130)

31.5% (41/130)

18.5% (24/130)

5.4% (7/130)

Control-1

(Cohorts mainly consisting of early-stage lung cancer with single lesions)

Qiu et al.

1

57.5% (23/40)

***

0.0% (0/40)

***

17.5% (7/40)

NS

47.5% (19/40)

***

Xiang et al. (preinvasive)

1

30.1% (74/246)

***

16.7% (41/246)

**

7.7% (19/246)

**

0.8% (2/246)

**

EAS-LUAD cohorts

1

46.8% (143/305)

***

3.2% (10/305)

***

11.1% (34/305)

*

36.1% (110/305)

***

Li et al.

1.11

63.2% (156/247)

***

5.3% (13/247)

***

6.1% (15/247)

***

12.6% (31/247)

*

Li et al.

1.28

50.0% (77/154)

***

2.6% (4/154)

***

4.5% (7/154)

***

13.0% (20/154)

*

Control-2

(MPLCs with fewer lesions)

Pei et al.
2.23
62.7% (42/67)
***
11.9% (8/67)
**
14.9% (10/67)
NS
17.9% (12/67)
**
Hu et al.
2.63
56.1% (143/255)
***
11.0% (28/255)
***
9.0% (23/255)
*
12.2% (31/255)
*
Cheng et al.
2.82
58.1% (18/31)
***
9.7% (3/31)
*
12.9% (4/31)
NS
19.4% (6/31)
*
Liang et al.
3.59
31.3% (36/115)
**
17.4% (20/115)
*
14.8% (17/115)
NS
7.0% (8/115)
NS

Control-3

(late-stage lung cancer)

Wu et al.

1

39.7% (91/229)

***

4.8% (11/229)

***

12.7% (29/229)

NS

50.7% (116/229)

***

Ding et al.

1

47.6% (799/1680)

***

1.7% (26/1680)

***

8.9% (149/1680)

***

-

-

Keywords: Super multiple primary lung cancer, EGFR mutation, BRAF mutation

P2.07B EARLY-STAGE NON-SMALL CELL LUNG CANCER - EVOLVING SURGICAL APPROACHES, SUNDAY, SEPTEMBER 8, 2024 - 18:15 - 19:45

P2.07B.01 Single Versus Multiple Segmentectomies: A Comparison of Short- And Long-Term Outcomes

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Introduction: Segmentectomy can provide equivalent oncologic outcomes as lobectomy in well-selected patients with early-stage non-small cell lung cancer (NSCLC). However, differences in indication and outcomes of single compared to multiple segmentectomy remain unclear. We compared short- and long-term outcomes of single versus multiple segmentectomies.

Methods: Patients who underwent segmentectomy for NSCLC from 08/2005-05/2023 were identified using a prospectively maintained institutional database. Patients who had positive clinical nodal disease or received neoadjuvant therapy were excluded. Patients were not excluded based on tumor size. Patients with ≥6 months of follow-up data were included in survival and recurrence analyses. Survival was estimated using Kaplan-Meier models and compared using log-rank tests. Cumulative incidence of recurrence was modeled with death as a competing risk for recurrence and compared with Gray's test. Cox and Fine-Gray models were constructed to evaluate cause-specific and subdistribution hazard ratios (CSHR and SDHR) for recurrence.

Results: Of 693 segmentectomy patients meeting study criteria: 354(51.1%) were single and 339(48.9%) multiple segmentectomy. Statistically significant differences were observed in median nodule size on imaging (1.6cm vs. 1.8cm, p=0.002) and pathologic lesion size (1.6 cm vs. 1.9 cm, p<0.001) for single vs. multiple segmentectomies, respectively. Median number of resected lymph nodes was higher in multiple segmentectomies (6 vs. 5; p=0.002). Other pathologic features did not differ between groups, nor did the incidence of postoperative complications, 30-or 90-day mortality. The 5-year overall survival was 72.8% (95%CI= 66.7-79.4) after single and 75.9% (95%CI=69.8-82.6) after multiple segmentectomy, respectively; this difference was not statistically significant (p=0.28). The 5-year cumulative incidence of locoregional recurrence was higher after single (17%, 95%CI=12-22%) than multiple (10%, 95%CI=6.4-15%) segmentectomies (p=0.03). After adjusting for high-risk pathologic features and tumor size, multiple segmentectomy remained associated with a lower risk of locoregional recurrence than single segmentectomy (CSHR=0.39, 95%CI=0.22-0.70; SDHR=0.40, 95%CI=0.22-0.73). Parenchymal margins were reported in 540 (77.9%) cases. In subgroup analyses adjusting for margin length and pathologic features, multiple segmentectomies remained associated with reduced risk of locoregional recurrence, but effect size was reduced (CSHR=0.55, 95%CI=0.31-0.98; SDHR=0.56, 95%CI=0.31-1.02).

Conclusions: Our results suggest that multiple segmentectomy may provide superior locoregional control compared to single segmentectomy without increasing perioperative morbidity by ensuring adequate margins. However, the disparity in locoregional recurrence was not reflected in significantly poorer overall survival after either procedure. Further study of indications and high-risk features for single and multiple segmentectomy will improve procedure selection and surgical decision-making for patients with early-stage NSCLC.

Keywords: Early-Stage Lung Cancer, Locoregional Recurrence, Segmentectomy

P2.07B EARLY-STAGE NON-SMALL CELL LUNG CANCER - EVOLVING SURGICAL APPROACHES, SUNDAY, SEPTEMBER 8, 2024 - 18:15 - 19:45

P2.07B.02 Is Wedge Resection Really Enough for the Treatment of Patient with Stage I Non-Small Cell Lung Cancer? A SEER Database Analysis.

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Introduction: The recent results of the CALGB140503 studies suggested a role for sublobar resection,including wedge resection,for the treatment of early-stage NSCLC.We aimed to investigate the role of wedge resection by comparing this technique's survival and perioperative outcomes to lobectomy in all stage I NSCLC.

Methods: We retrospectively analysed the Surveillance,Epidemiology and End Results(SEER) database of stage I NSCLC(≤4cm in size) patients who underwent either lobectomy or wedge resection from 2000 to 2017.We performed propensity score matching(PSM) to adjust for selection bias(1:1 matching, calliper:0.01, variables matched:age,gender,ethnicity,tumour location,size,histology and number of lymph nodes sampled).The primary endpoint was overall survival(OS) and lung cancer specific survival(LCSS),the secondary endpoints were 30-day and 90-day mortality.Univariate and multivariate Cox proportional hazard regression were applied to evaluate the effects on prognosis of both lobectomy and wedge resection.Results were presented as hazards ratio and 95% confidence interval(HR and 95%CI).

Results: Overall,32673 patients treated by lobectomy and 9073 patients treated by wedge resection were included in the analysis. After PSM,4764 patients in each group were considered and,except for stage IA1,OS and LCSS was greater after lobectomy than wedge resection(OS-Stage IA1-HR:0.88(0.74-1.04),p-value: 0.125-Stage IA2 -HR:0.82(0.76-0.89),p-value: <0.001-Stage IA3-HR:0.65(0.58-0.73), p-value: <0.001-Stage IB-HR:0.80(0.72-0.88), p-value: <0.001.LCSS-Stage IA1-HR:0.80(0.64-1.01),p-value: 0.065-Stage IA2- HR:0.72(0.64-0.81),p-value: <0.001-Stage IA3-HR:0.64(0.55-0.75),p-value: <0.001-Stage IB-HR:0.77(0.66-0.88),p-value: <0.001)(Fig.1-2).If a similar number of LN were removed during surgery(10 or more lymph nodes),the survival benefit of lobectomy disappeared until stage IA2,remaining superior to wedge resection for stage IA3 and IB(data not shown).The 30-day mortality was significantly higher after wedge resection(2.3%vs1.4%, p=0.01)but there was no significant difference in 90-day mortality(4.5%vs3.7%,p=0.10).

Conclusions: Although CALGB140503 showed similar benefits for wedge resection and lobectomy in NSCLC≤2cm, our study can confirm a similar outcome only in stage IA1.While in stage IA2 we may argue that survival may be the same after a proper lymph node dissection,in stage IA3 and IB lobectomy may still be the treatment of choice.

Keywords: Lobectomy, Wedge Resection, Survival

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P2.07B.03 Simultaneous Bilateral Video-Assisted Thoracic Surgery Is Safe and Feasible for Multiple Primary Lung Cancers

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Introduction: The treatment for bilateral synchronous multiple primary lung cancers (MPLC) remains challenging. Simultaneous bilateral video-assisted thoracic surgery (VATS) may be an optimal treatment with curative intent, but its safety and feasibility are controversial.

Methods: One hundred and fifty-eight patients who underwent simultaneous bilateral VATS (simultaneous group) and 79 who underwent two-staged bilateral VATS (two-staged group) were included in this study. Their medical records were retrospectively reviewed and analyzed.

Results: The majority of patients were female and non-smokers. Forty-one percent of patients underwent lobectomy and contralateral wedge resection. There was no significant difference in the postoperative complication rate between the simultaneous groups and two-staged group (13.3% vs 11.4%, p=0.73). Patients who underwent simultaneous bilateral resection had shorter hospital stays, shorter anesthesia time and less chest drainage compared with those who underwent two-staged resection. Male, current smoker, respiratory comorbidities and advanced TNM stage were risk factors for postoperative complications in simultaneous bilateral VATS (figure 1). Patients in two groups had similar overall survival and disease free survival (figure 2 p=0.2).

Conclusions: Simultaneous bilateral VATS for bilateral lung nodule resection is as safe and feasible as two-staged bilateral VATS. Patients who underwent simultaneous bilateral resection had similar or even better outcomes compared to that of the two-staged group. Simultaneous bilateral VATS is potentially an optimal treatment option based on appropriate patient selection.

Keywords: multiple primary lung cancers, simultaneous bilateral VATS

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P2.07B.04 Comparative Effectiveness of Sub-Lobar Resection vs Lobectomy for Medically Operable Stage I NSCLC: A VACCR Analysis

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Introduction: Lobectomy is standard of care surgical management for early-stage, non-small cell lung cancer (NSCLC), with sub-lobar resection reserved for patients lacking sufficient pulmonary reserve or who have small, peripheral tumors. Outside of a clinical trial, the role of sub-lobar resection for early-stage NSCLC irrespective of tumor location is not well defined. This study sought to compare overall survival (OS) and lung cancer-specific survival (LCSS) following lobectomy or sub-lobar resection in patients treated for Stage I NSCLC in an open access healthcare setting.

Methods: Patients diagnosed with Stage I NSCLC between 2000-2020 from the Veterans' Affairs Health System with an FEV1 or DLCO > 60% of predicted treated with lobectomy or sub-lobar resection were identified. OS and LCSS were compared using log-rank and Kaplan-Meier analyses, with hazard ratios calculated. Multivariable Cox regression analysis via stepwise approach included age, diagnosis period, sex, race, smoking status, FEV1, DLCO, tumor histology, and clinical T stage as covariates. Surgery type was included ad hoc for clinical suspicion.

Results: Overall, 1,267 patients were included. Patients were predominantly male (97%) and white (75%). 73% of patients had a Charlson comorbidity index of 0. Most sub-lobar resection patients underwent wedge resection (79%). Sub-lobar resection patients were older (mean age 68 vs 66, $p < 0.001$) and had worse lung function (mean predicted FEV1: 84% vs 91%; DLCO: 77% vs 85%, $p < 0.001$ for both) compared to lobectomy patients, respectively. Median follow-up was 5.6 years and 5-year OS was 58% (95% CI 56-61%). 90-day mortality rates were equivalent between lobectomy and sub-lobar resection (2.6% vs 2.4%, $p > 0.05$). Multivariable analysis showed no significant difference in OS and LCSS between surgery types (Table 1). Age, diagnosis period, and DLCO were significant predictors of OS and LCSS. Sex and smoking status were additionally found to be significant predictors of OS. When considering surgery type and these demographic factors, DLCO appears to be a predictor of mortality after surgery, while FEV1 does not.

Conclusions: In medically operable patients undergoing sub-lobar resection or lobectomy for Stage I NSCLC, there is no difference in OS

and LCSS on multivariable analysis, indicating the two are equivalent in this real world, open access healthcare setting. With recent phase III trials JCOG0802/WJOG4607L and CALGB 140503 supporting the use of sub-lobar resection for small peripheral tumors, this data supports future studies investigating the role of sub-lobar resection in an expanded population of medically operable patients.

Keywords: Sub-lobar Resection, Lobectomy, Survival

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P2.07B.05 Prospective Comparative Study of Postoperative Respiratory Function after Lobectomy Versus Segmentectomy

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Introduction: Preservation of postoperative respiratory function is one of the important indicators for expanding the indications for segmentectomy. In a recent Japan Clinical Oncology Group (JCOG) 0802 trial, the difference in the median reduction of forced expiratory volume in 1 second (FEV1) between lobectomy and segmentectomy at 12 postoperative months was only 3.5%. As there have been few reports comparing postoperative respiratory function by resected lobes or segments, we conducted this prospective non-randomized study at our institution.

Methods: Patients who underwent segmentectomy or lobectomy for lung cancer between January 2021 and March 2023 were included in this study. Respiratory function tests were scheduled preoperatively, and at 6 and 12 months postoperatively. Differences in the median FEV1 reduction rate (FEV1 Red) between segmentectomy and lobectomy were evaluated.

Results: The study included 537 patients (241 lobectomies and 296 segmentectomies). The median FEV1 Red after lobectomy/segmentectomy was 13.9%/8.3% at 6 months ($p < 0.001$) and 12.3%/7.6% at 12 months ($p < 0.001$).The median FEV1 Red at 6 months after lobectomy/segmentectomy were 14.0%/7.5% for right upper lobe (RUL) ($p < 0.001$), 20.4%/9.8% for left upper lobe (LUL) ($p < 0.001$), 9.0%/8.3% for right lower lobe (RLL) ($p = 0.199$), and 16.0%/8.9% for left lower lobe (LLL) ($p = 0.012$), respectively. The median FEV1 Red at 12 months after lobectomy/segmentectomy were 11.9%/6.6% for RUL ($p = 0.002$), 18.0%/8.8% for LUL ($p < 0.001$), 11.4%/6.3% for RLL ($p = 0.053$), and 12.8%/10.6% for LLL ($p = 0.060$), respectively. Among segmentectomy patients, the maximum FEV1 Red was observed in left S9+10 segmentectomy, with median FEV1 Red of 12.5%/12.5% at 6/12 months, respectively. The minimum FEV1 Red was observed in right S3 segmentectomy, with median FEV1 Red of 6.9%/6.6% at 6/12 months, respectively.

Conclusions: Compared to lobectomy, segmentectomy tended to preserve postoperative respiratory function. While significant differences were observed in the median FEV1 Red between lobectomy and segmentectomy for RUL and LUL, no significant differences were observed in RLL and LLL. The degree of preservation of postoperative respiratory function may vary depending on the site of resection, which might be one of the key criteria when choosing the candidate for segmentectomy.

Keywords: lung cancer, segmentectomy, respiratory function

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P2.07B.06 Segmentectomy for cIA1-2 Lung Cancer in the Lower Lobe with Solid-Predominant Opacity: Impact on Recurrence and Survival Rates

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Introduction: The JCOG0802/WJOG4607L trial revealed that segmentectomy is more advantageous in terms of overall survival for non-small cell lung cancer less than 2 cm. However, when it comes to the lung lobe, there is no significant difference in overall survival between lobectomy and segmentectomy. Depending on the location of the segment, lobectomy may be favored over segmentectomy. This study aims to understand better the surgical outcomes of segmentectomies in the lower lobe, which can be pretty intricate in surgical technique.

Methods: We conducted a study to analyze the survival rates and factors related to survival in patients with non-small cell lung cancer who underwent segmentectomy at two institutions in Yamagata Prefecture, Japan, between 2010 and 2022. The study focused on patients undergoing segmentectomy in the lower lobe for tumors with a maximum size of 2 cm and a consolidation to maximum tumor diameter (C/T) ratio of 0.5 or greater.

Results: Of the 493 patients who underwent segmentectomy, 89 underwent segmentectomy in the lower lobe, excluding basal segmentectomy, with 48 undergoing segmentectomy in the right lower lobe and 41 in the left lower lobe. The patients were divided into two groups: the S6 group (43 patients who underwent S6 segmentectomy) and the non-S6 group (46 patients who underwent other than S6 segmentectomy). The median follow-up was 5.2 years. The study found that the 5-year survival rate was 79% in the S6 group and 94%

in the non-S6 group ($p < 0.01$), while the 5-year recurrence-free survival rate was 74% in the S6 group and 87% in the non-S6 group ($p = 0.04$). On multivariate analysis, low FEV1 and omitted mediastinal nodal dissection were identified as poor prognostic factors for overall survival, while omitted mediastinal nodal dissection was a poor prognostic factor for recurrence-free survival. The study also found that there were five recurrences in the S6 group (2 ipsilateral lymph nodes, three lung metastases, one disseminated tumor, and one distant organ metastasis) and two in the non-S6 group (1 resection margin and one distant organ metastasis). The causes of death were 10 cases in the S6 group (4 deaths from primary disease, 2 from other cancers, three from other diseases, and one unknown) and 2 cases in the non-S6 group (1 from other cancers and one from other diseases).

Conclusions: The findings of our retrospective analysis indicate that among segmentectomies performed in the lower lobe, the prognosis of S6 segmentectomy is significantly worse than that of non-S6 segments. Therefore, we recommend that segmentectomy be carefully considered and indicated for lung cancer cases affecting the S6 segment. While our findings should be interpreted with caution due to the retrospective nature of the study, they provide important insights into the management of lung cancer and the potential risks associated with different types of segmentectomies.

Keywords: lung cancer, segmentectomy, surgery

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P2.07B.07 Multi-Institutional Retrospective Analysis of Segmentectomy Versus Lobectomy for Non-Small Cell Lung Cancer Larger Than 3 cm in Diameter

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Introduction: Segmentectomy for non-small cell lung cancer (NSCLC) smaller than 2 cm is well-supported by robust evidence and is being further explored in clinical trials for tumors 2 to 3 cm, where some supportive evidence already exists. This study investigates segmentectomy for NSCLC larger than 3 cm, which present challenges in achieving adequate surgical margins, and focuses on its potential to expand treatment options for these patients.

Methods: We retrospectively analyzed 1208 patients diagnosed with cN0 NSCLC >3 cm who underwent anatomical complete resection at three institutions from 2010 to 2022.Propensity Score Matching (PSM) was utilized to compare clinicopathologic characteristics and outcomes between segmentectomy (S) and lobectomy (L) groups.

Results: The study included 118 patients in the S group and 1090 patients in the L group; the median age of the S group was 74 years, 79 (66%) were male, and 83 (70%) had smoking history. The median radiological size of the tumors in the S group was 3.5 cm, the median diameter of the solid component was 3.1 cm, and the median value of SUVmax was 2.9.The most common surgical procedures were left upper segmentectomy in 30 cases (25%), right S6 segmentectomy in 18 cases (15%), left S1+2 segmentectomy in 16 cases (13%), and other complex segmentectomy were also observed. The major histological type was adenocarcinoma in 94 cases (79%), pathological whole tumor size was 3.4 (2.8-4.1) cm, 13 cases (11.0%) were positive for lymph node metastasis, and pStage 0-1, II, and III were 81, 15, and 10 cases, respectively. In the S group, the 5-year overall survival (5yOS) rate was 76.4% and 5-year recurrence-free survival (5yRFS) rate was 72.4%.After adjusting with PSM and analyzing 108 matched pairs, a higher incidence of adenocarcinoma and larger pathological tumor diameters were noted in the L group. However, no significant differences were observed in pT, pN, or pStage. The 5yOS rates were 75.9% for the S group versus 78.0% for the L group, with a p-value of 0.69 (Figure). Similarly, the 5yRFS rates were 68.0% for the S group compared to 79.0% for the L group, with a p-value of 0.10, indicating no significant differences (Figure).

Conclusions: Segmentectomy for NSCLC >3 cm might yield outcomes comparable to lobectomy if patient selection is well controlled. This finding implies the potential for expanding indications for segmentectomy and improving patient outcomes in NSCLC therapeutic strategies.

Keywords: Segmentectomy, Non-small cell lung cancer, Propensity Score Matching

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P2.07B.08 Outcome Comparison Between Left Upper Lung Lobectomy and Split Lobe Segmentectomy for Clinical Stage I Lung Cancer

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Introduction: The left upper lobe (LUL) can be divided into the upper division - proper segment (segment 1-3) and lingula segment (segment 4-5), akin to the segments in the right upper lobe and middle lobe. Does split-lobe segmentectomy for early lung cancer in the apical lung or lingula segment yield similar oncological outcomes to LUL lobectomy? While previous studies, like those by the Japan Clinical

Oncology Group (JCOG), have focused on smaller tumors (<2cm), we aim to assess if split-lobe segmentectomy is a viable approach for clinical stage I non-small cell lung cancer (NSCLC) patients with tumors between 2-4 cm, maintaining oncological efficacy comparable to LUL lobectomy.

Methods: From 2011 to 2021, we retrospectively included 377 clinical staged I NSCLC patients receiving LUL lobectomy, LUL S1-3 tri-segmentectomy, or LUL S4-5 lingular segmentectomy. Subsequently, we categorized them into two groups based on tumor size: 0-2 cm and 2-4 cm, enabling us to conduct subgroup analyses. To ensure comparability in preoperative demographics, a 1:1 propensity score matching procedure was implemented. Following matching, we obtained 42 patients in the 0-2 cm group and 146 patients in the 2-4 cm group. We systematically gathered retrospective data pertaining to clinical, pathological, perioperative, and oncological outcomes for these matched patient cohorts.

Results: The study focuses on the 2-4 cm group. Before matching, disparities existed between the two groups (split-lobe lobectomy and LUL lobectomy) in age, comorbidities (Charlson Comorbidity Index, CCI), and CT tumor diameters. After 1:1 propensity score matching based on age, CCI, tumor total diameters, and solid diameters, demographics and clinicopathological features showed no significant difference. Disparities persisted in operative times (p=0.001), postoperative hospital stays (p=0.001), and durations of ICU stay (p=0.023), suggesting comparable or superior perioperative outcomes with split-lobe segmentectomy. No significant differences in progression-free survival (PFS) (p=0.594) or overall survival (OS) (p=0.843) were found after matching, with a mean follow-up exceeding 4 years (figure). Split-lobe segmentectomy poses no heightened risks of cancer progression or mortality. The 0-2 cm group had similar outcomes as well. Multivariate analysis showed that surgical method was not a significant factor for survival (p=0.053).

Conclusions: We had presented the most recent and large matched comparative analysis in such topic in the recent 20-year literature. Left upper lobe split-lobe segmentectomy emerges as a secure and feasible surgical option for clinical stage I NSCLC, demonstrating comparable PFS and OS outcomes to LUL lobectomy, but with equivalent or even improved perioperative outcomes.

Keywords: Segmentectomy, Non-small cell lung cancer

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P2.07B.09 Real-World Validation for Impact of Sublobar Resection Over Lobectomy on Lung Cancer Survival and Frailty Using SEER-Medicare

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Introduction: Lung cancer is a disease of older adults with a median age at diagnosis of 71 years. While lobectomy is effective for treating early-stage lung cancer, older patients may be vulnerable to complications from this surgical procedure due to limited lung function and a high chronic disease burden. Recent phase-3 clinical trials indicate that sublobar resection may be non-inferior to lobectomy in terms of disease-free and overall survival in patients with early-stage non-small cell lung cancer (NSCLC). However, selection biases and younger patients in the trials can limit generalizability to real-world populations of older patients from different clinical and socioeconomic backgrounds. Furthermore, the long-term consequences of sublobar resection vs. lobectomy on subsequent development of an aging-related syndrome, such as frailty, has never been evaluated. To address this evidence gap, we used target trial emulation to provide real-world validation of non-inferiority of sublobar resection vs. lobectomy on lung cancer-specific survival and frailty.

Methods: Using data from SEER cancer registries linked to Medicare fee-for-service (SEER-Medicare) insurance claims, we identified 8,093 eligible patients (age≥65 years) with stage T1aN0 NSCLC (tumor size≤2 cm) diagnosed between 2008-2015 and followed through 2019 for trial emulation. Patients were excluded if they had not been continuously enrolled in Medicare Parts A and B from the year before diagnosis through 2019 or death, had received chemotherapy or radiotherapy before surgery, or were frail at the time of diagnosis. Frailty was defined by a validated claims-based frailty index (cFI) ranging from 0 to 1, with cut-points of non-frail (<0.25), or frail (≥0.25). The cFI assesses the accumulation of 93 aging-related deficits using diagnosis and procedure codes in Medicare Parts A and B claims annually over a 12-month look-back period.The primary outcome was the 5-year lung cancer-specific and overall mortality by different clinical and socioeconomic factors (i.e., 5-year age groups, histology, race/ethnicity, and neighborhood socioeconomic status [nSES]). The secondary outcome was the time to development of frailty. Target trial emulation based on the clone-censor-inverse probability weight method was used to minimize immortal time bias, mitigate selection bias and confounding, and mimic per-protocol analysis of the target trial via a discrete hazard model, which was approximated using a pooled logistic regression.

Results: To emulate the target trial of comparing sublobar vs. lobar resection within 3 weeks of diagnosis, 8,093 patients (75.4 median age at diagnosis; 40% male; 61.2% with adenocarcinoma; 5.7% Black; 4.2% Asian) from SEER-Medicare were analyzed. Those with sublobar resection (vs. lobectomy) had similar lung cancer-specific mortality (adjusted-weighted odds-ratio [awOR] 1.04 [0.81-1.33], p=0.73) and overall mortality (awOR=1.05 [0.89-1.23], p=0.57). This non-inferior result was observed across patient subgroups by age, histology, race, and nSES. Patients undergoing sublobar (vs. lobectomy) had a significantly lower risk of becoming frail over time (awOR=0.63 [95% CI: 0.44-0.89], p=0.01).

Conclusions: Clinical trials and our real-world emulated trial data show comparable survival benefits between sublobar resection and lobectomy. The lung cancer patients with sublobar resection were less likely to develop frailty, suggesting that thoughtful treatment decisions could support healthy aging while reducing cancer burden.

Keywords: Real-world evidence, Sublobar resection, Frailty

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P2.07B.10 Should Lymph Node Dissection Be Routinely Undertaken for Patients with Small-Sized Solid-Dominant Non-Small-Cell Lung Cancer?

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Introduction: Sublobar resection for early-stage non-small cell lung cancer (NSCLC) is expected to become increasingly common. We investigated the prognosis and incidence of lymph node metastasis and recurrence in patients with clinical stage IA small-sized (≤2 cm) NSCLC based on the presence of ground-grass opacity (GGO) components.

Methods: Consecutive 903 patients who underwent lobectomy, segmentectomy, or wedge resection for clinical stage IA (≤2 cm diameter and consolidation-to-tumor ratio [CTR] >0.5) NSCLC from 2017 to 2022 were included in this study. The patients divided into two groups based on the presence of GGO components (solid tumor group with CTR = 1 [S group] [n = 595] and part-solid tumor group with 0.5< CTR <1 [PS group] [n = 308]) and identified differences in incidence of nodal involvement and recurrence, and long-term prognosis.

Results: Adenocarcinoma was the most common histologic type in both groups and more frequently observed in PS group (74.6% vs. 99.0%, p <0.001). There was no significant difference in overall survival (OS) between the S and PS group (5-year OS rate, 89.0% vs. 93.3%; p = 0.134). However, recurrence-free survival (RFS) was better in PS group (5-year RFS rate, 75.1% vs. 91.1%; p <0.001). Nodal involvement (pN1-2) was more often detected in S group (9.7% vs. 0.6%, p <0.001). Furthermore, nodal recurrence and/or metastasis were observed in 85 (14.3%) in S group, which was significantly higher than 6 (1.9%) in PS group (p <0.001) (Table 1). In S group, the survival after wedge resection was significantly worse than after segmentectomy (5-year OS rate after lobectomy/segmentectomy/wedge resection, 86.6%/97.0%/82.2%, p <0.001; 5-year RFS rate, 72.6%/81.3%/72.8%, p = 0.039). However, in PS group, no significant difference was identified based on the extent of lung resection (5-year OS rate, 91.2%/96.2%/88.8%, p = 0.459; 5-year RFS rate, 84.2%/95.3%/88.8%, p = 0.080).

Conclusions: In patients with small-sized part-solid NSCLC, nodal involvement and recurrence were rarely observed, and mediastinal lymph node dissection can be omitted. In addition, due to the favorable prognosis and no survival difference based on the extent of lung resection, it may be possible to expand the indications for wedge resection without mediastinal lymph node dissection.

Table 1 Patterns of recurrence

Characteristic

0.5<CTR<1 (N = 308)

CTR = 1 (N = 595)

p value

Total recurrence

7 (2.3)

77 (12.9)

<0.001

Recurrence pattern

Locoregional

3 (1.0)

22 (3.7)

Distant

1 (0.3)

28 (4.7)

Both

3 (1.0)

27 (4.5)

Lymph node (LN) recurrence

6 (1.9)

45 (7.5)

<0.001

Hilar

4 (1.3)

19 (3.2)

Mediastinal

4 (1.3)

42 (7.1)

Other

4 (1.3)

9 (1.5)

Locoregional recurrence (not LN recurrence)

0

12 (2.0)

0.011

Surgical margin

0

10 (1.7)

Bronchial stump

0

1 (0.2)

Ipsilateral lung

0

1 (0.2)

Distant recurrence

4 (1.3)

55 (9.2)

<0.001

Lymph node recurrence and/or metastasis

6 (1.9)

85 (14.3)

<0.001

Keywords: lymph node metastasis, lymph node recurrence, sublobar resection

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P2.07B.11 Delays to Lung Cancer Surgery by Biopsy Technique

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Introduction: Excessive time-to-treatment initiation (TTI) for early-stage lung cancer remains a challenge for healthcare providers and patients. Recent literature found that for patients who undergo surgical resection for clinical stage I/II NSCLC, increased time from diagnosis to surgery is associated with a higher chance for pathological upstaging, as well as decreased overall survival. At our healthcare institution, over 90% of clinical stage I lung cancer patients undergo biopsy prior to surgery. Biopsy occurs either via percutaneous needle biopsy or bronchoscopy. As the biopsy contributes to delay, we sought to determine whether there was a significant difference in delays depending on technique. Additionally, we compared the TTI of patients who received biopsy versus those who received surgical biopsy. A secondary aim of this research was to quantify how much added delay there was from biopsies that did not yield results suggestive of malignancy.

Methods: We reviewed all participants of the prospective cohort study, Initiative for Early Lung Cancer Research on Treatment (IELCART), from 2016-2024. We included patients who received surgical resection for clinical stage I (T1a-c, T2a) lung cancer (TNM 8th edition modified). Using the methodology from our prior research, time intervals measuring days from suspicious imaging to biopsy, biopsy to surgery, and suspicious imaging to surgery were compared across groups for significant differences.

Results:

Table 1. Summary statistics for TTI and Kruskal Wallis tests by biopsy technique

Category (N)

TTI imaging to biopsy (days)

TTI biopsy to surgery (days)

TTI imaging to surgery (days)

All patients (N = 1061)

40

40

87

Surgical biopsy (n = 96)

50.5

0

50.5

At least 1 needle biopsy, 0 bronchoscopy (n = 744)

40

40

89

At least 1 bronchoscopy, 0 needle biopsy (n = 109)

28

42

74

At least 1 needle biopsy, at least 1 bronchoscopy (n = 112)

44

69

116.5

P-value

p<0.001

p<0.001

p<0.001

Data are presented as median or (P-value) for KS test of medians. P≤0.05 indicates statistical significance.

Table 2. Pairwise median comparisons using Dunn test

Category 1 - category 2

TTI imaging to biopsy (days)

TTI biopsy to surgery (days)

TTI imaging to surgery (days)

Both - bronch only; difference in medians (P-value)

16 (<.001)

27 (<.001)

42 (<.001)

Both - needle only

4 (1)

29 (<.001)

27 (<.001)

Bronch - needle

-12 (<.001)

2 (1)

-15 (.02)

Both - surgical

-6 (.12)

69 (<.001)

66 (<.001)

Bronch - surgical

-22 (<.001)

42 (<.001)

24 (.03)

Needle - surgical

-10 (<.001)

40 (<.001)

39 (<.001)

Data are presented as median(category 1) - median(category 2) (P-value). P-values are adjusted using the Bonferroni correction; P≤0.05 indicates statistical significance.

TTI from biopsy to surgery (84 vs 40; p<0.001) and TTI from suspicious imaging to surgery (139 vs 87; p<0.001) is significantly higher for biopsies that yielded non-malignant findings versus malignant findings.

Conclusions: Bronchoscopies resulted in lower TTI than needle biopsies, though they were less likely to confirm a malignant diagnosis. Surgical biopsies had a significantly lower TTI than either biopsy technique but has the disadvantage of potentially operating on benign lung nodules. Biopsies that did not confirm a malignant diagnosis added 52 days to delay.

Keywords: lung biopsy, delays to treatment, early-stage lung cancer

P2.07C EARLY-STAGE NON-SMALL CELL LUNG CANCER - PERIOPERATIVE THERAPY FOR OPERABLE EARLY STAGE NSCLC, SUNDAY, SEPTEMBER 8, 2024 - 18:15 - 19:45

P2.07C.01 LCMC3: Clinical Utility of Suvmax on Preoperative 18F-FDG PET-CT in Resectable NSCLC Treated with Neoadjuvant Atezolizumab

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Introduction: We examined the prognostic value of SUVmax change on clinical outcomes following neoadjuvant atezolizumab (anti-PD-L1) treatment in patients with resectable NSCLC from the LCMC3 study (NCT02927301).

Methods: LCMC3 was a Phase II, open-label, single-arm study in patients with resectable stage IB-IIIA or select IIIB NSCLC. Patients were aged ≥18 years, had an ECOG performance status of 0 or 1 and received neoadjuvant atezolizumab 1200 mg IV every 3 weeks for

2 cycles followed by surgery. Patients in the primary efficacy population were EGFR/ALK negative or unknown status. This post hoc analysis examined a subset of this population that had major pathologic response assessment and paired PET-CT scans before and after neoadjuvant atezolizumab treatment, prior to surgery. 18F-FDG uptake was quantified using SUV, with the highest pixel value within the primary tumor defined as SUVmax. P values were nominal and not adjusted for multiple comparisons.

Results: This analysis included 183 enrolled patients (2 patients were excluded as ineligible), 159 of whom had surgical resection; 119 patients (65%) had a major pathologic response assessment and were evaluated with pre- and post-atezolizumab PET-CT. The SUVmax from pre- to post-neoadjuvant atezolizumab decreased in 77 patients and increased in 42. Baseline and disease characteristics were generally balanced between these 2 groups, except that the decreasing vs increasing SUVmax group had a numerically greater median decrease in tumor size (−10% vs 0%) and a numerically greater prevalence of high (TPS ≥50%) PD-L1 expression (36% [28/77] vs 26% [11/42]; Table). All 5 patients in the analysis with pathologic complete response had decreasing SUVmax (P=0.160). Three-year disease-free survival improved by 16% in individuals with decreasing SUVmax (P=0.071; Table). Patients with decreasing vs increasing SUVmax demonstrated a significantly higher major pathologic response rate (30% [23/77] vs 7% [3/42]; P=0.005) and 3-year overall survival (88% vs 72%; P=0.043; Table).

Conclusions: Decreasing vs increasing SUVmax following neoadjuvant atezolizumab treatment was associated with improved clinical outcomes, including a trend toward longer DFS and significant improvements in major pathologic response and overall survival. These results suggest that assessment of SUVmax may be a valuable tool for clinicians that should be further evaluated for pre-surgery prognostic stratification of patients with resectable NSCLC.

Keywords: Atezolizumab, neoadjuvant, SUVmax

P2.07C EARLY-STAGE NON-SMALL CELL LUNG CANCER - PERIOPERATIVE THERAPY FOR OPERABLE EARLY STAGE NSCLC, SUNDAY, SEPTEMBER 8, 2024 - 18:15 - 19:45

P2.07C.02 Prognostic Impact of Adjuvant Immunotherapy in Patients with Non-Small Cell Lung Cancer Following Neoadjuvant Immunotherapy

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Introduction: Whether adjuvant immunotherapy can bring further survival benefits for resectable non-small cell lung cancer (NSCLC) after neoadjuvant chemoimmunotherapy still remains unknown. This study aims to evaluate the prognostic impact of adjuvant immunotherapy and identify potential factors associated with prognostic benefits from adjuvant immunotherapy.

Methods: A total of 439 patients, diagnosed with an IB-IIIB NSCLC, receiving neoadjuvant chemoimmunotherapy or immunotherapy between August 2019 and October 2022 at Shanghai Pulmonary Hospital were enrolled in our study, with a median follow-up time of 24.8 months. To minimize the influence of potentially prognostic confounders, propensity-score matching (PSM) was adopted between patients following adjuvant immunotherapy and non-adjuvant immunotherapy groups with a 1:1 ratio. Recurrence-free survival (RFS) was estimated using Kaplan-Meier methods and tested by log-rank test, and unstratified Cox proportional hazards models fitted to the subgroups.

Results: In the entire cohort, we reported that 29.61% of patients (n=130) reached pathological complete response (pCR). Patients with a pCR had significantly better RFS than those without (p<0.001) (Figure 1A). After PSM between patients following adjuvant immunotherapy and non-adjuvant immunotherapy groups, there were 110 patients in each matched set and the median number of cycles of adjuvant immunotherapy in the adjuvant immunotherapy group was 10. Patients who received adjuvant immunotherapy experienced survival benefits over those who did not (hazard ratio [HR]: 0.51, 95% confidence interval [CI]: 0.28-0.94, p=0.012) (Figure 1B). We noted that patients who did not achieve pCR (HR: 0.54, 95% CI: 0.28-1.05, p=0.066) were more likely to benefit from adjuvant immunotherapy compared to the pCR subgroup (HR: 0.35, 95% CI: 0.07-1.80, p=0.188) (Figure 1C). The forest plot of subgroup analysis showed that patients with squamous cell carcinoma and patients without lymph node involvement were significantly benefit from adjuvant immunotherapy (HR:0.40, 95% CI: 0.18-0.89; HR:0.34, 95% CI: 0.12-0.997) (Figure 1D).

Conclusions: To our knowledge, our result is the first to demonstrate the addition of adjuvant immunotherapy to neoadjuvant chemoimmunotherapy is significantly associated with improved RFS for patients with resectable NSCLC and patients with squamous cell carcinoma and patients without lymph node involvement experienced significant benefits from adjuvant immunotherapy. We validated that pCR would translate into prognostic superiority, but we also found that the non-pCR subgroup tended to benefit more from adjuvant immunotherapy, which suggests that the extent of pathologic response observed at surgery could guide adjuvant treatment escalation or de-escalation strategies.

Keywords: Adjuvant Immunotherapy, Neoadjuvant Immunotherapy, Non-small Cell Lung Cancer

P2.07C EARLY-STAGE NON-SMALL CELL LUNG CANCER - PERIOPERATIVE THERAPY FOR OPERABLE EARLY STAGE NSCLC, SUNDAY, SEPTEMBER 8, 2024 - 18:15 - 19:45

P2.07C.03 Limited Efficacy of Immunochemotherapy in Pulmonary Invasive Mucinous Adenocarcinoma and Mucoepidermoid Carcinoma as Neoadjuvant Setting

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Introduction: Recently, clinicians have successfully integrated immune checkpoint inhibitors (ICIs) alongside chemotherapy into perioperative regimens for locally advanced lung cancer. However, the specific efficacy of chemoimmunotherapy in addressing invasive mucinous adenocarcinoma (IMA) and mucoepidermoid carcinoma (MEC), characterized by mucinous cell presence, remains to be comprehensively elucidated.

Methods: We retrospectively review patients diagnosed with IMA and MEC at Guangdong Provincial People's Hospital (GDPH) and Cancer Hospital Chinese Academy of Medical Sciences (CAMS). Inclusion criteria comprised patients who underwent surgery following induction chemoimmunotherapy. Driver gene mutation status was determined via NGS before therapy. Otherwise, EGFR and ALK status were assessed using ARMS and Ventana methods, respectively. PD-L1 expression (Dako 22C3) was quantified using tumor proportion score (TPS). Event-free survival (EFS) was defined as the duration from initial surgery to recurrence or metastasis.

Results: A total of 14 patients (12 IMA and 2 MEC) were included. Among them, 6 had KRAS mutations, 2 had HER2 mutations, and 1 had RET mutations; no patients exhibited EGFR mutations or ALK alternation. Overall, low-level PD-L1 expression was observed, with only one case showing a TPS of 10%, and the rest at 0 or ≤1%. All patients underwent 2-4 cycles of neoadjuvant chemoimmunotherapy, with 13 (92.9%) achieving R0 resection. The sole patient with R2 resection received adjuvant radiotherapy post-surgery. Only one exhibited a partial response (-30.38%), while the remaining 13 maintained stable disease following neoadjuvant therapy. In terms of pathological assessment, none had achieved MPR or pCR (defined as 0% and <10% viable tumor cell). Totally 5 patients experienced postoperative recurrence or metastasis, resulting in one mortality, after a median follow-up period of 19.6 months (Fig A). The median EFS time was 16 months, with all five patients experiencing their first relapse as intrapulmonary metastases (Fig B).

Conclusions: Limited efficacy of chemoimmunotherapy in the neoadjuvant setting for resected IMA and MEC was observed. Only one case exhibited radiological partial response, with no partial or complete pathological responses observed. However, further validation on a larger scale is still on going.

Keywords: Mucinous adenocarcinoma, Mucoepidermoid carcinoma, Neoadjuvant immunochemotherapy

P2.07C EARLY-STAGE NON-SMALL CELL LUNG CANCER - PERIOPERATIVE THERAPY FOR OPERABLE EARLY STAGE NSCLC, SUNDAY, SEPTEMBER 8, 2024 - 18:15 - 19:45

P2.07C.04 Surgical Complexity of Anatomical Lung Resections after Induction Immunotherapy for Locally Advanced or Metastatic Non-Small Cell Lung Cancer

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Introduction: Neoadjuvant immunotherapy has become an integral part of the multimodal treatment in advanced NSCLC. However, an increasing procedural complexity after neoadjuvant immunotherapy is described by many surgeons. We therefore aim to score the surgical complexity of anatomical resections after induction immunotherapy.

Methods: We performed a single-institutional retrospective review of patients with clinical stage IIIA-IVB NSCLC who underwent anatomical lung resection and mediastinal lymphadenectomy after neoadjuvant immunotherapy. Surgical complexity and hilar fibrosis were scored according to the proposed scoring system by Rusch et al. (https://doi.org/10.1016/j.jtcvs.2022.10.007).

Results: 25 patients met the inclusion criteria, among which 4 (16%) were treated with neoadjuvant immunotherapy alone, 18 (72%) with neoadjuvant immunochemotherapy and 3 (12%) with neoadjuvant immunotherapy and chemoradiotherapy. Clinical UICC-stages were IIIA in 8 (32%), IIIB in 2 (8%), IVA in 9 (36%) and IVB in 6 patients (24%). Surgical access was primarily open in 13 (52%), RATS in 5 (20%) and VATS in 7 patients (28%). Resections included 15 lobectomies, 4 bilobectomies, 5 pneumonectomies and 1 segmentectomy. Conversion from minimally invasive to open approach was required in 5 patients (2 VATS and 3 RATS cases), all due to extensive hilar fibrosis. A hilar fibrosis score of 2 was present in 15 cases and a score of 0 was only seen in 4 patients. The presence of a high fibrosis score was not associated with an increased risk for perioperative complications (p=0.66), but patients with a fibrosis score of 2 showed a longer median length of hospital stay (9.4±3.9 versus 6.7±1.8 days), although not statistically significant (p=0.056).

Conclusions: Surgical complexity after neoadjuvant immunotherapy for advanced NSCLC can be objectified by a hilar fibrosis score. The prognostic relevance of the hilar fibrosis score for early outcomes such as perioperative complications and length of stay needs to be assessed in larger prospective cohorts.

Keywords: Surgical Complexity, Neoadjuvant Immunotherapy, Anatomical resection

P2.07C EARLY-STAGE NON-SMALL CELL LUNG CANCER - PERIOPERATIVE THERAPY FOR OPERABLE EARLY STAGE NSCLC, SUNDAY, SEPTEMBER 8, 2024 - 18:15 - 19:45

P2.07C.05 Perioperative (Neoadjuvant Plus Adjuvant) Immunotherapies for Resectable NSCLC:A Systematic Review and Meta-Analysis of Phase 3 Trials

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Introduction: Meta-analysis based on phase III trials which investigated the efficacy and safety of perioperative (neoadjuvant plus adjuvant) immunotherapies in resectable non-small cell lung cancer (NSCLC) patients are lacking. In addition, existing phase III studies have described inconsistent results of perioperative immunotherapies in some important subgroups of patients and requires further investigation.

Methods: PubMed, Embase and Cochrane Library were systematically searched for phase III trials of perioperative immunotherapies in resectable NSCLC patients before March 23, 2024. The pooled hazard ratios (HR) were determined through the generic inverse variance methods model, the pooled risk difference (RD) derived through the inverse variance method. Random-effect model was applied depending on the heterogeneity. The protocol of this study was registered with the International Platform of Registered Systematic Review and Meta-analysis Protocols (INPLASY202440003).

Results: We identified 5 trials (N=2855) that met eligibility criteria, with 1420 and 1435 patients receiving perioperative (neoadjuvant plus adjuvant) immunotherapies and perioperative chemotherapy, respectively. Pooled event-free survival (HR: 0.58; 95%CI: 0.51-0.65), pathological complete response (RD: 21%; 95%CI: 15-27) and major pathological response (RD: 29%; 95%CI: 21-37) favored perioperative immunotherapies over perioperative chemotherapy. No clinically meaningful differences were observed between perioperative immunotherapies and perioperative chemotherapy across the incidence of any grade TRAE (RD: 1%; 95%CI: -1-3), grade≥3 TRAE (RD: 5%; 95%CI: 2-8), surgical resection rate (RD: 3%; 95%CI: 1-6) and R0 resections rate (RD: 4%; 95%CI: 2-6). For subgroup patients, perioperative immunotherapies provide more efficacy benefits compare with perioperative chemotherapy regardless of disease stage, histology and PD-L1 expression (Table).

Conclusions: This meta-analysis demonstrated that perioperative (neoadjuvant plus adjuvant) immunotherapies was associated with prolonged EFS, higher pCR and MPR rates compare with perioperative chemotherapy across disease stage, histology and PD-L1 expression, with no increased safety risk and no impact on the feasibility and completeness of surgery. The study supports the use of perioperative immunotherapies for patients with resectable NSCLC.

Table. Efficacy outcomes

EFS HR (95% CI)

pCR RD (95% CI)

MPR RD (95% CI)

ITT

0.58 (0.51-0.65)

21% (15-27)

29% (21-37)

Disease Stage

Stage II

0.64 (0.49-0.82)

25% (17-33)

28% (21-35)

Stage III

0.56 (0.49-0.64)

21% (9-33)

32% (11-53)

Histology

squamous

0.51 (0.43-0.61)

24% (15-34)

32% (13-50)

nonsquamous

0.67 (0.56-0.8)

18% (9-28)

23% (18-29)

Tumor PD-L1 expression

PD-L1<1%

0.75 (0.62-0.9)

7% (3-11)

/

PD-L1 1-49%

0.52 (0.37-0.72)

16% (7-25)

/

PD-L1≥50%

0.47 (0.37-0.61)

33% (15-52)

/

EFS, event-free survival; HR, hazard ratio; RD, risk difference; CI, confidence interval; MPR, major pathological response; pCR, pathological complete response

Keywords: perioperative, immunotherapy, resectable Non-Small Cell Lung Cancer

P2.10A METASTATIC NON-SMALL CELL LUNG CANCER - CYTOTOXIC THERAPY - CLINICAL TRIALS IN PROGRESS, SUNDAY, SEPTEMBER 8, 2024 - 18:15 - 19:45

P2.10A.01 Phase 2 Study of Disitamab Vedotin in Patients with HER2-Expressing Non-Small Cell Lung Cancer (DV-005; Trial in Progress)

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Introduction: Patients with advanced non-small cell lung cancer (NSCLC) without targetable driver alterations or those who become resistant to targeted therapy have limited treatment options after progression on platinum-based chemotherapy or immune checkpoint blockade. Hence, there is a need for effective therapies in the late-line setting. Human epidermal growth factor receptor 2 (HER2) expression detected by immunohistochemistry (IHC; range 1+-3+) occurs at a higher frequency than activating HER2 mutations and has been reported in approximately 50% of lung cancers (Uzunparmak 2023). Patients with tumors that express HER2, including HER2-low (IHC 1+ or IHC 2+/in situ hybridization-negative) tumors, may be targeted with HER2-directed antibody-drug conjugates (ADCs). Disitamab vedotin (DV; RC48-ADC) is an investigational ADC comprising a fully humanized HER2-directed monoclonal antibody, disitamab, conjugated to monomethyl auristatin E (MMAE) via a protease-cleavable mc-vc linker. DV elicits antitumor activity through multimodal mechanisms of action, including MMAE-mediated direct cytotoxicity, bystander effect, and immunogenic cell death. Disitamab targets different epitopes of the HER2 receptor, with a higher molecular affinity for HER2, than trastuzumab. DV monotherapy has shown promising clinical activity across several HER2-expressing advanced solid tumors (Xu 2021, Peng 2021, Sheng 2023, Wang 2021). Available data from

these studies suggest DV may be a potential treatment option in previously treated advanced NSCLC with HER2 expression.

Methods: DV-005 (NCT06003231) is a phase 2, multicohort, multicenter, open-label basket trial assessing DV monotherapy for the treatment of patients with previously treated advanced solid tumors that express HER2 (≥1+ determined by local IHC). Patients with HER2 mutations will be eligible. In this multicohort study, Cohort 2 will enroll patients with metastatic or locally advanced unresectable NSCLC. DV will be administered intravenously every 2 weeks until disease progression, unacceptable toxicity, death, termination of study, or withdrawal of consent. Patients with NSCLC enrolled in Cohort 2 must have progressed during or after platinum-based therapy or within 6 months of platinum-based adjuvant, neoadjuvant, or concomitant chemoradiotherapy for early or locally advanced-stage disease. Patients must have also received prior anti-programmed cell death receptor 1 (PD-1)/programmed cell death ligand 1 (PD-L1) therapy unless contraindicated. Those patients with known EGFR, ALK, ROS1, or other actionable alterations must have received targeted therapy. Prior HER2-directed therapy is permitted, including HER2-directed ADCs. All patients must have measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 and Eastern Cooperative Oncology Group performance status 0 or 1. Patients are ineligible if they have received MMAE-based therapy or have clinically significant cardiopulmonary disease, chronic liver disease, or uncontrolled central nervous system metastases. The primary endpoint is overall response rate, defined as confirmed complete or partial response per RECIST v1.1, as assessed by the investigator. Secondary endpoints include safety and tolerability, disease control rate, duration of response, progression-free survival, overall survival, incidence of antidrug antibodies, and pharmacokinetic parameters. Enrollment is ongoing in the US and Canada.

Keywords: Disitamab vedotin, HER2 expressing, Antibody–drug conjugate

P2.10A METASTATIC NON-SMALL CELL LUNG CANCER - CYTOTOXIC THERAPY - CLINICAL TRIALS IN PROGRESS, SUNDAY, SEPTEMBER 8, 2024 - 18:15 - 19:45

P2.10A.02 Phase 1/1b Trial of MBRC-101, An Anti-EphA5 Monomethyl Auristatin (MMAE) Antibody Drug Conjugate, In Advanced Refractory Solid Tumors

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Introduction: EphA5 receptor is a member of the Ephrin receptor tyrosine kinase (RTK) family. Several lines of robust nonclinical evidence indicate EphA5 is a novel and selective target for solid tumor-directed therapy. Expressed only minimally in normal tissues, it is highly expressed in non-small cell lung carcinoma (NSCLC) and other malignancies. MBRC-101 is a novel antibody drug conjugate (ADC) composed of an anti-EphA5 antibody conjugated to an MMAE payload (drug-to-antibody ratio of 4) through a valine citrulline cleavable linker. In pre-clinical testing against a variety of cell-derived (CDX) and patient-derived (PDX) xenograft solid tumor models, MBRC-101 demonstrated robust anti-tumor activity against NSCLC and other EphA5-expressing malignancies.

Methods: This first-in-human, Phase 1/1b, multicenter, open-label study is examining the safety and efficacy of MBRC-101 in patients with advanced metastatic solid tumors refractory to standard treatment. Phase 1 will identify potential optimal biologically relevant doses (OBRD) and the maximum tolerated dose (MTD) of MBRC-101 at one or more dosing regimens. Phase 1b will evaluate the safety and preliminary clinical activity of MBRC-101 at potential OBRDs. Phase 1 will enroll patients (n ≈ 30) with advanced or metastatic solid tumors. A modified toxicity probability interval (mTPI-2) method will guide dose escalation using a pre-specified decision matrix. The primary endpoints are MTD, dose limiting toxicities (DLTs), treatment emergent adverse events (TEAEs), and clinical laboratory tests. Phase 1b will enroll patients (n ≈ 60) into 3 expansion cohorts (n ≈ 20 per cohort): Cohort A, NSCLC; Cohort B, triple negative or HR+/HER2- breast cancer; and Cohort C, pancreatic adenocarcinoma, gastric adenocarcinoma, hepatocellular carcinoma, ovarian adenocarcinoma, and squamous cell carcinoma including primary malignancies of the head and neck, esophagus, cervix, and skin. The primary endpoints are TEAEs, clinical laboratory tests, and investigator-assessed objective response rate (ORR) by RECIST v1.1 and clinical evaluation. Secondary endpoints for Phase 1 and 1b include PK analytes and EphA5 expression as determined by immunohistochemistry (IHC). Expression of EphA5 in primary or metastatic tumor tissue will not be required for enrollment into Phase 1 or 1b but will be assessed retrospectively. A Safety Review Committee will monitor safety at each dose escalation in Phase 1 and at regular intervals throughout Phase 1b.

Results: As of April 1, 2024, n = 13 patients (n =2 with NSCLC) had been enrolled. No DLTs were observed through 3 escalating dose levels.

Conclusions: This Phase 1/1b trial is evaluating MBRC-101, a novel ADC composed of an anti-EphA5 antibody and MMAE payload, in patients with NSCLC and other advanced refractory solid malignancies.

Keywords: Ephrin, ADC

P2.10A METASTATIC NON-SMALL CELL LUNG CANCER - CYTOTOXIC THERAPY - CLINICAL TRIALS IN PROGRESS, SUNDAY, SEPTEMBER 8, 2024 - 18:15 - 19:45

P2.10A.03 RESOLUTION: Phase II Study of Disitamab Vedotin in Combination with Tislelizumab and Bevacizumab in Patients with HER2 Alteration Advanced NSCLC

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Introduction: Nowadays, there are limited approved targeted therapies for metastatic non-small cell lung cancer (mNSCLC) with HER2 alterations. Disitamab vedotin (RC48) is a novel antibody-drug conjugate (ADC) that carries a tubulin inhibitor targeting the HER2 protein on the surface of tumor cells, specifically recognizing and killing these tumor cells. It has demonstrated considerable anti-tumor effects in solid tumors. The synergy between ADCs and immunological or anti-vascular agents holds promise for enhancing the efficacy of treating HER2-altered NSCLC. Consequently, further investigation into the potential of combination therapy for NSCLC harboring HER2 alterations is warranted.

Methods: RESOLUTION (Clinical Trial Number: ChiCTR2300077938) is a dual-cohort, phase 2 study. 56 eligible patients who have locally advanced or metastatic NSCLC with HER2 alterations will be enrolled. There are two cohorts: (1) Patients who have previously received ≥1 line of systemic therapy (2) Cohort 2: patients with locally advanced or metastatic NSCLC who have not received prior systemic therapy.The primary endpoint is objective response rate (ORR). Secondary study endpoints are progression-free survival (PFS), overall survival (OS), disease control rate (DCR), and duration of response (DOR). Disease response will be assessed by investigator according to RECIST 1.1. Patients enrollment is ongoing.

Keywords: HER2 alteration, ADC

P2.10A METASTATIC NON-SMALL CELL LUNG CANCER - CYTOTOXIC THERAPY - CLINICAL TRIALS IN PROGRESS, SUNDAY, SEPTEMBER 8, 2024 - 18:15 - 19:45

P2.10A.04 Valemetostat and Datopotamab Deruxtecan in Previously Treated, Advanced, Unresectable, or Metastatic Non-squamous NSCLC

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Introduction: Valemetostat tosylate (valemetostat) is a novel, potent, and selective dual inhibitor of enhancer of zeste homolog (EZH)2 and EZH1. Valemetostat 200 mg/day PO has demonstrated clinical efficacy and favorable tolerability in multiple hematologic malignancies. EZH2 controls the expression of multiple genes, including those involved in the DNA damage response, like DNA/RNA helicase Schlafen 11 (SLFN11). In response to DNA damage, SLFN11 binds to chromatin, causing a replication block and inducing apoptosis. Expression levels of SLFN11 indicate sensitivity to DNA-damaging agents (DDAs) in lung cancer and are downregulated in chemotherapy-resistant tumor cells due to trimethylation of histone H3 at lysine 27 at the SLFN11 gene locus. EZH2 inhibition by valemetostat is expected to upregulate SLFN11 and sensitize tumor cells to DDAs. Topoisomerase inhibition causes DNA strand breaks, which may synergize with valemetostat. Datopotamab deruxtecan (Dato-DXd) is a novel, investigational trophoblast cell surface protein 2 (TROP2)-directed antibody-drug conjugate (ADC) composed of a humanized anti-TROP2 IgG1 monoclonal antibody covalently linked to a potent topoisomerase I inhibitor payload (DXd) via a plasma-stable tetrapeptide-based cleavable linker. In the phase 3 TROPION-Lung01 trial, Dato-DXd significantly improved progression-free survival (PFS) vs standard chemotherapy in previously treated, locally advanced, or metastatic non-small-cell lung cancer (NSCLC). This study is structured as a Master Protocol trial evaluating the clinical activity and safety of valemetostat in combination with DXd-ADCs, including Dato-DXd and the human epidermal receptor 2 (HER2)-directed ADC, trastuzumab deruxtecan (T-DxD), in patients with NSCLC or other solid tumors, respectively.

Methods: This global, phase 1b, multicenter, two-part, open-label Master Protocol study will enroll ~ 70 patients per sub-protocol in multiple regions including the US and Japan. The NSCLC sub-protocol will enroll adult patients with 2L+ locally advanced, unresectable, or metastatic non-squamous NSCLC with or without actionable genomic alterations (Figure). A preliminary dose-escalation part will assess escalating valemetostat doses of 50-200 mg PO QD with fixed-dose Dato-DXd 6.0 mg/kg IV Q3W, to determine the valemetostat recommended dose for expansion (RDE). A subsequent dose-expansion part will evaluate the efficacy of valemetostat (at the RDE) + Dato-DXd. Primary endpoints of this study are safety and tolerability of valemetostat in Part 1 and objective response rate in Part 2. Secondary endpoints include duration of response, PFS, overall survival and pharmacokinetics. An interim futility analysis will be performed when 20 patients have been enrolled and completed ≥ 6 months of follow-up. Clinical trial information: NCT06244485.

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Keywords: NSCLC, Valemetostat, Dato-DXd

P2.10A METASTATIC NON-SMALL CELL LUNG CANCER - CYTOTOXIC THERAPY - CLINICAL TRIALS IN PROGRESS, SUNDAY, SEPTEMBER 8, 2024 - 18:15 - 19:45

P2.10A.05 Ipat-Lung: A Multi-Center Phase 2 Study of Ipatasertib Plus Docetaxel in NSCLC Patients who Have Failed or Are Intolerant to 1st

Line Immunotherapy

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Introduction: For advanced/metastatic non-small cell lung cancer (NSCLC) patients who do not have targetable driver mutations, either immunotherapy using immune checkpoint inhibitors alone or in combination with platinum-based chemotherapy is now a standard of care. However, many patients do not derive benefit due to primary, adaptive, or acquired resistance, as well as immune-related adverse effects (irAEs), necessitating the discovery of novel therapeutics to benefit patients who have failed or are intolerant to first-line immunotherapy. Here, we propose a multi-center phase II study to use ipatasertib, an AKT1 inhibitor, in combination with docetaxel, based on the following rationales: 1) Aberrant activation of the PI3'K-AKT pathway due to either the hyperactivation of oncogenes and/or loss-of-function of tumor suppressors occurs in more than half of NSCLC patients; 2) Hyperactivation of the PI3'K-AKT pathway also confers a suppressive tumor immune microenvironment; 3) The combination of ipatasertib and taxane has demonstrated safety and efficacy in earlier studies.

Methods: Eligible patients must have advanced/metastatic NSCLC and have failed or are intolerant to first-line anti-PD1/PD-L1, either single-agent or in combination with chemotherapy and/or anti-CTLA4. Patients who were treated with concurrent chemoradiation therapy followed by durvalumab, upon progression on or after durvalumab, will also be eligible if there is no other systemic anti-cancer treatment given. In addition, patients who are qualified for FDA-approved targeted therapy may be eligible if they have failed at least one line of such targeted therapy, followed by the failure or intolerance to only one line of anti-PD1/PD-L1 therapy, either single-agent or in combination with chemotherapy and/or anti-CTLA4. Participants will receive ipatasertib 400 mg PO daily on days 1-14 plus docetaxel at 75 mg/m2 intravenously on day 1 of each 21-day cycle. G-CSF support is started from cycle 1. The primary endpoint is progression-free survival (PFS). Secondary endpoints include objective response rate (ORR), overall survival (OS), and safety. The exploratory endpoints include the correlation of PFS with cfDNA, PTEN status, microbiome, and ex vivo testing using tumor organoids. Using PFS ~4.6 months in this population as a comparison, we hypothesize that this proposed therapy will yield a 50% increase in median PFS (6.9 vs. 4.6 months). Assuming that PFS follows an exponential distribution, we will need to enroll 45 participants in order to have 80% power to detect a 50% improvement in median PFS using a type I error of 5% with a one-sided test. Allowing for a 25% censoring rate, we therefore plan to enroll 60 evaluable participants. This study is currently ongoing.

Keywords: Ipatasertib, NSCLC, Immunotherapy failure

P2.10A METASTATIC NON-SMALL CELL LUNG CANCER - CYTOTOXIC THERAPY - CLINICAL TRIALS IN PROGRESS, SUNDAY, SEPTEMBER 8, 2024 - 18:15 - 19:45

P2.10A.06 Phase 3 TroFuse-004 Study: Sac-TMT vs Chemotherapy for Previously Treated Advanced NSCLC with EGFR/Other Genomic Alterations

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Introduction: Trophoblast cell-surface antigen 2 (TROP2), a cell surfaceglycoprotein involved in the regulation of tumor growth and invasion, isbroadly expressed and upregulated in several cancers, including NSCLC. Sacituzumab tirumotecan (sac-TMT; also known as MK-2870/SKB264) is an antibody-drugconjugate (ADC) composed of the humanized anti-TROP2 monoclonal antibody, ahydrolytically cleavable linker, and the cytotoxic drug KL610023. Sac-TMT has demonstratedencouraging antitumor activity and manageable toxicity in phase 1 and 2 studiesof patients with solid tumors, including heavily pretreated EGFR-mutant NSCLC.We describe the design of the ongoing phase 3 TroFuse-004 study (NCT06074588) thatwill evaluate the efficacy and safety of sac-TMT vs chemotherapy for previouslytreated advanced or metastatic nonsquamous NSCLC with EGFR mutations orother genomic alterations.

Methods: The global, randomized,open-label, phase 3 TroFuse-004 studywill enroll ~556 patients, including 456 with exon 19del or L858R EGFRmutations, and 100 with other genomic alterations. Eligible patients are aged≥18 years with histologically or cytologically documented advanced (stage IIInot eligible for resection or curative radiation) or metastatic nonsquamousNSCLC with exon 19del or exon 21 L858R EGFR mutations or other genomicalterations in ALK, ROS1, BRAF V600E, NTRK, METexon 14 skipping, or RET and those with less common EGFRmutations (exon 20 S768I, exon 21 L861Q, and/or exon 18 G719X). Patients must have progressive disease on or after 1 or 2lines of prior tyrosine kinase inhibitor therapy and a platinum-based therapy(may contain anti-PD-[L]1), measurable disease per RECIST v1.1, an availabletumor sample, and adequate organ function. Prior EGFR tyrosine kinaseinhibitor therapy must include a third-

generation tyrosine kinase inhibitor forpatients with T790M EGFR-mutant NSCLC. Patients with active centralnervous system metastases or carcinomatous meningitis are ineligible, althoughthose with previously treated and untreated stable brain metastasis are eligiblefor enrollment. Patients will be randomized (1:1) to sac-TMT 4 mg/kg Q2W onDays 1, 15, and 29 of every 6-week cycle, or chemotherapy (docetaxel 75 mg/m2Q3W or pemetrexed 500 mg/m2 Q3W) on Days 1 and 22 of every 6-weekcycle. Randomization will be stratified by EGFR mutations with priorthird generation tyrosine kinase inhibitor vs EGFR mutations with noprior third generation tyrosine kinase inhibitor vs other genomic alterations,brain metastasis (yes vs no), and TROP2 expression (low vs medium vs high). Dualprimary endpoints are PFS (per RECIST v1.1 by blinded independent centralreview) and OS in patients with EGFR-mutant NSCLC. Key secondary endpointsinclude PFS and OS in all patients with NSCLC, ORR, DOR, patient-reportedoutcomes (PROs), and safety. Health-related quality oflife PROs will be measured using the EORTC QLQ-C30 and EORTC QLQ-LC13. Enrollmentstarted in November 2023 and is currently ongoing.

Keywords: Antibody-drug conjugate (ADC), Topoisomerase II inhibitor, EGFR TKI resistance

P2.10A METASTATIC NON-SMALL CELL LUNG CANCER - CYTOTOXIC THERAPY - CLINICAL TRIALS IN PROGRESS, SUNDAY, SEPTEMBER 8, 2024 - 18:15 - 19:45

P2.10A.07 Trofuse-009: Phase 3 Study of Sac-TNT vs Platinum-Doublet Chemotherapy for Previously Treated EGFR-Mutated Advanced NSCLC

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Introduction: Sacituzumab tirumotecan (sac-TMT; also known as MK-2870/SKB264) is an antibody-drug conjugate composed of a humanized anti-trophoblast cell-surface antigen 2 (TROP2) monoclonal antibody, a hydrolytically cleavable linker, and the cytotoxic topoisomerase I inhibitor KL610023. TROP2 is a cell-surface glycoprotein associated with cancer growth and invasion and is overexpressed in several cancers, including non-small-cell lung cancer (NSCLC). Phase 1 and 2 studies of sac-TMT, including in patients with heavily pre-treated EGFR-mutated NSCLC, have shown encouraging antitumor activity and manageable toxicity. We describe the design of the phase 3 TroFuse-009 study (NCT06305754), which will evaluate the efficacy and safety of sac-TMT vs platinum-based doublet chemotherapy in patients with EGFR-mutated locally advanced or metastatic nonsquamous NSCLC with disease progression following prior EGFR tyrosine kinase inhibitor (TKI) therapy.

Methods: This global, randomized, open-label, phase 3 study will enroll approximately 520 patients aged ≥18 years with histologically or cytologically confirmed stage III not eligible for resection or curative chemoradiation or stage IV nonsquamous NSCLC with one of the following tumor-activating EGFR mutations: exon 19del, L858R, G719X, S7681, or L861Q. Patients must have experienced disease progression on prior EGFR TKI therapy (those who previously received a first- or second-generation EGFR TKI as first-line therapy must have documentation of the absence of EGFR T790M mutation on a biopsy sample obtained after disease progression; if T790M mutation was acquired after receiving a first- or second-generation EGFR TKI, the patient must have subsequently received a third-generation EGFR TKI before enrollment). Patients must also have a tumor tissue sample for biomarker analysis (TROP2 expression will be assessed centrally by immunohistochemistry), measurable disease per RECIST version 1.1, and ECOG PS of 0 or 1. Patients with known central nervous system metastases and/or carcinomatous meningitis are ineligible, except those with previously treated brain metastases (if clinically stable for ≥2 weeks, with no evidence of new/enlarging brain metastases and no steroids within 3 days before study treatment) or known untreated, asymptomatic brain metastases. Patients will be randomized 1:1 to receive either sac-TMT 4 mg/kg every 2 weeks or pemetrexed 500 mg/m2 plus carboplatin AUC 5 mg/mL/min every 3 weeks for 4 doses followed by pemetrexed 500 mg/m2 every 3 weeks until disease progression or unacceptable toxicity. Randomization will be stratified by brain metastases at baseline (yes vs no), TROP2 expression (no or low vs medium vs high), and type of EGFR TKI received in first line (third-generation vs first- or second-generation, including those with third-generation in second line). Tumor imaging will be performed every 6 weeks from randomization through week 48 and every 12 weeks thereafter. Safety will be assessed from the time of randomization through 30 days after discontinuation of study treatment; AEs will be graded according to National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0. Dual primary endpoints are progression-free survival (per RECIST version 1.1 by blinded independent central review) and overall survival. Secondary endpoints include objective response rate, duration of response, patient-reported outcomes, and safety. Enrollment in this study will begin in May 2024.

Keywords: Non–small-cell lung cancer, Antibody-drug conjugate, Topoisomerase I inhibitor

P2.10B METASTATIC NON-SMALL CELL LUNG CANCER - CYTOTOXIC THERAPY - CYTOTOXIC CHEMOTHERAPY AND ADCS, SUNDAY,

SEPTEMBER 8, 2024 - 18:15 - 19:45

P2.10B.01 Exploratory Analyses of Tusamitamab Ravtansine vs Docetaxel in Previously Treated Non-squamous NSCLC Patients: CARMEN-LC03

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Introduction: CARMEN-LC03 was a phase 3, open-label, randomized (1:1), multicenter study that evaluated tusamitamab ravtansine (tusa rav), an antibody-drug conjugate with a microtubule-destabilizing payload (DM4), vs docetaxel in patients with advanced nonsquamous non-small cell lung cancer (NSCLC) previously treated with chemotherapy and immunotherapy and whose tumors highly expressed CEACAM5 (defined as ≥2+ intensity in ≥50% of tumor cells assessed by immunohistochemistry [IHC]). The primary analysis showed that tusa rav did not improve progression-free survival (PFS), showed a trend towards improved overall survival (OS), favorable safety, toxicity profile, and patient-reported outcomes (PROs). Here we present results from post-hoc exploratory analysis of PFS and OS.

Methods: Patients were randomized to receive tusa rav 100 mg/m2 Q2W IV or docetaxel 75 mg/m2 Q3W IV. The two primary endpoints of PFS and OS were analyzed by stratified Cox regression model to estimate the hazard ratio (HR) and 95% confidence interval (CI) of tusa rav versus docetaxel in all randomized participants (intent-to-treat [ITT] population). Post-hoc exploratory analyses were performed for several subgroups of interest, including different cut-off for CEACAM5-IHC expression, actionable genomic alterations (AGA), and prior taxane use (using unstratified Cox-regression model).

Results: As of September 22, 2023, 194 patients were randomized to tusa rav and 195 to docetaxel. Median age was 64 years; 59.6% were male. In patients without AGAs (that needed immunotherapy) and no prior taxanes (overlapping mechanism of action with tusa rav payload), OS favored tusa rav versus docetaxel with a HR (0.71 [0.52-0.97]), while PFS was not affected (HR=1.00 [0.73-1.38]). Both PFS (HR=0.87 [0.60-1.26]) and OS (HR=0.71 [0.49-1.03]) favored tusa rav in participants with CEACAM5 ≥2+ in ≥80% tumor cells compared to population with CEACAM5 ≥2+ in 50-79% tumor cells (PFS: HR=1.38 [0.92-2.07], and OS: HR=1.02 [0.69-1.50]). Dividing patients into terciles of CEACAM5 expression showed that patients with >90% achieved the greatest benefit (PFS, OS, and PROs) with tusa rav. Further analysis revealed that median OS substantially improved with increasing CEACAM5 expression, irrespective of treatment. In the post-hoc exploratory analyses, the greatest relative clinical benefit with tusa rav was observed among patients with CEACAM5 >90%, median OS (tusa rav vs docetaxel) was 18.63m vs 15.24m, respectively (HR=0.65 [0.39-1.08]; Table).

Conclusions: These exploratory analyses identify patients likely to derive clinical benefit from tusa rav and suggest a previously unknown prognostic role for CEACAM5 in NSCLC. Additional research is needed to corroborate these findings.

Keywords: CEACAM5, NSCLC, tusamitamab ravtansine

P2.10B METASTATIC NON-SMALL CELL LUNG CANCER - CYTOTOXIC THERAPY - CYTOTOXIC CHEMOTHERAPY AND ADCS, SUNDAY, SEPTEMBER 8, 2024 - 18:15 - 19:45

P2.10B.02 Cutoff Determination for C-met Protein Overexpression by VENTANA MET (SP44) IHC to Determine Teliso-v Eligibility in NSCLC

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Introduction: c-Met (also known as MET protein) overexpression occurs in approximately 25% of patients with advanced epidermal growth factor receptor wildtype non-squamous non-small cell lung cancer (EGFR WT NSQ NSCLC) and is associated with poor prognosis. Telisotuzumab vedotin (Teliso-V) is a first-in-class, c-Met protein-directed antibody-drug conjugate that has shown efficacy in patients with c-Met protein-overexpressing advanced EGFR WT NSQ NSCLC. The VENTANA MET (SP44) immunohistochemical (IHC) assay measures c-Met protein expression on formalin-fixed paraffin-embedded tumor samples. This study aimed to determine the optimal cutoff values for c-Met protein overexpression to identify patients with EGFR WT NSQ NSCLC who are most likely to benefit from treatment with Teliso-V.

Methods: Tumor samples from patients with EGFR WT NSQ NSCLC enrolled in an ongoing first-in-human study of Teliso-V (NCT02099058) were retrospectively analyzed for c-Met protein expression using the VENTANA MET (SP44) IHC assay. The membrane staining intensity and the percentage of c-Met staining positivity on tumor cells were assessed and their association with best objective response to Teliso-V treatment was evaluated. Receiver operating characteristic (ROC) analysis was used to determine the membrane staining intensity threshold (ie, 1+, 2+, or 3+) that best associated with best objective response. Statistical analyses, including sensitivity, specificity, positive predictive value, negative predictive value, and Fisher's exact test p-value were performed for each of the prespecified candidate cutoffs to determine the percentage of tumor cells indicating c-Met positivity: 10%, 25%, 50%, 75%, 90%, and 100%. Statistical outcome evaluation and comparison of Fisher's exact test p-values and the Youden index were used to determine the optimal cutoff value of c-Met protein overexpression to identify eligibility for Teliso-V treatment. Reported p-values are nominal.

Results: Best objective response rates above and below each potential threshold for each intensity were compared in 30 patients. Among evaluated staining intensities and candidate cutoffs, 25% c-Met positivity with 3+ staining intensity on tumor cells was identified as the most optimal cutoff and intensity, with best objective response rates of 56% and 10% for those above (n=9) and below (n=21) the cutoff

(p=0.0139) and an area under the ROC curve of 0.736 for the staining intensity. A threshold of 50% cell positivity with 3+ staining intensity resulted in best objective response rates of 67% and 12% for those above (n=6) and below (n=24) the cutoff (p=0.0157).

Conclusions: A cutoff value of 25% c-Met-positive tumor cells with 3+ intensity was selected to determine positivity of c-Met protein overexpression in patients with EGFR WT NSQ NSCLC eligible for Teliso-V treatment. A cutoff value of 50% was selected to determine high expression of c-Met protein.

Keywords: c-Met, NSCLC, Teliso-V

P2.10B METASTATIC NON-SMALL CELL LUNG CANCER - CYTOTOXIC THERAPY - CYTOTOXIC CHEMOTHERAPY AND ADCS, SUNDAY, SEPTEMBER 8, 2024 - 18:15 - 19:45

P2.10B.03 Efficacy of Platinum Pemetrexed in Patients with EGFR Mutated Advanced Lung Cancer after Progression on Osimertinib - A Prospective Cohort Study

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Introduction: Platinum doublet chemotherapy is a standard of care option for treatment of patients with epidermal growth factor receptor mutation-positive (EGFR+) advanced non-small cell lung cancer (aNSCLC) after disease progression on osimertinib. Evidence for second-line (2L) platinum chemotherapy after osimertinib from a pragmatic clinical trial is lacking.

Methods: OCELOT (NCT04335292) is a multicentered phase II open-label multi-cohort investigator-initiated study of osimertinib for the third-line treatment of EGFR+ aNSCLC (Cohort A), following first-line (1L) treatment with osimertinib then 2L treatment with platinum-pemetrexed chemotherapy, and (Cohort B) 1L treatment of EGFR+ aNSCLC for patients with uncommon EGFR mutations. Patients in Cohort A were enrolled at the time of 2L chemotherapy and patients in Cohort B were enrolled prior to 1L osimertinib. We analyzed response rate as per RECIST 1.1 and survival outcome of patients with EGFR+ aNSCLC treated prospectively in both cohorts of OCELOT clinical trial with platinum-pemetrexed chemotherapy (in 2L) after progression on osimertinib. The chemotherapy dosing was at the investigator's discretion. The primary outcome of this analysis was objective response rate (ORR). The secondary outcome was progression free survival (PFS) and time to treatment failure (TTF).

Results: At data cut off for this analysis, a total of 29 patients received 2L treatment with platinum pemetrexed. 52% (n = 15) of patients were male. The median age was 63 years (range, 36-87 years). 22 had evaluable disease. The ORR in the whole cohort was 31.8% and the disease control rate (DCR) was 81.8% (partial response in 7, stable disease in 11 and progressive disease in 4 patients). The ORR and DCR among six patients having uncommon EGFR mutations was 50% (n = 3) and 83% (n = 5) respectively. The median PFS in the whole cohort was 6.6 months and 6-month PFS was 50% (the results for PFS are the same when restricted to common mutations). The median TTF was 7.0 months and the 6-month TTF was 53.3%. OS data are immature.

Conclusions: The response rate and progression free survival of patients with EGFR+ aNSCLC treated with 2L platinum pemetrexed after progression on osimertinib is comparable to published literature. This supports that the benefit of platinum pemetrexed translates for a pragmatic population receiving chemotherapy dosed at the investigators' discretion.

Keywords: advanced NSCLC, EGFR, platinum pemetrexed

P2.10B METASTATIC NON-SMALL CELL LUNG CANCER - CYTOTOXIC THERAPY - CYTOTOXIC CHEMOTHERAPY AND ADCS, SUNDAY, SEPTEMBER 8, 2024 - 18:15 - 19:45

P2.10B.04 Paclitaxel Liposome Combined with Immunotherapy in the First-Line Treatment of Advanced NSCLC: A Multicenter Real-World Study

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Introduction: Paclitaxel liposome is paclitaxel encapsulated by liposomes made from lecithin and cholesterol. Paclitaxel liposome reduces the incidence of drug-induced toxicity especially hypersensitivity reactions compared with solvent paclitaxel formulation because

polyethoxylated castor oil is not used. This study aimed to evaluate the real-world effectiveness and safety of paclitaxel liposome-based chemotherapy plus immunotherapy as first-line treatment among Chinese patients with advanced non-small cell lung cancer (NSCLC).

Methods: The data for this study were sourced from the "Efficacy and Safety of Immunotherapy in NSCLC Patients: A Multi-Center Observational Study" project within the real-world lung cancer database initiative launched by the Lung Cancer Special Committee of the China Medical Education Association, with a specific focus on the use of paclitaxel liposome plus immunotherapy. Patient data was drawn from an online hospital platform. The study evaluated advanced NSCLC patients who underwent first-line treatment with paclitaxel liposome-based chemotherapy and immunotherapy in nine Chinese hospitals between April 2020 and November 2023. The primary outcome was progression-free survival (PFS), with objective response rate (ORR) and safety as secondary outcomes.

Results: Among 200 patients who met the criteria, 188 were male with an overall median age of 66 (range: 59 to 69). Of all patients, 163 (81.5%) were squamous cell carcinoma, 10(5.0%) were adenocarcinoma, and 27 (13.5%) were NSCLC where specific pathological subtypes were not recorded. 27% of the patients were at stages IIIB-IIIC, and 73% were at stage IV. The percentage of patients with and without EGFR mutations were 1.0% and 69.0% respectively, with 31.0% had unkown status. The median treatment cycles for first-line paclitaxel liposome-based chemotherapy and immunotherapy were 4. The immunotherapy agents used included tislelizumab (n=120), pembrolizumab (n=30), sintilimab (n=29) and others (n=21). All patients were co-administered platinum with 92.5% receiving carboplatin. The median duration of follow-up was 9.5 months. The median PFS was 11.4 months (95% CI: 9.8-13.3). The 1-year PFS rate was 44% (95% CI: 36-54). Multivariate analysis identified treatment cycles of paclitaxel liposome as independent risk factors for PFS (P<0.05), with patients received >3 cycles having better PFS. Out of the 164 patients evaluated for effectiveness, 11 achieved a complete response, 86 demonstrated a partial response, 52 had stable disease, and 15 experienced progressive disease. The overall ORR was 59.1%, and the DCR was 90.9%. Adverse events of all grades were recorded in 59% of the patients, with 16.5% were of grade 3 or higher. It should be noted that the non-laboratory adverse events were based on analyses of patient-reported outcome(PRO) data. The most common adverse events included bone marrow suppression, gastrointestinal reactions, and liver function abnormalities. The adverse events observed in > 10% of the patients were decreased neutrophil count and anaemia. 16 deaths were recorded till the cut-off date of 29th February 2024.

Conclusions: Paclitaxel liposome-based chemotherapy plus immunotherapy demonstrated substantial effectiveness and safety for advanced NSCLC in the real-world setting. The study is currently ongoing.

Keywords: Paclitaxel liposome, Immunotherapy, Non-small cell lung cancer

P2.10B METASTATIC NON-SMALL CELL LUNG CANCER - CYTOTOXIC THERAPY - CYTOTOXIC CHEMOTHERAPY AND ADCS, SUNDAY, SEPTEMBER 8, 2024 - 18:15 - 19:45

P2.10B.05 Renal Toxicity in Patients with Non-Small Cell Lung Cancer Receiving Maintenance Therapy with Pemetrexed and Pembrolizuma

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Introduction: Both pemetrexed and pembrolizumab have been associated with renal toxicity but there are limited data comparing the rates of renal toxicity in patients with metastatic non-small cell lung cancer (NSCLC) who receive maintenance therapy with pemetrexed, pembrolizumab, or both.

Methods: A retrospective analysis of patients with metastatic NSCLC who were treated at the University of Colorado Cancer Center from 2019-2023 with at least 4 cycles of platinum, pemetrexed, and pembrolizumab followed by at least 1 cycle of maintenance therapy with pemetrexed, pembrolizumab, or both was conducted. Baseline characteristics were collected at the time of treatment initiation. Patients were defined as having one of the co-morbidities of interest if they had been assigned a corresponding ICD-10 code at the time of treatment initiation. The outcome of interest was renal events that occurred while patients were on maintenance therapy. A renal event was defined as having any ICD-10 code corresponding to abnormal results of kidney function studies, acute kidney injury (AKI), or chronic kidney disease (CKD) assigned while on maintenance therapy. CKD was only counted as a renal event if it was not present at baseline. Differences between cohorts were evaluated with the Kruskal-Wallis rank sum test for continuous variables, the Chi-square test for categorical variables, and the Fisher Exact test for categorical variables with low cell counts.

Results: A total of 166 patients were included in this study of whom 58 received maintenance pemetrexed, 30 received maintenance pembrolizumab, and 78 received maintenance pemetrexed/pembrolizumab. The baseline characteristics of the patients are summarized in Table 1.

Table 1: Baseline Characteristics

Pemetrexed (N=58)

Pemetrexed/Pembrolizumab (N=78)

Pembrolizumab (N=30)

p-value

Demographics

Age, years, median (IQR)

67 (58, 75)

68 (63, 76)

62 (59, 74)

0.2

Sex, N (%)

0.6

Female

35 (60.3%)

50 (64.1%)

16 (53.3%)

Male

23 (39.7%)

28 (35.9%)

14 (46.7%)

Race, N (%)

0.4

Asian

2 (3.4%)

2 (2.6%)

1 (3.3%)

Black

0 (0%)

2 (2.6%)

0 (0%)

Hispanic/Latino

2 (3.4%)

3 (3.8%)

4 (13.3%)

White

47 (81.0%)

67 (85.9%)

24 (80.0%)

Data unavailable

7 (12.1%)

4 (5.1%)

1 (3.3%)

Smoking status, N (%)

0.003

Current

0 (0%)

7 (9.0%)

5 (16.7%)

Former

15 (25.9%)

33 (42.3%)

13 (43.4%)

Never

6 (10.3%)

1 (1.3%)

1 (3.3%)

Data unavailable

37 (63.8%)

37 (47.4%)

11 (36.7%)

Pack-years, median (IQR)

12 (0, 35)

30 (15, 45)

23 (11, 40)

0.083

Co-morbidities

Chronic kidney disease, N (%)

6 (10.3%)

11 (14.1%)

1 (3.3%)

0.3

Diabetes, N (%)

6 (10.3%)

12 (15.4%)

6 (20.0%)

0.4

Hypertension, N (%)

27 (34.6%)

41 (52.6%)

16 (53.3%)

0.7

Sites of Metastatic Disease

Adrenal, N (%)

10 (17.2%)

12 (15.4%)

4 (13.3%)

>0.9

Bone, N (%)

41 (70.7%)

48 (61.5%)

9 (30.0%)

0.002

Brain, N (%)

32 (55.2%)

34 (43.6%)

10 (33.3%)

0.2

Extra-thoracic lymph nodes, N (%)

29 (50.0%)

28 (35.9%)

14 (46.7%)

0.1

Liver, N (%)

13 (22.4%)

26 (33.3%)

5 (16.7%)

0.2

Pleura, N (%)

20 (34.5%)

24 (30.8%)

3 (10.0%)

0.072

Data unavailable, N (%)

6 (10.3%)

6 (7.7%)

6 (20.0%)

0.2

Treatment Details

Exposed to cisplatin, N (%)

8 (13.8%)

2 (2.6%)

3 (10.0%)

0.033

Number of doses of platinum received, mean (SD)

6 (2)

6 (3)

5 (1)

0.3

Number of doses of maintenance pemetrexed received, mean (SD)

8 (9)

8 (8)

0.5

Number of doses of maintenance pembrolizumab received, mean (SD)

10 (12)

11 (12)

0.9

There was a trend towards increased incidence of any renal event in the pemetrexed (19.0%) and pemetrexed/pembrolizumab (21.8%) cohorts compared to the pembrolizumab cohort (3.3%, p=0.07). This was driven by a significantly higher incidence of AKI in the pemetrexed (17.2%) and pemetrexed/pembrolizumab (17.9%) cohorts compared to the pembrolizumab cohort (0%, p=0.02). There was no significant difference in the incidence of abnormal results of kidney function studies or CKD between the cohorts.

Conclusions: In this retrospective analysis, no AKIs were observed in patients with metastatic NSCLC who received maintenance therapy with pembrolizumab, while AKIs were observed at a significantly higher rate in patients who received maintenance therapy with pemetrexed with or without pembrolizumab. There was a trend towards less renal events in general with pembrolizumab maintenance therapy. These data suggest that pembrolizumab does not add significant risk of renal toxicity in the maintenance treatment of metastatic NSCLC.

Keywords: non-small cell lung cancer, pemetrexed, pembrolizumab

P2.10B METASTATIC NON-SMALL CELL LUNG CANCER - CYTOTOXIC THERAPY - CYTOTOXIC CHEMOTHERAPY AND ADCS, SUNDAY, SEPTEMBER 8, 2024 - 18:15 - 19:45

P2.10B.06 Improvements in Survival Outcomes of Large Cell Carcinoma Over Past Two Decades (2000-2020)

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Introduction: Large cell carcinoma (LCC) is an aggressive subtype of lung cancer, characterized by poor prognosis. Little has been done to explore the long term trends in improvement of Large Cell carcinoma over time. This study aimed to assess trends in 5-year survival rates for LCC patients diagnosed from 2000 to 2015, examining improvements trends.

Methods: We utilized data from the Surveillance, Epidemiology, and End Results (SEER) database, focusing on Large Cell Carcinoma (LCC) spanning from 2000 to 2020. This dataset included year of diagnosis and treatment modalities encompassing radiation therapy, and chemotherapy for a cohort of 16,175 patients. To assess the impact of various factors on survival, we employed a Cox proportional hazards model. This model specifically examined the influence of the year of diagnosis, and detailed treatment modalities such as the type and receipt of chemotherapy and radiation therapy, alongside surgical interventions. The objective was to quantify their effects on survival months, providing insights into the evolving effectiveness of lung cancer treatment practices.

Results: We looked at survival rate by 5 year cohort, as well as effect of chemotherapy and radiation therapy on survival outcomes. There

was a slight improvement in survival in 2005-2009 (HR 0.95, p = 0.007), compared to 2000-2004, while 2010-2014 showed a HR of 0.97 (p = 0.38), suggesting marginal improvement. For 2015-2019, the HR was 0.83, demonstrating significant 17.4% improvement in survival outcomes (p <0.0001). Chemotherapy led to a 21.3% improvement in survival outcomes (HR of 0.79, p <0.0001). Declination of radiation therapy resulted in 47% decrease in survival outcomes (HR of 1.47, p = 2.04e-06).

Conclusions: Overall, we identified an improvement of survival trends over time in patients with LCC. This analysis emphasizes the notable progress in cancer treatment post-2015, aligning with survival improvements. Chemotherapy's role in substantially reducing the hazard rate is confirmed, underscoring its importance in treatment protocols. The adverse outcomes associated with refusing radiation therapy stress the necessity of following recommended treatments. A limitation of our analysis is the impact of data censoring for patients diagnosed from 2015 to 2019, whose follow-up does not cover the full five-year period due to the dataset concluding in 2020. Although survival analysis techniques accommodate censored data, this constrains our insights into the definitive long-term outcomes for these recent cohorts. Further, we were missing staging data to control for severity of disease process.

Keywords: Large Cell Carcinoma, Mortality, Radiation Therapy

P2.10B METASTATIC NON-SMALL CELL LUNG CANCER - CYTOTOXIC THERAPY - CYTOTOXIC CHEMOTHERAPY AND ADCS, SUNDAY, SEPTEMBER 8, 2024 - 18:15 - 19:45

P2.10B.07 Chemotherapy in Combination with Anti-PD1 in PD-L1-Negative Non-Small Cell Lung Cancer Patients: A Single-Center Experience

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Introduction: Non-small cell lung cancer (NSCLC) represents a significant burden in Western countries. In this study, we aim to examine the clinical course of patients diagnosed with PD-L1-negative adenocarcinoma and metastatic squamous cell carcinoma of NSCLC, specifically focusing on their response to first-line treatment combining chemotherapy and anti-PD-1 therapy.

Methods: A retrospective study was designed, including patients diagnosed with adenocarcinoma and squamous cell carcinoma without actionable mutations and negative for PD-L1, who were treated with chemo-anti-PD1 from 2019 to the present. Demographic variables were collected, with particular interest in those related to tumor presentation characteristics, progression-free survival (PFS), and overall survival (OS) time.

Results: We collected data from a total of 45 patients with a median age of 68 years (range: 49-78 years). Approximately 20% of our patients presented with brain metastases, liver metastases, or both (9 cases), with pulmonary metastases being the most common at diagnosis (51.1%). This was followed by bone metastases (37.8%), lymph node involvement (26.7%), brain metastases (11.1%), and liver metastases (6.7%). Tumor progression was observed in 48.9% of patients, with the lungs being the most frequently affected organ. Among the 5 patients diagnosed with brain metastases, 40% (2 patients) were eligible for radiosurgery, while the remaining patients received whole-brain radiotherapy. Following first-line progression, only 20% of patients (9 patients) underwent subsequent chemotherapy. Mutation data were obtained using Next Generation Sequencing (NGS) techniques, revealing that 42% of tumors were negative for mutations, while 17% harbored KRAS mutations, and 4% had MET mutations. The median PFS for our population is 7 months (95% CI 0-14.3), and the median OS is 8 months (95% CI 4.2-11.8). Currently, 48.8% (22 patients) are still alive. The median PFS for adenocarcinoma and squamous cell carcinoma was 6 months (95% CI 3.3-8.7) and 5.3 months (95% CI 2.4-8.2), respectively. The median OS was 8 months (95% CI 3.5-12.4) and 6 months (95% CI 2-11.5), respectively.

Conclusions: The combination of chemo-anti-PD1 therapy shows promise in enhancing the survival outcomes of these patients. However, our study reveals that this patient population exhibits a higher tumor burden and is of more advanced age compared to the cohorts in pivotal trials. Moreover, only a minority of our patients were eligible for second-line treatment following disease progression. It is anticipated that with the expansion of patient cohorts in future studies, we will be able to better characterize this population and delineate specific strategies to improve current outcomes.

Keywords: Non-small cell lung cancer PD-L1-negative, overall survival, progression-free survival

P2.10B METASTATIC NON-SMALL CELL LUNG CANCER - CYTOTOXIC THERAPY - CYTOTOXIC CHEMOTHERAPY AND ADCS, SUNDAY, SEPTEMBER 8, 2024 - 18:15 - 19:45

P2.10B.08 Opportunities for ADC Development in 2L NSCLC Leveraging Predictive Biomarkers

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Introduction: Despite advances in 2L treatment options for metastatic Non-Small Cell Lung Cancer (mNSCLC), these have limited

benefits and substantial toxicity. The recent approval of Antibody-drug conjugates (ADCs) has spurred advancements in these treatments combining monoclonal antibodies with cytotoxic payloads. The complex structure of ADCs makes it critical to identify biomarkers that predict response.

Methods: A systematic review in LARVOL CLIN, an outcomes database of 100,000 trials, was conducted to identify trials comparing ADC versus non-ADC treatments in 2L+ mNSCLC. Predictive biomarkers of response to ADCs assessed in those trials were verified using LARVOL VERI, a precision oncology database.

Results: Four P2/3 trials comparing ADC to non-ADC treatments in 2L+ for mNSCLC have published outcome data (Table 1 and Image 1). DESTINY-Lung01 and DESTINY-Lung02 led to HER2-targeting trastuzumab deruxtecan (T-DXd) approval. TROP2-targeted datopotamab deruxtecan (Dato-DXd) tested in non-squamous NSCLC showed significant PFS over chemotherapy, but OS is pending final assessment. HER3-targeting patritumab deruxtecan (HER3-DXd) has been evaluated in HERTHENA-LUNG01 for EGFR-mutated NSCLC.

Table 1. LARVOL CLIN/VERI Trials summary - ADC vs non-ADCs in 2L+ for NSCLC.

T-DXd (Daiichi Sankyo, AstraZeneca - Marketed)

Dato-DXd (Daiichi Sankyo, AstraZeneca - Filed)

HER3-DXd (Daiichi Sankyo, Merck - Filed)

HER2; Deruxtecan; Cleavable

TROP2; Deruxtecan; Cleavable

HER3; Deruxtecan; Cleavable

DESTINY-Lung01; P2 (181)

DESTINY-Lung02; P2 (152)

TROPION-LUNG01; P3 (604)

HERTHENA-Lung01; P2 (420)

Intervention

T-DXd (N=49 - HER2 overexpressing, 6.4mg/kg; N=91- HER2-mutated, 6.4mg/kg)

T-DXd (N=102 - 5.4mg/kg; N=50 - 6.4 mg/kg)

Dato-DXd (N=299)

Dato-DXd (N=299)

Control

-

-

Doce (N=305)

-

Status

Active, not recruiting

Active, not recruiting

Active, not recruiting

Active, not recruiting

Primary Outcome

ORR

ORR

PFS, OS

ORR

OS HR (mOS, months)

- (11.3 (HER2-overexpressing, 6.4mg/kg) and 17.8 (HER2-mutated, 6.4mg/kg))

- (19.5 (5.4 mg/kg) and NR (6.4 mg/kg))

0.9 (12.4 vs 11)

- (11.9)

PFS HR (mPFS, months)

- (5.4 (HER2-overexpressing, 6.4mg/kg) and 8.2 (HER2-mutated, 6.4mg/kg))

- (9.9 (5.4 mg/kg) and 15.4 (6.4 mg/kg))

0.75* (4.4 vs 3.7)

- (5.5)

ORR (%)

24.5 (HER2-overexpressing, 6.4mg/kg)

49 (5.4 mg/kg) and 56 (6.4 mg/kg)

26.4 vs 12.8

29.8

CR (%)

1 (HER2-overexpressing, 6.4mg/kg)

1 (5.4 mg/kg) and 4 (6.4 mg/kg)

-

1

PR (%)

11 (HER2-overexpressing, 6.4mg/kg)

48 (5.4 mg/kg) and 52 (6.4 mg/kg)

-

66

* $p < 0.05$; NR: not reached

Biomarkers predicting response in NSCLC are emerging from the data for Dato-DXd and HER3-DXd. In the P1b TROPION-LUNG02 trial, Dato-DXd combined with pembrolizumab proved effective regardless of PD-L1 expression. HER3-DXd used in the presence of EGFR and HER2 mutations indicates its efficacy isn't dependent on wild-type HER3 heterodimerization. In contrast, HER2-targeting T-DXd response has yet to be accurately correlated with HER2. While T-DXd is effective in HER2 overexpressing NSCLC (DESTINY-Lung01), it showed superior efficacy in HER2-mutated NSCLC (DESTINY-Lung01/2).

Conclusions: Dato-DXd and HER3-DXd would be the first non-HER2-targeting ADCs approved for mNSCLC 2L+, targeting TROP2 and HER3, respectively. While T-DXd and HER3-DXd have been tested in HER2 and EGFR mutated cohorts, respectively, Dato-DXd use has not shown to be impacted by any specific biomarker. These results indicate the need to identify predictive biomarkers of response for improved patient population selection.

Keywords: antibody drug conjugates, biomarkers, NSCLC

P2.11A METASTATIC NON-SMALL CELL LUNG CANCER - IMMUNOTHERAPY - IMMUNOBIOLOGY, SUNDAY, SEPTEMBER 8, 2024 - 18:15 - 19:45

P2.11A.01 Racial/ethnic Differences in Real-World Adverse Events and Survival Among Patients on Immunotherapy for Advanced NSCLC

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Introduction: Incidence of immune-related adverse events (irAEs) has been linked to improved clinical outcomes among patients with advanced non-small cell lung cancer (advNSCLC) receiving immunotherapy (IO), but this trend may differ across racial/ethnic groups. Prior studies have also documented higher rates of irAEs among White patients relative to Latinx and Black patients, but were limited by single institution bias and/or small sample size. We examined associations between real-world adverse events (rwAEs) and survival by race/ethnicity in a large IO-treated advNSCLC cohort.

Methods: We used the nationwide Flatiron Health electronic health record (EHR)-derived de-identified database. Patients with advNSCLC who initiated IO between January 1, 2015 and October 31, 2023 were included. Real-world adverse events (diarrhea, kidney toxicity, liver toxicity, colitis, rash, adrenal insufficiency, hyperthyroidism, pneumonia, cough, dyspnea, hyperglycemia) occurring during IO treatment were extracted from unstructured clinician documentation in the EHR using machine learning. We employed Cox proportional-hazard models to assess racial/ethnic differences in rwAE incidence, and its association with survival outcomes, adjusting for age, sex, performance status, mono-/combination therapy, line of therapy, stage, and diagnosis year.

Results: The study cohort included 33,943 patients (3.4% Latinx, 10.3% non-Latinx [NL] Black, 2.1% NL-Asian, 67.0% NL-White patients, 17.0% Other/Unknown/Not documented). On average, Latinx (75.1%) and NL-Black (83.0%) patients were less likely than NL-White (85.0%) patients to have documentation of any of the selected rwAEs (adjusted Hazard Ratio [HR], 0.74; 95% CI, 0.69-0.79; HR, 0.90; 95% CI, 0.87-0.94 respectively), while incidence of any rwAE was similar for NL-Asian (85%) and NL-White patients (HR, 1.07; 95% CI, 0.99-1.16). In adjusted analysis, Latinx (HR, 0.90; 95% CI, 0.83-0.97), NL-Black (HR, 0.89; 95% CI, 0.86-0.93), and NL-Asian patients (HR, 0.79; 95% CI, 0.71-0.87) exhibited longer survival compared to NL-White patients. We observed similar trends for PFS, except for NL-Asian patients who had similar survival relative to NL-White patients (HR, 0.99; 95% CI, 0.91-1.08). Overall, presence of at least one rwAE was associated with better OS (HR, 0.46; 95% CI, 0.44-0.47) and PFS (HR, 0.63, 95% CI, 0.61-0.65). When stratified by race/ethnicity, the rwAE-survival benefit was similar among groups except for Latinx patients for whom we observed a smaller OS (HR, 0.84; 95% CI, 0.70-1.00) and no PFS (HR, 0.90; 95% CI, 0.76-1.07) benefit compared to NL-White patients.

Conclusions: Latinx, NL-Black, and NL-Asian patients exhibited fewer rwAEs and better survival outcomes relative to NL-White patients. Notably, within each race/ethnicity group, except Latinx, the presence of rwAEs conferred strong survival benefits. This study supports previous work demonstrating that equitable access to IO can mitigate survival inequities among patients with NSCLC and furthermore, underscores the importance of diversity in oncology IO trials. Future research should examine mechanisms underlying associations between adverse events and survival among racially/ethnically diverse patients receiving IO.

Keywords: racial differences in real world adverse events, immunotherapy, real world survival

P2.11A METASTATIC NON-SMALL CELL LUNG CANCER - IMMUNOTHERAPY - IMMUNOBIOLOGY, SUNDAY, SEPTEMBER 8, 2024 - 18:15 - 19:45

P2.11A.02 Proteomics-Based Target Identification for Optimizing Bispecific Antibody Use in NSCLC

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Introduction: Bispecific antibodies (BsAbs) are designed to bind two different antigens, redirecting and activating T cells against tumor cells, thus augmenting tumor cell elimination and treatment efficacy. BsAbs have attained approval as standard-of-care interventions for several malignancies, notably primary lung adenocarcinoma (LUAD). With the continued exploration of BsAbs in clinical trials targeting various tumor antigens, it is imperative to elucidate their specific targets to optimize drug development strategies tailored to LUAD.

Methods: We examined the expression of BsAbs targets in a cohort of 110 primary LUAD patients and 101 normal adjacent lung tissue controls in a prior study. BsAbs targets of interest in this study included MET, EGFR, EpCAM, PD-L1 (CD274), CTLA4, BCMA (TNFRSF17), TIGIT, HAVCR2, LAG3, HER2 (ERBB2), HER3 (ERBB3), DLL3, DLL4, VEGFR1 (FLT1), PSMA (FOLH1), B4GALNT1, ALK, CD226, PVR, PDCD1, CD3E, CD19, CD20 (MS4A1), IL3RA, TNFRSF8, CEACAM5. Proteomic analysis of these samples was performed using TMT 10-plex isobaric labeling coupled with LC-MS/MS. Protein abundance was assessed through TMT ratios relative to a common reference sample, and hierarchical clustering was employed to identify tumor subsets with similar BsAbs target expression profiles.

Results: After quality control of the proteomic data, the expression could be assessed for MET, EGFR, EPCAM, PD-L1, ERBB2, ERBB3, FLT1, PVR, CD3E, MS4A1, IL3RA, and CEACAM5. Hierarchical clustering robustly segregated tumors from normal lung tissue samples (Figure 1). Normal lung tissue was associated with increased expression of FLT1 isoform 1 as well as IL3RA. Tumor subsets clustered according to three distinct BsAbs proteomic profiles: 1) CEACAM5 overexpression, 2) MS4A1 with CD3E overexpression, and 3) B7H3, MET, or EPCAM overexpression. Mutual exclusivity was most notable between the overexpression of CEACAM5, MS4A1, and PDL1.

Conclusions: In conclusion, our proteomics-based evaluation identified actionable target signatures of LUAD for the application of existing BsAbs. Despite notable intertumoral heterogeneity, these profiles stratify into three predominant patterns of BsAbs target expression. Our findings underscore the significance of biomarker-guided strategies for effective BsAbs selection and the rationale for combinatorial BsAbs therapy in NSCLCs.

Keywords: Bispecific Antibody, Proteomics, NSCLC

P2.11A METASTATIC NON-SMALL CELL LUNG CANCER - IMMUNOTHERAPY - IMMUNOBIOLOGY, SUNDAY, SEPTEMBER 8, 2024 - 18:15 - 19:45

P2.11A.03 Association of LIPI with Patterns of Response, Resistance, and Survival in Patients with Metastatic NSCLC Treated with PD(L)-1 Blockade

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Introduction: While immune checkpoint inhibitors (ICIs) have revolutionized the treatment landscape for non-small cell lung cancer (NSCLC), a significant proportion of patients still experience primary resistance (PR) to PD-(L)1 blockade, and half of individuals eventually develop acquired resistance (AR) within 12-24 months after the initial response. Despite these challenges, predictors of resistance remain poorly understood. Recent insights have highlighted the role of persistent inflammation in resistance to PD-(L) 1 blockade. The Lung Immune Prognostic Index (LIPI), a novel and readily accessible score reflecting systemic host inflammation, has been identified as an independent adverse prognostic factor in patients with NSCLC undergoing ICI treatment. Therefore, LIPI may serve as a predictive tool for discerning response and resistance patterns in patients with NSCLC undergoing PD-(L)1 blockade therapy

Methods: This retrospective study included 153 patients with metastatic NSCLC treated with PD-(L)1 blockade alone or in combination with chemotherapy. We investigated the association between LIPI and primary resistance (PR), defined as progressive or stable disease lasting less than 3 months, and AR, characterized by an initial complete or partial response followed by disease progression. We further categorized AR into oligo-(≤3 distinct sites of progression) or systemic (>3 sites) resistance patterns. Additionally, we explored the patterns of response, distinguishing between long-term response (LTR) (≥24 months) and early progressive disease (progression ≤6 months), as well as progression-free survival (PFS) and overall survival (OS). We assessed the relationship between the LIPI and clinical outcomes using multiple logistic and Cox regression models.

Results: Based on the LIPI category, 50 patients (32.7%, [95% confidence interval [CI], 25.3 - 40.7%]) were classified as good risk, 68 (44.4%, [95% CI, 36.4 - 52.7%]) as intermediate-risk, and 35 (22.9%, [95% CI, 16.5 - 30.4%]) as poor-risk LIPI. Good-LIPI was significantly associated with LTR (adjusted odds ratio [aOR] 5.13, 1.36-19.33, p=0.015), AR (aOR 3.27, 1.34-7.97, p=0.001), and oligo-AR (aOR 3.51, 1.13-10.85, p=0.03). Similar positive associations for good-LIPI were observed for progression-free survival (PFS) (mPFS 12.4 months [95% CI 8.5 - 16.3], adjusted hazard ratio [aHR] 0.64, [95% CI, 0.43 - 0.96]; p=0.029) and overall survival (mOS 25.6 months [95% CI 19.8 - 31.4], aHR 0.48, [95% CI, 0.30 - 0.75]; p=0.002).

Conclusions: LIPI serves as a valuable predictive tool for discerning distinct response and resistance patterns to PD-(L)1 blockade and supports the negative role of systemic host inflammation in patients with ICI-based therapy. Further prospective studies are necessary to validate these findings.

Keywords: Lung Immune Prognostic Index, Acquired Resistance, Primary Resistance

P2.11A METASTATIC NON-SMALL CELL LUNG CANCER - IMMUNOTHERAPY - IMMUNOBIOLOGY, SUNDAY, SEPTEMBER 8, 2024 - 18:15 - 19:45

P2.11A.04 Exhaled Breath Biomarkers of Response to Immunotherapy in Advanced Non-Small Lung Cancer

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Introduction: Dynamic changes in cell-free DNA (cfDNA) may represent a biomarker of response to immune checkpoint inhibitor-based therapy (ICI) in non-small cell lung cancer (NSCLC). While the majority of plasma cfDNA is not tumour-related (circulating tumour DNA), exhaled breath is acellular and cfDNA within exhaled breath condensate (EBC) may be more representative of tumoural changes. We sought to explore the hypothesis that molecular response (MR) in cfDNA detected in EBC is associated with a clinical benefit to ICI+/- chemotherapy for participants with advanced NSCLC.

Methods: Participants due to commence ICI+/- chemotherapy for newly diagnosed advanced NSCLC were eligible. Patient demographics and tumour features were collected. Baseline EBC (R-TubeTM) and peripheral whole blood were collected from participants pre-treatment, and at 3, 6 and 12 weeks following commencement of systemic ICI+/-chemotherapy. The QIAamp Circulating Nucleic Acid kit (Qiagen) was used to extract cfDNA from all samples, while the RNaseP Real-Time digital droplet PCR assay was used to quantify cfDNA. MR was defined as >=50% reduction in cfDNA in EBC at 3 or 6 weeks following commencement of therapy. The association between MR in cfDNA of the

EBC and response to treatment at 3 months was assessed using standard statistical methods. Response to treatment was determined by clinician-assessed radiographic/clinical assessment at 3 months.

Results: At the time of this interim analysis, a total of 47 participants were enrolled with available EBC and response assessments. Four participants were excluded due to insufficient EBC (absence of baseline/follow-up EBC samples for analysis). The median age was 67 years (range: 48 - 81) , and 68% of (32/47) participants were male. The majority of participants (30/47, 63%) received ICI + chemotherapy which consisted mainly of pembrolizumab plus chemotherapy (28/30, 94%). The remainder (17/30, 27%) received pembrolizumab monotherapy. Amongst 43 evaluable participants, a MR was identified in 37% (16/43) at 3 and/or 6 weeks. In those with a MR, 81% (13/16) had a response to treatment at 3 months, while 19% (3/16) had clinical progression at this timepoint. Dynamics of cfDNA in the EBC in those who did not achieve an MR will be presented descriptively. Comparing the proportions of those with clinical benefit/progression in those with and without MR was associated with a trend towards significance (Chi2=3.28, p = 0.07).

Conclusions: In this interim analysis, we identify that dynamic changes in cfDNA are detectable in the exhaled breath condensate of participants with advanced NSCLC, treated with ICI+/-chemotherapy. Our interim results indicate a trend towards significance that a 'molecular response' in the exhaled breath at 3 weeks and/or 6 weeks[JN1] [DO2] is associated with a radiographic response at 3 months. Future work will focus on those who have clinical benefit but do not sustain an MR, completion of the analysis in a larger cohort (n=108) of participants, an analysis including blood-based circulating tumour DNA and longer clinical follow-up.

P2.11A METASTATIC NON-SMALL CELL LUNG CANCER - IMMUNOTHERAPY - IMMUNOBIOLOGY, SUNDAY, SEPTEMBER 8, 2024 - 18:15 - 19:45

P2.11A.05 The Impact of Tumor Molecular Features and Smoking History on Survival with Chemo-Immunotherapy in EGFR-Mutant NSCLC

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Introduction: Recent phase III trials evaluating anti-PD-1 with platinum-based chemotherapy in patients with EGFR-mutant NSCLC failed to demonstrate a significant improvement in progression-free survival versus (vs.) chemotherapy alone. While these studies were negative, there is a small subset of patients with EGFR-mutant tumors that derive durable benefit from chemo-immunotherapy. However, markers for predicting checkpoint inhibitor response in this patient population are lacking. Prior data from retrospective cohorts suggest the presence of uncommon EGFR alterations (e.g. G719X mutations, exon 20 insertions), high PD-L1, or a smoking history may be predictive of single-agent checkpoint inhibitor response in patients with EGFR disease. Limited research has been performed evaluating such markers in patients with EGFR-mutant NSCLC treated with chemo-immunotherapy. In addition, little attention has been given to the impact of TP53 alterations on the immunogenicity of EGFR-mutant NSCLC; a co-mutation correlated to greater benefit with checkpoint inhibitors in other oncogene-driven tumors. Our study used real-world data to determine real-world progression-free survival (rwPFS) in patients with EGFR-mutant NSCLC treated with chemo-immunotherapy and evaluated differences in outcomes by EGFR subtype, smoking history, tumor PD-L1 expression, and co-mutations in TP53.

Methods: The Flatiron Health-Foundation Medicine clinicogenomic database, a nationwide de-identified EHR-derived database linked to comprehensive genomic profiling, was used to evaluate patients with advanced NSCLC bearing EGFR alterations treated with pembrolizumab plus carboplatin/pemetrexed. The de-identified data originated from 280 US cancer clinics (~800 sites of care). Kaplan-Meier curves estimated rwPFS (based on clinician documentation of progression) and accounted for left truncation in cases where molecular profiling occurred after start of treatment. Median rwPFS in months (m) was determined and comparisons were assessed using univariate Cox regression.

Results: In our analysis of 127 patients with EGFR-mutant NSCLC treated with chemo-immunotherapy, median rwPFS (5.8 m, 95% CI 5.2-7.0) mirrored findings reported in prior phase III trials. Smoking history (yes vs. no), PD-L1 positivity (≥1% vs. <1%), and PD-L1 high (≥50% vs. <50%) were not predictive of greater rwPFS. However, patients with a tumor co-mutation in TP53 had longer rwPFS (6.6 m, 95% CI 5.5-8.4) as compared to patients without this mutation (4.3 m, 95% CI 3.0-7.8, p=0.02). In our cohort, 58 patients had tumors bearing exon 19 deletions, 45 had L858R mutations, and 24 had uncommon EGFR alterations. Uncommon alterations included exon 20 insertions, G719X, L861Q, or S768I mutations. Median rwPFS did not significantly differ between patients with exon 19 deletion (5.8 m, 95% CI 4.6-7.0) and L858R (5.4 m, 95% CI 4.7-10.2, p=0.68), and uncommon (8.4 m, 95% CI 2.8-15.8, p=0.69) alterations. Percent PFS at 12 m was similar for exon 19 deletion (19.1%), L858R (21.1%), and uncommon (22.6%) EGFR-mutant tumors.

Conclusions: Findings suggest that smoking history, the subtype of EGFR, and tumor PD-L1 expression do not aid in identifying patients with EGFR-mutant NSCLC that obtain greater benefit from chemo-immunotherapy. The co-occurrence of TP53 mutations in EGFR-driven disease warrants further study as a potential biomarker of immunotherapy response.

Keywords: EGFR, Checkpoint inhibitor, Real-World Data

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P2.11A.06 Tumor-Informed ctDNA Status Guiding 1st-line Immuno-Chemotherapy in Advanced NSCLC: CHOICE-01 Retrospective Analysis

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Introduction: Predictive biomarkers are needed to identify patients who are suitable for immune checkpoint inhibitors (ICIs) plus chemotherapy in treatment-naïve advanced non-small cell lung cancer (NSCLC). Circulating tumor DNA (ctDNA) status has the potential to indicate tumor burden and immunogenicity to select suitable patients.

Methods: From a randomized phase III trial of first-line toripalimab plus chemotherapy (ICI-chemo) versus chemotherapy in advanced NSCLC (the CHOICE-01 study), 393 patients with sequencing data of both pre-treatment cancerous tissue (whole-exome sequencing) and ctDNA (targeted capture panel) were included. Tumor-informed ctDNA positivity was defined as the presence of tissue-derived variants in plasma. In addition, dynamic ctDNA statuses for treatment efficacy of ICI-chemo of 91 patients were further evaluated at the first day of the third cycle (C3D1). The mechanisms were investigated between patients with tumor-informed ctDNA positivity or negativity.

Results: In the CHOICE-01 study, ICI-chemo prolonged progression-free survival (PFS, HR=0.45 [95% CI: 0.34-0.60], P<0.001) and overall survival (OS, HR=0.66 [95% CI: 0.49-0.88], P=0.0048) in patients with positive tumor-informed ctDNA rather than those with negative results (PFS, HR=0.74 [95% CI: 0.46-1.21], P=0.23; OS, HR=1.13 [95% CI: 0.58-2.23], P=0.72). The neoantigen, weighted Genome Instability Index (wGII), loss of heterozygosity (LOH), and ploidy were significantly increased in the ctDNA-positive group compared to the ctDNA-negative group (P<0.05). In the ICI-chemo arm, patients who had a positive status of tumor-informed ctDNA at baseline and achieved ctDNA clearance at C3D1 exhibited longer PFS and OS compared with those without clearance (P<0.05). Patients who were progressed from chemotherapy received ICI crossover showed longer OS than those received non-ICI crossover in the tumor-informed ctDNA positive group (P<0.05).

Conclusions: These results suggested that ICI-chemo was associated with improved outcomes compared with chemotherapy in patients with tumor-informed ctDNA positivity. Our study highlights the potential of tumor-informed ctDNA as a valuable tool in guiding first-line treatment decisions in advanced NSCLC patients.

Keywords: immune checkpoint inhibitors plus chemotherapy, predictive biomarker, tumor-informed ctDNA

P2.11A METASTATIC NON-SMALL CELL LUNG CANCER - IMMUNOTHERAPY - IMMUNOBIOLOGY, SUNDAY, SEPTEMBER 8, 2024 - 18:15 - 19:45

P2.11A.07 Selected Shared Neoantigens for Personalized Tumor Neoantigen Peptide Vaccine in the Treatment of Advanced Tumors

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Introduction: Tumor neoantigens are derived from immunogenic mutated epitopes that are specific to tumor tissue. Previous research has demonstrated that these neoantigens are highly individualized and heterologous, so immunotherapy based on neoantigens can be personalized. However, the development of neoantigen vaccines is time-consuming and labor-intensive. Furthermore, the complex condition of advanced tumors poses challenges in the application of individually tailored neoantigens. The discovery of shared neoantigens holds promise for the development of neoantigen vaccines. The purposes of this study were to investigate the feasibility to discover shared tumor neoantigens through panel gene sequencing form advanced tumor patiens to personalized neoantigen peptide vaccine.

Methods: Advanced tumor patients with panel gene sequencing results form 520-gene NGS panel and 680-gene NGS panel were eligible. Paired plasma, white blood cells and tumor biopsy tissue (if available) were obtained and tested by commercial vendors. Tumor neoantigens were selected by the binding affinity of mutant peptides to patient-specific HLA, with a threshold of less than less than 500 nM using ImmuneMirror. The correlations among TMB, bTMB, and total neoantigen load (TNN) were assessed by Pearson's corelation. Significance on patient survivals were analyzed by multivariate Cox regression models with significance set at P < 0.05.

Results: We recruited 115 lung cancer patients with panel gene sequencing data from 3 industrial venders. Total 85 tissue samples and 86 ctDNA were collected. A total of 17 mutant genes with mutation frequency greater than 10% were detected, with TP53 [Normally, mutation EGFRc.2573T>G (p.L858R) can be labelled as EGFRT2573G in the form of gene or EGFRL858R as a protein.] mutation frequency reaching 50% (520-gene NGS panel) and 57.3% (680-gene NGS panel). TMB, bTMB and TNN were highly correlated with each other. Three shared candidate neoantigens namely TP53c.818G>A (p.R273H), EGFRc.2573T>G (p.L858R), and KRASc.34G>T (p.G12C) were identified based on the both panel gene sequencing.

Conclusions: Tumor neoantigen prediction based on both independent gene panel sequencings proved to be feasible and reliable, particularly for shared neoantigens. This study opens the possibility of utilizing panel gene sequencing for neoantigen-based personalized immunotherapy. Notably, we identified TP53 p.R273H, KRAS p.G12C and EGFR p.L858R- derived neoantigens, which may improve prognostic evaluation and provide a promising treatment option for patients with resistance to conventional targeted therapy or immunotherapy.

Keywords: tumor neoantigen, circulating tumor DNA, NGS panel sequencing

P2.11A METASTATIC NON-SMALL CELL LUNG CANCER - IMMUNOTHERAPY - IMMUNOBIOLOGY, SUNDAY, SEPTEMBER 8, 2024 - 18:15 - 19:45

P2.11A.08 Molecular and Immunological Features Associated with Long-Term Benefit in Metastatic NSCLC Patients Undergoing Immune Checkpoint Blockade

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Introduction: Immunotherapy is firmly established as a treatment regimen in various solid tumors, driven by its exceptional benefits in a selected group of patients. Despite widespread adoption of immune checkpoint blockade (ICB) across diverse solid tumors, the quest for a clinically informative biomarker for long-term benefit remains unmet.

Methods: A total of 49 patients with metastatic NSCLC treated with ICB were included. Long-term (LTR) and short-term responders (STR) were defined as those with a response to ICB lasting more than 24 months or less than 6 months, respectively. Longitudinal blood specimens were collected before ICB treatment initiation and early-on treatment. Plasma ctDNA next-generation sequencing panel (NGS) and serum proteomics were performed. GeoMx DSP on baseline tumor tissue was performed in a subset of patients.

Results: Our analysis revealed specific characteristics of LTR compared with STR, namely higher PD-L1 in tumor cells (p=0.005) and higher incidence of irAEs (p=0.001). Genomic features associated with lack of benefit from ICB included co-occurring mutations in KRAS/STK11 and TP53/KMT2D (p<0.05). At a baseline LTR patients exhibited higher serum levels of proteins related with apoptosis (CASP8, PRKRA), chemotaxis, immune proteasome, processing of MHC class I (S100A4, PSMD9, RNF41) and immune homeostasis (HAVCR1, ARG1) (p<0.05). Protein spatial profiling of tumor samples showed higher levels of proteins linked with the presence of immune cells (CD45), T cells (CD8), antigen presentation (HLA-DR) and immune regulation proteins (PD-L1, IDO1) within the tumor and tumor microenvironment (p<0.05) in LTR patients. Serum longitudinal analysis identified a set of proteins that presented distinct dynamics in LTR compared to STR, making them interesting candidates to evaluate as early predictors of treatment efficacy.

Conclusions: Our multimodal analysis of patients with metastatic NSCLC treated with ICB identified clinicopathological and immunological features associated with long-term benefit. The presence of pre-existing antitumor immunity emerged as a strong predictor of long-term benefit providing insights for potential biomarkers and therapeutic strategies for enhancing ICB outcomes in metastatic NSCLC.

Keywords: Long-term responders, Digital spatial profiling, Serum proteomics

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P2.11A.09 Survival Outcomes of Lung Adenocarcinoma with Intestinal Differentiation in the Era of Immunotherapy

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Introduction: Lung adenocarcinoma with intestinal differentiation (LAID) comprises a rare and heterogeneous non-small cell lung carcinoma subgroup. LAID can display distinct morphological patterns including mucinous, enteric, and colloid. In the era of chemotherapy, LAID have been associated with a poorer prognosis compared to other lung adenocarcinomas. However, outcome data for these tumors compared with other adenocarcinomas is unknown in the immunotherapy era. Leveraging the National Cancer Database (NCDB), which includes data for approximately 70% of lung cancers diagnosed in the United States, we compared survival outcomes of LAID to other lung adenocarcinoma (LUAD) subtypes based on treatment type in the modern era.

Methods: The National Cancer Database (NCDB) was queried for histologically confirmed stage IV adenocarcinoma patients diagnosed from 2016 to 2019. LAID was defined as invasive mucinous adenocarcinoma, colloid adenocarcinoma, or enteric adenocarcinoma according to the 2015 WHO lung cancer classification. A log-rank test was used for survival analysis and adjusted by Cox multivariate regression for age, gender, race, disease grade, treating facility type, insurance status, and comorbidity. Overall survival (OS) was defined as the time from the treatment initiation date to the date of death or the last follow-up. P < 0.05 was considered to be statistically significant. All statistical tests performed were two-tailed.

Results: A total of 52,393 patients were identified, including 51,355 LUADs and 1,038 LAIDs (729 colloid adenocarcinoma, 300 invasive mucinous adenocarcinoma and 9 enteric-type adenocarcinoma). 7.5% of LAID patients received immunotherapy alone, 48% received chemoimmunotherapy combination, and 45% of patients received chemotherapy alone. Compared with LUAD, LAID had significantly shorter overall survival (median = 13.45 months vs median = 10.18 months, HR 1.22 95% CI [1.14 - 1.31], respectively). LAID was associated with poorer survival compared to other adenocarcinomas across all treatment regimens (immunotherapy alone: HR 1.38, 95% CI [1.04 - 1.84] chemoimmunotherapy combination: HR 1.19, 95% CI [1.07 - 1.34], and chemotherapy alone: HR 1.21, 95% CI [1.08 - 1.35]). Among LAID,

chemoimmunotherapy combination is associated with improved survival compared to chemotherapy alone (HR 0.77, 95% CI [0.66 - 0.90]). The sample size of patients LAID patients receiving immunotherapy alone was small and thus underpowered to draw conclusions (HR 0.87, 95% CI [0.65- 1.18]) compared to chemotherapy alone.

Conclusions: Our study represents the first time the NCDB has been leveraged to compare outcomes of LAID versus LUAD in the era of immunotherapy. Compared with other LUAD, LAID remains associated with poorer survival in the era of immunotherapy. However, combined chemoimmunotherapy appears to be associated with improved survival compared to chemotherapy alone in this rare subgroup.

Keywords: lung adenocarcinoma, intestinal differentiation, immunotherapy

P2.11A METASTATIC NON-SMALL CELL LUNG CANCER - IMMUNOTHERAPY - IMMUNOBIOLOGY, SUNDAY, SEPTEMBER 8, 2024 - 18:15 - 19:45

P2.11A.10 Impact of Baseline Glucocorticoid Use on the Efficacy of Immunoradiotherapy in NSCLC Patients with Brain Metastases

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Introduction: Glucocorticoids (GCs) plays an important therapeutic role for the cerebral edema due to radiative acute brain injury or brain metastases, but it also poses negative impact on the efficacy to immunotherapy. Our study focuses on the patients with NSCLC brain metastases treated by immunotherapy combined with intracranial radiotherapy and analyses the influence of different doses of baseline GCs use on the control of intracranial lesions, PFS and OS of the patients.

Methods: 62 patients with NSCLC brain metastases who received immunotherapy combined with intracranial radiotherapy (interval between immunotherapy and intracranial radiotherapy is less than 28 days) were collected, all of whom had received baseline (28 days before and after the first cycle of immunotherapy) GCs during concurrent therapy. The patients were divided into three groups according to the purpose of GCs administration (low GCs use: receiving GCs doses less than 30mg; median GCs use: receiving GCs doses greater than or equal to 30 mg and less than 100 mg; high GCs use: receiving GCs doses greater than or equal to 100 mg). Survival outcomes (iPFS, PFS and OS) were analyzed and Propensity score matching (PSM) was used to balance the variables that were significantly different at baseline in different groups of dose stratification of GCs.

Results: The median iPFS of patients in the group of high GCs use was significantly shorter than the group of median GCs use and low GCs use (5.23 months vs 12.70 months vs 16.43 months, p<0.001). However, there was no significant difference between the group of median GCs use and the group of low GCs use in their median iPFS (12.70 months vs 16.43 months, p=0.362). As for median OS and median PFS among the three groups of patients, we observed results consistent with median iPFS. The propensity score matching proved that the group of high GCs use still had significant differences in median iPFS (5.23 months vs 8.93 months, p=0.023), median PFS (4.33 months vs 8.10 months, P=0.046) and median OS (7.47 months vs 14.63 months, P=0.033) comparing with the patients of median GCs use and low GCs use (Figure1).

Conclusions: The application of GCs often increased in patients with NSCLC brain metastases receiving immunotherapy combined with intracranial radiotherapy and the baseline high dose GCs use (GCs≥100mg) will reduce the efficacy of the combination therapy and impair the survival outcomes.

Keywords: NSCLC brain metastases, Immunoradiotherapy, Glucocorticoids

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P2.11A.11 Impact of Proton Pump Inhibitor Use on Faecal Microbiome in Patients with NSCLC Treated with Immune Checkpoint Inhibitor

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Introduction: Emerging data suggests that concomitant medications, such as proton pump inhibitors (PPI) influence immune-related adverse events (irAE) and the host gut microbiome. We aim to study the microbiome taxonomic and functional features associated with PPI and development of irAE in patients with non-small cell lung cancer (NSCLC) treated with ICI-based therapy.

Methods: Stool samples were obtained from patients with Stage III or IV NSCLC treated with ICI from September 2016 to August 2023. DNA from stool samples was extracted using FastDNA Spin Kit (MP-Biomedicals). Metagenomic libraries were constructed using TruSeq3 (Illumina) and sequenced on NovaSeq6000 2x 150PE platform (Illumnia), targeting ~2.5Gb of sequences per aliquot. Metagenomic taxonomic and functional profiles were generated using the bioBakery meta'omic workflow v4. IrAEs were characterized and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v5.

Results: Of the 36 patients enrolled, the median age was 63 years, the majority male (86.1%), Chinese (83.3%), smokers (83.3%), ECOG PS 0-1 (52.8%), stage IV at diagnosis (72.2%), and adenocarcinoma histology (77.8%). PD-L1 TPS was ≥50% in 41.7% of patients. Nineteen percent of patients had concomitant chemotherapy with ICI. The commonest ICIs used were pembrolizumab (55.6%), durvalumab (22.2%) and atezolizumab (13.9%). Half of the patients developed irAEs, of which skin (30.6%), liver (11.1%), endocrine (8.3%) and pulmonary toxicities (8.3%) were the commonest. Some 58% of patients (n=21) received PPI whilst on ICI with two-thirds of patients on PPI (n=14) subsequently developing irAEs. PPI use was associated with occurrence of irAE (OR 5.5 (95%CI 1.28 - 23.7, p=0.02). Stool analysis identified 13 and 8 significant microbial species, as well as 35 and 86 microbial enzymes associated with PPI use and subsequent irAE, respectively. Of note, both the use of PPI and subsequent irAE were associated with increased abundance of Collinsella sp (i.e. SGB4121) and decreased abundance for microbial potential for tropinesterase (EC 3.1.1.10).

Conclusions: Use of PPI was associated with IrAE and resulted in gut microbiome dysbiosis. To our knowledge, this is the first study to describe the association between PPI, irAE and faecal microbiome changes. Future larger studies with longitudinal sampling are required to study the impact of PPI on outcomes of NSCLC patients on ICI.

Keywords: Proton pump inhibitors, Stool microbiome, Immune related adverse events

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P2.11A.12 Machine Learning-Based Clinicogenomic Prediction of Response to PD-(L)1 Inhibition in KRAS Altered Non-Small Cell Lung Cancer

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Introduction: KRAS altered non-small cell lung cancer (NSCLC) is characterized by comutations which confer differential sensitivity to immune checkpoint inhibitors (ICI). Further studies are needed to disentangle the predictive effects of known biomarkers and to identify novel biomarkers to help guide treatment selection.

Methods: Patients with EGFR/ALK-negative metastatic NSCLC who received PD-(L)1 inhibitor therapy at three institutions were included, and patients with (KRASa) and without (KRASwt) KRAS alterations (mutations and amplifications) were analyzed separately. Clinical progression-free survival (PFS) and overall survival (OS) were compared between patients with previously untreated metastatic PDL1+ NSCLC and ECOG 0-1 who received ICI alone (ICI-mono) or with chemotherapy (ICI-chemo). Inverse propensity weighting (IPW) for clinical characteristics was used to control for differences in treatment selection. Among patients with complete clinical and genomic annotation, we trained elastic-net regularized logistic regression models to predict complete or partial response from stable or progressive disease. An 80/20 split was used to separate the training and testing cohorts. Repeated (n=10) stratified 10 fold cross-validation was performed to optimize hyperparameters for area under the receiver operating characteristic curve (AUROC).

Results: A total of 3864 patients (51% female, median age 67, KRASa 1652, KRASwt 2212) were identified. Among KRASa patients, those treated with ICI-chemo vs ICI-mono had similar PFS but worse OS (unadjusted: HR=1.1, p=0.018, IPW-adjusted: HR=1.5, p=1.4e-7) in unadjusted and IPW-adjusted analysis. Among KRASwt patients, those treated with ICI-chemo had increased PFS on unadjusted (HR=0.8, p=0.088) and adjusted analysis (HR=0.5, p=0.0033), whereas OS was increased on IPW-adjusted (HR=1.3, p=0.00098) but not unadjusted analysis. Next, we developed integrated clinico-genomic models that outperformed PDL1 in predicting response to ICI (KRASa: AUROC 0.65 vs 0.54; KRASwt: AUROC 0.74 vs 0.64). In both models, features predictive of response were PDL1>=50%, TMB>50th percentile, ICI-chemo treatment, and TP53 alterations; features predictive of non-response were ECOG>=2 and higher line of therapy. In the KRASa model, alterations in NTRK3, KIT, TP53 were predictive of response while alterations in KEAP1, STK11, and SMARCA4 were predictive of non-response. In the KRASwt model, alterations in WT1 were predictive of response and PDL1<1% was predictive of non-response. Among previously untreated patients with ECOG<2 and co-occurring alterations in KRAS and STK11, PFS and OS were improved among patients with alterations in NTRK3 (PFS: HR=0.5, p=0.035; OS: HR=0.5, p=0.047) and KIT (PFS: HR=0.3, p=0.027; OS: HR=0.3, p=0.056).

Conclusions: In this study, we found that among PDL1+ patients, treatment with PD-(L)1 monotherapy versus in combination with chemotherapy was associated with improved OS regardless of KRAS status, but improved PFS in patients without but not with KRAS alterations. Additionally, we developed models to predict response to ICI which outperformed PDL1, and identified independently predictive biomarkers of response to ICI therapy in patients with and without KRAS alterations.

Keywords: KRAS, Immunotherapy, Biomarkers

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P2.11A.13 Cytokine Release Syndrome from Dual Immune Checkpoint Blockade in Non-Small Cell Lung Cancer: FAERS Analysis

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Introduction: Combining immune checkpoint blockade (ICB) agents mainly targeting PD-1/PD-L1 and CTLA-4 has been established as a standard of care for several cancer types including non-small cell lung cancer (NSCLC). Cytokine release syndrome (CRS) rarely occurs with ICB monotherapy but recent studies suggest CRS may arise in a particular population receiving dual ICB in NSCLC. This study aims to comprehend the clinical characteristics of CRS from dual ICB therapy.

Methods: We searched the US Food and Drug Administration Adverse Events Reporting System (FAERS) using the term "Cytokine release syndrome" to identify CRS cases with NSCLC treated with ICB labeled as "suspect product active ingredients". Clinical and demographic characteristics were analyzed and compared between the dual ICB and the ICB monotherapy group using Fisher's exact test. We also performed a systematic review to elucidate the clinical factors of CRS associated with dual ICB, including patient characteristics, timing of the CRS onset, levels of C-reactive protein (CRP) at the onset of CRS, and treatment details such as the dose of glucocorticoid and other immunosuppressants.

Results: In the FAERS database, 8615 CRS cases were analyzed, and 195 solid tumor cases of CRS associated with ICB were identified. Among these cases, 81 patients were diagnosed with NSCLC (Dual ICB: n=58, ICB monotherapy: n=23). In the dual ICB group, the median age was 68 years (Interquartile range [IQR] 61-75) and 41 patients (70.7%) were male. In the ICB monotherapy group, the median age was 69 years (IQR 64-71) and 12 patients (52.2%) were male. In the dual ICB group, 67.2% (n=39/58) and 32.8% (n=19/58) of patients received dual ICB alone and dual ICB with chemotherapy, respectively. In the ICB monotherapy group, PD-1 and PD-L1 blockade were used in 60.9% (n=14/23) and 39.1% (n=9/23). In 85 patients with NSCLC, most of the CRS cases came from Asia for both dual ICB (96.6%, n=56/58) and ICB monotherapy (56.5%, n=13/23). For treatment outcomes of CRS, our systematic review identified 12 articles comprising 15 with solid tumors with clinical course of CRS. In 15 cases, NSCLC was most common (66.7%, n=10/15). The median age of patients with NSCLC was 67 years (IQR 55-70). Median onset of CRS in NSCLC was 47.5 days (IQR 22.5-90.25) after dual ICB therapy, and median CRP levels at the CRS onset were 12.6 mg/dL (IQR 10.4-15.1). Excepting two cases where patients died soon after dual ICB therapy, all patients required high or pulse-dose glucocorticoids, and one case required tocilizumab administration.

Conclusions: This pharmacovigilance study found that CRS from ICB occurs in patients with NSCLC predominantly from Asia, particularly with dual ICB, which merits further investigation on risk factors and immune homeostasis in these patients. Most cases required pulse-dose glucocorticoids and thus, establishment of early detection and treatment strategies is needed.

Keywords: Immunotherapy, Non-small cell lung cancer, Cytokine release syndrome

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P2.11A.14 Research of the Predictive Role of Immune Cells and Intestinal Flora on Immune-related Adverse Event in Lung Cancer

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Introduction: Immune checkpoint inhibitors (ICIs) have opened a new direction in the treatment of unresectable advanced lung cancer by targeting tumour cells through the immune system. However, use of ICIs disrupts the normal mechanisms of immune tolerance, leading to immune-related adverse event (irAE), which carries the risk of drug discontinuation, drug switching, and deterioration of the patient's condition. It is necessary to find effective biomarkers for predicting irAE in lung cancer patients.

Methods: Unresectable primary stage III-IV lung cancer patients who were treated with at least one of the ICIs and attended the Second Affiliated Hospital of Dalian Medical University from 01 May 2021 to 30 September 2023 were included. Peripheral blood and stool samples were collected at baseline (before receiving the first treatment) and before receiving each cycle of treatment. Peripheral blood immune cells were tested using flow cytometry. Stool samples were tested through metagenomics and untargeted metabolomics. Treatment efficacy and irAE during treatment were assessed.

Results: A total of 88 patients were included, with 41 in the group developing irAE. The median onset time of irAE was 118 days. 1. Characteristics of the peripheral blood immune cells in patients with irAE: (1) patients who developed irAE had a higher percentage of baseline CD8+ T cell PD-1 expression compared to patients who did not develop irAE. (2) patients who developed irAE had lower peripheral blood B-cell counts and higher percentage of activated CD4+ T cells, activated CD8+ T cells, early activated CD8+ T cells, late activated helper T cells, late activated suppressor T cells and Th2 cell when developing irAE compared to baseline. 2. Characteristics of the intestinal flora of patients with irAE: the most significantly enriched groups of flora at baseline in the patients who developed irAE (Group N) was Micrococcus, while the group that did not develop irAE(Group NI) was enriched with Phocaeicola coprocola and Oscillibacter. There were significant differences in baseline gut flora metabolites and metabolic pathways between patients with or without irAE. Calcitriol and L-Isoleucine may serve as a biomarker that is predictive of the development of irAE (Figure 1).

Conclusions: In lung cancer patients who developed irAE after immunotherapy, baseline peripheral blood immune cells and intestinal flora differed from those who did not develope irAE and changed significantly during progression of irAE, and monitoring changes in these indicators may help to predict irAE and guide better treatment.

Keywords: lung cancer, immunotherapy, immune-related adverse event

P2.11A METASTATIC NON-SMALL CELL LUNG CANCER - IMMUNOTHERAPY - IMMUNOBIOLOGY, SUNDAY, SEPTEMBER 8, 2024 - 18:15 - 19:45

P2.11A.15 Gut Metatranscriptomics Predict Survival in Anti-PD Immunotherapy Treated Advanced-Stage Non-Small Cell Lung Cancer

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Introduction: Emerging evidence highlights the gut microbiome's role in modulating the efficacy of anti-programmed death (PD) immunotherapies (ICI) in different cancers. However, more knowledge is needed to understand their functional activity using metatranscriptomics (MTR). We aim to analyze the association between the gut microbiome MTR signatures and ICI treatment outcomes in advanced-stage non-small cell lung cancer (NSCLC) patients.

Methods: We applied a De Novo Assembly-based MTR analysis on fecal samples from 29 advanced-stage NSCLC patients who received anti-PD ICI therapy. We categorized patients based on progression-free survival (PFS) into long (>6 months) and short (≤6 months) PFS groups. Through RNA sequencing, we employed the Trinity pipeline for assembly, MMSeqs2 for taxonomic classification, and DESeq2 for differential gene expression (DEG) analysis. We constructed principal component analysis (PCA), Random Forest (RF), and Support Vector Machine (SVM) machine learning algorithms and comprehensive microbial profiles. Clinicopathological variables such as Age, Gender, Histology, PD-L1, Stage, Smoking pack year (PY), Chronic obstructive pulmonary disease (COPD) comorbidity, and Body Mass Index (BMI) were included as clinical confounders.

Results: We identified 7849 protein-coding gene transcripts. Significant microbial composition variances were observed between the two PFS groups. Notably, Actinomycetota was significantly overrepresented in patients with short PFS (vs. long PFS, 36.7% vs. 5.4%, p<0.001), as was Euryarchaeota (1.3% vs. 0.002%, p=0.009). At the same time, Bacillota showed higher prevalence in the long PFS group (vs. short PFS, 66.2% vs. 42.3%, p=0.007). The 120 significant DEGs identified were analyzed using the UniProtKB and UniRef90 databases to determine their functional annotations and potential protein matches. A cluster analysis of the top 120 protein-coding transcripts revealed a subgroup of patients showing a homogeneous profile associated with longer PFS and another, more heterogeneous group associated with shorter PFS. This finding was further confirmed using PCA, which separated the PFS groups. We confirmed the predictive role of n=6 Trinity IDs with multivariate analysis, including Bacterial surface antigen and domain-containing proteins. RF and SVM machine learning models verified the microbial signatures' predictive effect with accuracies of 78.1% and 75.6%, respectively. Furthermore, multivariate analyses incorporating clinical variables, including PD-L1 expression and chemotherapy treatment, underlined the impact of multiple RNA-based microbial biomarkers on PFS.

Conclusions: Specific gut microbiome MTR signatures predict survival in ICI-treated advanced NSCLC. Specific gene clusters and species' MTR gene expression might differentiate short vs. long PFS. Our data warrant further research to validate these MTR associations and explore their clinical implications.

Keywords: Immunotherapy, Gut microbiome, Progression-free survival

P2.11A METASTATIC NON-SMALL CELL LUNG CANCER - IMMUNOTHERAPY - IMMUNOBIOLOGY, SUNDAY, SEPTEMBER 8, 2024 - 18:15 - 19:45

P2.11A.16 Categorizing Steroid-Response Types in Checkpoint Inhibitor-Related Pneumonitis

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Introduction: Glucocorticoids (GCs) are the first-line treatment of checkpoint inhibitor-related pneumonitis (CIP). However, there is a large heterogeneity in the response efficiency to GCs in different CIP patients, and its efficacy assessment requires enhancement. Herein, based on the effectiveness of GCs at different times, we proposed a novel steroid-response typing of CIP and explored their different characteristics.

Methods: In this retrospective cohort study, we analyzed 98 CIP patients, categorizing them as steroid-sensitive, refractory, dependent, or resistant based on GC efficacy. We explore the incidence and interplay of these types and associated features, including clinical characteristics, cytokine levels, immune-cell counts, and autoantibody levels.

Results: In this study, 80 patients (81.6%) showed steroid-sensitive status, and 18 (18.4%) were steroid-refractory. Among those with three-month follow-ups, 42.5% of steroid-sensitive patients relapsed without ICI stimulation; 66.7% were steroid-dependent, and 33.3% were steroid-resistant. Steroid-refractory patients had three patients relapses: one steroid-dependent and two steroid-resistant. Both steroid-refractory and -resistant types had higher CIP severity and poorer performance status when they began to use immunotherapy (P < 0.050) than sensitive and dependent groups. Steroid-resistant cases had more combined other immune-related adverse events (P =

0.030) than steroid-dependent types. Cytokine analysis showed higher IL-8 in steroid-resistant CIP (58.4 vs. 18.9 pg/mL, P = 0.034), and steroid-refractory patients had lower CD4+ T-cell counts (70.0 vs. 181.0 /UL, P = 0.023). However, there was no significant difference in autoantibody levels among different steroid types. Lastly, steroid-refractory and -resistant patients tended to have shorter overall survival than steroid-sensitive or -dependent cases.

Conclusions: CIP steroid-response categorization includes four types: sensitive, refractory, dependent, and resistant. Refractory and resistant types exhibit higher mortality rates and shorter survival. Severe grades of CIP, concurrent irAEs, peripheral blood IL-8, and T-cell counts are related to steroid-response types.

Keywords: checkpoint inhibitor-related pneumonitis, glucocorticoid, efficacy

P2.11A METASTATIC NON-SMALL CELL LUNG CANCER - IMMUNOTHERAPY - IMMUNOBIOLOGY, SUNDAY, SEPTEMBER 8, 2024 - 18:15 - 19:45

P2.11A.17 Impact of Mutation Class and Smoking Status in BRAF-Mutant Non-Small Cell Lung Cancer (NSCLC) Treated with Immune Checkpoint Inhibitors (ICI)

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Introduction: Oncogenic BRAF mutations are found in ~4% of NSCLC. These mutations are subdivided into class I and non-class I (i.e., class II and III) and are frequently associated with smoking. We previously reported the efficacy of frontline ICI in the treatment of BRAF-mutant NSCLC. It is unclear, however, if the mutation class and/or smoking status impact the response and outcomes to therapy.

Methods: We conducted a retrospective analysis of individuals with BRAF-mutant NSCLC using next-generation sequencing or genotyping methods from January 1, 2012 through August 4, 2023. Patient demographics, smoking status, and disease stage were collected through electronic medical record review. PD-L1 expression (22C3 or SP263) was also assessed. Overall survival (OS) and progression-free survival (PFS) were calculated using the Kaplan-Meier method with log-rank test. A p-value ≤0.05 was considered significant.

Results: Among 110 individuals with BRAF-mutant NSCLC, 54% were females (n=59), 92% were white (n=101), 95% had adenocarcinoma (n=104), 82% were current/former smokers (n=90), 51% had non-class I (n=25 class II, n=31 class III), 75% had PD-L1 ≥1%, and 57% had PD-L1 ≥50%. There were 88 evaluable individuals with advanced disease treated with systemic therapy: 49 received frontline ICI, 19 received chemotherapy, and 20 received targeted therapies (e.g., anti-BRAF/MEK). Among those treated with frontline ICI, there were no significant differences in PFS between class I and non-class I (9.2 vs. 10.8 months, respectively; p 0.53); however, there was a trend towards improved OS for class I versus non-class I (42.6 vs. 18.5 months; p 0.28). Current/former smokers had significantly better PFS than never-smokers, while never-smokers with class I mutations had significantly better OS compared to those with non-class I (Table 1). Current/former smokers with non-class I mutations and no brain metastasis also had an improved OS compared to their never-smoker counterparts (24.6 vs. 8.8 months, respectively; p 0.024). There was an improved OS among individuals with PD-L1 ≥1%, current/former tobacco users, or those with class I mutations treated with frontline ICI compared to chemotherapy. PFS was also significantly better for those with non-class I mutations, current/former smokers, and there was a trend towards improved OS amongst never-smokers (Table 2).

Conclusions: Individuals with BRAF mutations treated with frontline ICI had improved OS and PFS compared to those treated with chemotherapy. OS benefit was particularly pronounced for never-smokers and for those with class I mutations.

Keywords: Immunotherapy, BRAF Mutations, Non-small Cell Lung Cancer

P2.11A METASTATIC NON-SMALL CELL LUNG CANCER - IMMUNOTHERAPY - IMMUNOBIOLOGY, SUNDAY, SEPTEMBER 8, 2024 - 18:15 - 19:45

P2.11A.19 Invasive Lymph Node Patterns and Prognosis in Lung Adenocarcinoma

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Introduction: Tumor-draining lymph nodes (TDLNs) are usually the first station of tumor metastasis in lung cancer. TDLNs+ have distinct pathomorphologic and tumor microenvironment (TME)-compositional patterns, which still need to be thoroughly investigated in lung adenocarcinoma (LUAD).

Methods: Here, we enrolled 312 LUAD patients with TDLNs+ from our institution between 2015 and 2019. 3DHISTECH was used to scan all of the TDLNs+. Based on morphologic features, TDLNs+ patterns were classified as polarized-type or scattered-type, and TME-compositional patterns were classified as colloid-type, necrosis-type, specific-type, and common-type.

Results: Multivariate analysis revealed an increased risk of early recurrence associated with scattered-type (HR 2.37, 95%CI:1.06-5.28), colloid-type (HR 1.95, 95%CI:1.03-3.67), and necrosis-type (HR 2.21, 95%CI:1.13-4.89). NanoString transcriptional analysis revealed an immunosuppression and vascular invasion hallmark in scattered and necrosis patterns and an immunoactivated hallmark in polarized and common patterns. According to imaging mass cytometry (IMC), the scattered and necrosis patterns revealed that germinal centers (GC) were compromised, GCB cell and T cell proliferation were deficient, tumor cells had the potential for proliferation, and the immune attack may be weaker.

Conclusions: In this study, we present evidence that LUAD patients have distinct patterns and immune hallmarks of TDLNs+ related to their prognosis.

Keywords: lymph node metastasis, pathomorphologic pattern, lung adenocarcinoma

P2.11A METASTATIC NON-SMALL CELL LUNG CANCER - IMMUNOTHERAPY - IMMUNOBIOLOGY, SUNDAY, SEPTEMBER 8, 2024 - 18:15 - 19:45

P2.11A.20 Metformin Enhances Immune Checkpoint Inhibitor Response in Overweight Lung Cancer Patients: A Retrospective Cohort Study

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Introduction: Metformin has shown potential benefits in conjunction with immune checkpoint inhibitors (ICIs) in preclinical studies. However, the results from retrospective clinical studies and prospective trials for non-small cell lung cancer (NSCLC) are inconsistent. We aimed to investigate whether metformin's efficacy varies based on patients' body mass index (BMI).

Methods: We conducted a retrospective review of NSCLC patients treated with ICIs between 2015-2023. Patient response was assessed using Recist 1.1 coding and chart review to determine progression-free survival (PFS). Patients were categorized based on BMI into overweight (BMI ≥ 25) and non-overweight (BMI < 25) groups. Cox proportional hazards modeling was used to evaluate univariate and multivariable PFS with metformin. Multivariable analysis was adjusted for age, sex, smoking status, histology, and first-line regimen.

Results: In the final cohort (n=480; overweight = 292, non-overweight = 187), a higher proportion of overweight patients had a history of regular metformin use compared to non-overweight patients (22% vs. 11%, p = 0.003). Univariate analysis revealed a trend towards better PFS among metformin users in the overweight group (Hazard Ratio [HR] = 0.68; 95% Confidence Interval [CI] = 0.457 - 1.011, p = 0.057), whereas the opposite trend was observed in the non-overweight group (Figure 1). Multivariable analysis showed significantly improved PFS for patients with history of metformin use, as compared to those without (HR = 0.629, 95% CI = 0.418 - 0.947, p = 0.027) (Table 1).

Conclusions: We demonstrate that combining metformin with ICI may enhance PFS in overweight but not in non-overweight NSCLC patients. These findings suggest that BMI could serve as a predictive factor for the response to ICI therapy in patients receiving metformin. They also offer guidance for patient selection in clinical trials investigating metformin in NSCLC, with a particular focus on overweight/obese individuals.

Keywords: Metformin, Immune Checkpoint Inhibitor, BMI

P2.11A METASTATIC NON-SMALL CELL LUNG CANCER - IMMUNOTHERAPY - IMMUNOBIOLOGY, SUNDAY, SEPTEMBER 8, 2024 - 18:15 - 19:45

P2.11A.21 CCL4 Attenuated the Efficacy of Immunotherapy via Regulating the Phenotype and Function of Treg in EGFR-TKI Resistant NSCLC

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Introduction: The efficacy of immune checkpoint inhibitors (ICI) in advanced NSCLC patients with sensitive EGFR mutation was controversial. Our previous study demonstrated that those with acquired resistance to EGFR-TKI responded worse to ICIs, but the mechanism is unclear.

Methods: Advanced NSCLC patients with resistance to EGFR-TKIs and received ICI treatment from January 2016 to June 2021

were retrospectively analyzed. single cell sequencing and flow cytometry were conducted to explore the cell components in tumor microenvironment. In vitro experiments were carried out to clarify the efficacy of CCL4 regulating the phenotype and function of Tregs. Western blot, RT-PCR, flow cytometry and co-culture system were adopted to uncover the possible mechanisms.

Results: Fifty-eight NSCLC patients with EGFR sensitive mutation and treated with anti-PD-(L) 1 based immunotherapy were enrolled. Those with acquired resistance to EGFR-TKI showed significantly higher frequency of primary resistance to immunotherapy. Flow cytometry analysis revealed significantly increased CD39+ Treg and decreased CD8+ T cells infiltration in the tumor microenvironment. Bulk RNA sequencing analysis showed that differently expressed genes between EGFR-TKI acquired resistance cohort versus primary resistance cohort were significantly enriched in chemokine signaling pathway, and CCL4 was highly expressed in EGFR-TKI acquired resistance patients. Single-cell RNA sequencing demonstrated that it was tumor cells, not immune cells or fibroblasts, highly expressing CCL4 after a long-term treatment with EGFR-TKI. And this finding was further verified in vitro experiments as that cell lines with resistance to EGFR-TKI (H1975, PC9GR, PC9OR) expressed higher CCL4 than those without (PC9, L858R). In vitro experiments verified that exogenous supplementation of CCL4 could significantly improve the expression of CD39 on Tregs. Additional CCL4 to the co-culture system of Tregs with CD8+ T cells could decrease the production of IFN-— and granzyme B, attenuating the cytotoxicity of CD8+ T cells, and previously added anti-CD39 inhibitors to the co-culture system could offset this effect. The effects from exogenous CCL4 could be replaced by co-culturing with EGFR-TKI resistant cell lines.

Conclusions: NSCLC tumor cells with acquired resistance to EGFR-TKI upregulated the expression of CD39 on Tregs by secreting CCL4 in tumor microenvironment, attenuating the cytotoxicity of CD8+ T cells, ultimately affecting the efficacy of anti-PD-(L) 1 immunotherapy.

Keywords: EGFR-TKI resistance, immunotherapy, CCL4

P2.11A METASTATIC NON-SMALL CELL LUNG CANCER - IMMUNOTHERAPY - IMMUNOBIOLOGY, SUNDAY, SEPTEMBER 8, 2024 - 18:15 - 19:45

P2.11A.22 Higher Blood TMB/Tissue TMB Ratio as an Inferior Prognostic Biomarker for Survival in Advanced Stage NSCLC

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Introduction: High tumor mutation burden, calculated from tissue next-generation sequencing (tTMB), is known to have predictive value for favorable survival outcomes with immune checkpoint inhibitor treatment (ICI) in certain cancers. Blood-based TMB (bTMB) is increasingly utilized as an alternative to tTMB, primarily due to challenges in obtaining tissue samples for sequencing. However, the prognostic significance of bTMB in relation to tTMB is not well understood.

Methods: Patients treated for advanced-stage non-small cell lung cancer (NSCLC) with both available pre-treatment tTMB and bTMB results (blood NGS collected from October 2020 to February 2024) were included in the analysis. Survival outcomes according to bTMB (High defined as ≥ 16 Mut/Mb, Low defined as <16 Mut/Mb), tTMB levels (High defined as ≥ 10 Mut/Mb, Low defined as <10 Mut/Mb), and bTMB/tTMB ratio were analyzed. The Spearman's rank correlation coefficient was used to assess the concordance between bTMB and tTMB.

Results: Among 84 patients, 32 (38%) received ICI monotherapy, 30 (35%) received ICI and chemotherapy combination therapy, 17 (20%) received cytotoxic chemotherapy, and 15 (18%) received targeted therapy. The median tTMB was 6.3 (Q1: 3.2, Q3: 11.5), and the median bTMB was 11.5 (Q1: 7.8, Q3: 21.1). The median interval between tTMB collection and bTMB collection was 20 days (Q1: 12 days, Q3: 105 days, range 0-1540 days). The median bTMB/tTMB ratio was 1.99 (Q1: 0.98, Q3: 3.48). The median interval between bTMB collection and treatment initiation was 14 days (Q1: 7 days, Q3: 28 days, range: 0-134 days), with 67 patients (80%) having an interval of <30 days. There was no difference in PFS and OS of patients who received immunotherapy between groups with high and low tTMB. Similar findings were observed with bTMB. When patients were divided into two groups according to bTMB/tTMB tertiles (1st and 2nd tertile vs 3rd tertile), the third tertile group had a significantly inferior OS in both all regimen group (84 patients, p 0.002, HR 2.70, 95% CI 1.26-5.77) and immunotherapy group (62 patients, p 0.03, HR 2.43, 95% CI 0.97-6.13) (figure 1). However, no significant difference in PFS was observed for all regimen group and immunotherapy group.

Conclusions: A higher blood TMB/tissue TMB ratio can serve as an inferior prognostic biomarker for survival of patients with advanced stage NSCLC. A high bTMB/tTMB ratio may be indicative of increased tumor heterogeneity and/or higher metastatic tumor burden. Further studies are warranted to explore the role of bTMB/tTMB ratio.

Keywords: tumor mutation burden, biomarker, NSCLC

P2.11A METASTATIC NON-SMALL CELL LUNG CANCER - IMMUNOTHERAPY - IMMUNOBIOLOGY, SUNDAY, SEPTEMBER 8, 2024 - 18:15 - 19:45

P2.11A.23 Fecal Microbiota Transplantation Plus Rechallenging Immunotherapy in Patients with Advanced Non Small Cell Lung Cancer: An

Exploratory Study

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Introduction: Previous studies have associated the gut microbiota with response to immunotherapy and fecal microbiota transplantation (FMT) has been applied as an effective tool for reestablishing gut microbiota. However, whether FMT could reverse immunotherapy resistance in patients with non small cell lung cancer (NSCLC) has not been investigated.

Methods: Here, we conducted a clinic trial to detect the safety and efficacy of healthy donor FMT plus PD-1 blockade re-challenging therapy in 7 patients with advanced NSCLC who have progressed after initial response to immunotherapy.

Results: During the follow-up, a total of 66 adverse events (AEs) were reported (Grade 1: 69.7%, Grade 2: 22.7%, Grade 3: 7.6%) and no serious adverse event above grade 3 was identified. Treatment related AEs were mainly associated with immunotherapy, only Grade 1 FMT-related AEs (nausea, diarrhea, bloating, constipation etc.) were reported. Additionally, the disease control rate (DCR) was 28.6%, including one partial responses (PR) and one stable disease (SD) with PFS of 14.6 months and 8.1 months, respectively. The median progression-free survival (PFS) was 1.5 months (95% CI: 1.24 - 1.75) and the overall survival (OS) was 12.1 months (95% CI: 0.3 - 23.9) for all patients. Moreover, the composition of the intestinal flora in all patients was modulated after treatment. At genus level, most of species decreased while two original species (Prevotella_9 and Veillonella) increased and two new species (Megamonas and Alloprevotella) appeared post-treatment. And the alpha diversity increased in responders, whereas it decreased in non-responders. Additionally, 73 metabolites elevated and 41 metabolites reduced in stool specimens of recipients ($p<0.05$ VIP>1).

Conclusions: The combined therapy of FMT and anti-PD-1 antibody has a tolerable safety profile and preliminary therapeutic effect, warranting further investigation.

Keywords: fecal microbiota transplantation, anti-PD-1, non small cell lung cancer

P2.11A METASTATIC NON-SMALL CELL LUNG CANCER - IMMUNOTHERAPY - IMMUNOBIOLOGY, SUNDAY, SEPTEMBER 8, 2024 - 18:15 - 19:45

P2.11A.24 Characterization of Circulating Tumor-Associated and Immune Cells in Advanced-Stage NSCLC

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Introduction: Non-small cell lung cancer (NSCLC) is the most prevalent form of lung cancer and the leading cause of cancer-related deaths globally. There is an increasing need to better understand biomarkers that may be predictive of clinical outcomes which can be assessed using non-invasive means.

Methods: Our study sought to investigate circulating peripheral blood cells in NSCLC, including epithelial, immunological, tumour-associated and hybrid subtypes. We performed enrichement of blood samples using spiral microfluidic technology, followed by comprehensive characterisation of the enriched cell fraction in n=50 NSCLC patient blood samples prior to commencement of therapy. Peripheral blood assessments were measured against clinical endpoints (response to therapy, overall survival).

Results: We identified a distinctive class of tumor-associated macrophages (TAMs) that exhibits a unique morphology and cell size, in addition to homotypic circulating tumour cell clusters, heterotypic clusters and single CTCs. Our study reveals a heterogeneous landscape of circulating tumor cells and clusters, underscoring the complexity of cell types found in the circulation of NSCLC patients.

Conclusions: Our study sheds light on the diverse landscape of circulating tumor cells and associated macrophage populations in NSCLC patients. We have detected various cell subpopulations, including tumour-associated macrophages and CTC clusters that exhibit varied cell compositions. Notably, the presence of TAMs correlates with late disease stages and poor clinical outcomes, highlighting their potential roles in tumor progression and metastasis.

Keywords: circulating tumour cells, macrophages, liquid biopsy

P2.11A METASTATIC NON-SMALL CELL LUNG CANCER - IMMUNOTHERAPY - IMMUNOBIOLOGY, SUNDAY, SEPTEMBER 8, 2024 - 18:15 - 19:45

P2.11A.25 Clinicogenomic Profile of Different Resistance Patterns to Immune Checkpoint Inhibitors in Non-Small Cell Lung Cancer

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Introduction: Immune checkpoint inhibitors (ICIs) can achieve durable responses in non-small cell lung cancer (NSCLC) patients without EGFR/ALK driver alterations. However, primary or acquired resistance is common, occurring in over half of patients, and mechanisms of resistance are poorly understood.

Methods: The GEMINI database was queried to identify metastatic NSCLC patients without targetable EGFR/ALK alterations who were treated with ICI alone or in combination with chemotherapy (ICI-chemo). Mutational profiling was performed on tissue or blood using targeted NGS. Radiographic response was assessed using RECIST guidelines (version 1.1).

Results: A total of 1914 patients with NSCLC treated with PD-(L)1 blockade were identified, of whom 641 (33.5%) had progressive disease (PD) at their first on-treatment scan evaluation (primary resistance: Pres) and 465 cases (24.3%) achieved initial response (complete or partial response; CR/PR). Acquired resistance (AR) was common, occurring in 57% (265 out of 465) of initial responders. The onset of AR was variable, occurring within 6 months in 26 (9.8%) patients (AR_S), 179 (67.5%) in 6-24 months (AR_M), and 60 (22.6%) > 2 years (AR_L). Squamous cell histology, liver metastasis, and ICI-chemo combination therapy were enriched in the AR_S group compared to other AR and Pres groups. High PD-L1 expression was enriched among patients with AR > 6 months compared to Pres and AR_S groups. An elevated peripheral blood derived neutrophil-to-lymphocyte ratio (dNLR) was observed in the Pres and AR_S groups compared to the other AR groups (p=0.01). A total of 145 patients had paired tissue or blood sequencing at baseline and at ICI progression. The mean level of PD-L1 expression decreased at the time of progression compared to the baseline level (p=0.02). Genes related to PI3K/AKT/mTOR (PIK3CA) and RAF/MEK/ERK (ARAF, BRAF) signaling pathways, as well as the ErbB family genes (EGFR, ERBB2 and MET), were more abundant in the post-ICI set than the pre-ICI set.

Conclusions:

Liver metastases and dNLR associate with earlier time to acquired resistance. The genomic profile at resistance in NSCLC patients is heterogeneous. A deeper understanding of the mechanisms of resistance evolution is needed to optimize sequential or combinatorial treatment strategies to overcome resistance.

Keywords: NSCLC, Immune checkpoint inhibitors, Acquired resistance

P2.11A METASTATIC NON-SMALL CELL LUNG CANCER - IMMUNOTHERAPY - IMMUNOBIOLOGY, SUNDAY, SEPTEMBER 8, 2024 - 18:15 - 19:45

P2.11A.26 Prognostic Utility of Peripheral Myeloid Cells for Clinical Outcomes in Patients with NSCLC Treated with Cemiplimab

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Introduction: A high neutrophil/lymphocyte ratio (NLR) has a reported association with poor prognosis in non-small cell lung cancer (NSCLC) patients, but data are limited on the potential contribution of other immune cells such as monocytes and eosinophils in modulating the systemic immune response. The aim of this analysis was to validate the prognostic importance of the NLR and other peripheral myeloid cells, including monocytes and eosinophils, in patients with NSCLC treated with cemiplimab in the EMPOWER-Lung 1 (NCT03088540) and EMPOWER-Lung 3 (NCT03409614) phase 3 trials. We also aimed to develop a nomogram derived from the joint Cox model enabling physicians to predict 1- and 2-year outcomes based on individual characteristics of patients with NSCLC treated with the programmed cell death-1 (PD-1) inhibitor, cemiplimab.

Methods: Overall survival (OS) was assessed in patients from the full analysis set with an available blood differential test at baseline that included monocyte, lymphocyte, and neutrophil measurements. For hypothesis testing and cut-point derivation, data were randomly split into training (70%) and testing (30%) cohorts using random sampling. The multivariable model developed in the training set was validated in the testing set using Harrell's concordance index to estimate discrimination and calibration plots to visualize model calibration. A graphical representation of the individual effect sizes from a statistical regression model, and their relationship with predicted probability of the dependent variable, was provided using a nomogram, enabling estimation of the predictive probability of 1-year and 2-year OS for any given patient.

Results: In the testing cohort our model (Figure) yielded a concordance index of 0.61, indicating a modest predictive performance. Calibration curves between observed and predicted probabilities of death indicated that for higher-risk individuals above a 1-year mortality probability of 30%, the model is mis-calibrated and underestimated the 1-year mortality probability. However, most patients had a predicted 1-year mortality below 30%, with few patients above 75%.

Conclusions: This analysis shows that peripheral blood cell count parameters, including putative immunosuppressive neutrophils and monocytes as well as protective lymphocytes and eosinophils, may predict outcomes with anti-PD-1 therapy in patients with advanced NSCLC. While the variables in the nomogram were statistically significant and enhanced the ability to discern difference over the baseline model, overall discrimination was moderate, indicating that more data are needed to better predict clinical outcomes in this setting.

Keywords: Non-small cell lung cancer, Cemiplimab, Prognostic

P2.11A METASTATIC NON-SMALL CELL LUNG CANCER - IMMUNOTHERAPY - IMMUNOBIOLOGY, SUNDAY, SEPTEMBER 8, 2024 - 18:15 - 19:45

P2.11A.27 Generalizability of Radiomics Based Progression Risk Models in Immunotherapy Treated Mnsclc Subjects

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Introduction: Radiomics have shown promise in improving prognostication in metastatic non-small cell lung cancer (mNSCLC) subjects treated with immunotherapy (IO). However, ensuring generalizability across different centers still represents an open challenge to clinical adoption. We sought to develop and test the generalizability of a radiomics model aimed at predicting risk of progression in IO treated subjects with mNSCLC.

Methods: Pretreatment CT scans of IO treated mNSCLC subjects and with known outcome data were collected from a single institution (Discovery cohort) to develop the model. Radiomics features were extracted from the segmentation of the largest lung tumor lesion. The 8 most predictive radiomics features were selected using a least absolute shrinkage and selection operator (LASSO) cox regression and combined using a survival random forest algorithm. The radiomics risk model was trained via cross-validation using censored progression-free survival (PFS) data. To determine what learned features were predictive of IO outcome, we tested the model in a cohort of mNSCLC subjects treated with 1L chemotherapy (Chemo cohort). To test model generalizability, we used a publicly available retrospective cohort of pretreatment CT scans of mNSCLC treated with IO and with known PFS data from an independent institution (External cohort). Risk models were evaluated by splitting the data into high and low risk groups, and evaluating the hazard ratios (HR) and log rank test p-values between the predicted risk groups.

Results: The Discovery cohort included 108 mNSCLC subjects who received IO as 1L therapy. Sixty-seven (62%) subjects received a combination of IO and chemotherapy. The cohort (51% female) had a median age of 68 (range 25->89) years and a median PFS of 11.5 (95% CI 8.3-15.8) months. The chemo-cohort of 55 patients (45% female) had a median age of 65 (range 45-82) years and a median PFS of 10.3 months (95% CI 5.3-12.9). The External cohort included 174 mNSCLC subjects (52% female) who underwent IO as first (33%), second (54%) or subsequent (13%) line of therapy. Nine (5%) subjects received IO combination therapies. These subjects had a median age of 68 (range 38->89) years and a median PFS of 2.7 (95% CI 2.2-3.6) months. The model cross-validated on the discovery cohort produced a HR of 1.79 (95% CI 1.08-2.95), p-value=0.024. In the Chemo-cohort, the HR was of 1.93 (95% CI 1.07-3.47), p-value=0.026. On the independent test cohort the HR was of 1.45 (95% CI 1.04-2.03), p-value=0.029. When focusing on subjects treated with IO as 1L therapy, the HR was of 1.74 (95% CI 0.92-3.32), p-value=0.089.

Conclusions: The derived radiomics model showed promising risk stratification and generalizability capabilities in IO treated subjects. However, results from the Chemo cohort suggest the model might be predictive of overall risk of disease progression rather than response to IO therapy.

Keywords: mNSCLC, Radiomics, Risk Modeling

P2.11B METASTATIC NON-SMALL CELL LUNG CANCER - IMMUNOTHERAPY - IMMUNORESISTANCE, SUNDAY, SEPTEMBER 8, 2024 - 18:15 - 19:45

P2.11B.01 Deciphering Immunotherapy Resistance Mechanisms in Metastatic NSCLC, Insights from Plasma Proteomics Analysis

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Introduction: Treatment management in patients with metastatic non-small cell lung cancer (NSCLC) who are eligible for systemic therapy lacks reliable biomarkers to choose from approved first-line treatments. Currently approved biomarkers include PD-L1 expression scores and tumor mutational burden, which provide only a limited view of the tumor immune environment. The PROphet NSCLC test was recently developed in a multicenter observational trial (ClinicalTrials.gov identifier: NCT04056247) of NSCLC patients undergoing PD-1/PD-L1 inhibitor-based therapy to address clinical needs. The PROphet NSCLC test combines pretreatment plasma proteomics and machine learning to assist first-line treatment management and provides treatment considerations based on the levels of 388 plasma proteins, termed resistance-associated proteins (RAP). In this study, the biological mechanisms underlying RAPs were analyzed. Notably, biological analysis of plasma proteins in cancer patients presents a challenge given the intricate interplay between the tumor, immune system, and other tissues. Advanced analysis methods were employed to decipher the biological mechanisms associated with RAP, resulting in six distinct groups of RAP proteins related to the immune system, tumor, and other tissues that can be linked to resistance mechanisms.

Methods: Biological analysis was performed on 388 RAP proteins measured in plasma samples obtained from 206 advanced-stage NSCLC

patients before PD-1/PD-L1 inhibitor treatment initiation. A correlation matrix was constructed for all 388 RAPs across 206 patients, assuming that proteins exhibiting similar expression levels may correlate and be involved in the same biological process. Subsequently, a weighted graph was constructed based on the correlation matrix. In this graph, every node corresponds to a protein, and the strength of the correlation between the two proteins is depicted by the weight of the edge connecting their respective nodes. Finally, a correlation strength threshold was applied to the weighted graph, whereby only edges above the threshold were considered. This threshold was determined to optimize the occurrence of clusters containing multiple proteins, while minimizing the presence of isolated proteins. Enrichment analysis was performed for each protein cluster using standard enrichment databases.

Results: The RAP protein correlation analysis resulted in nine clusters containing 114 of the 388 RAP, of which the two most significant clusters included 46 and 30 RAP. In contrast, the smallest clusters contained only two RAP proteins. Significant enrichment of cellular compartments and tissues was observed in the six clusters. Notably, no significant enrichment was observed when all 388 RAPs were included in the analysis because of the mixture of signals derived from various biological mechanisms. The largest cluster, comprising 46 RAP proteins, predominantly comprised extracellular proteins associated with the acute-phase response, whereas the other large cluster of 30 RAP proteins comprised proteins enriched in nuclear and alveolar cells. The different clusters were enriched in proteins related to the extracellular matrix, endoplasmic reticulum, liver, and intracellular ferritin complexes.

Conclusions: Our study provides valuable insights into the biological processes associated with the clinical benefits of immunotherapy. This underscores the potential of plasma proteomics to identify mechanisms related to therapy resistance and biomarkers for clinical outcomes.

Keywords: Plasma Proteomics, Immunotherapy Resistance Mechanisms, biomarkers

P2.11B METASTATIC NON-SMALL CELL LUNG CANCER - IMMUNOTHERAPY - IMMUNORESISTANCE, SUNDAY, SEPTEMBER 8, 2024 - 18:15 - 19:45

P2.11B.02 Genomic Correlates of Response to Chemoimmunotherapy in STK11MUT and KEAP1MUT Metastatic Non-Small Cell Lung Cancer

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Introduction: Mutations in STK11 and KEAP1 are associated with primary and acquired resistance to immune checkpoint inhibition (ICI)-based regimens in patients with advanced non-small cell lung cancer (NSCLC). However, STK11 and KEAP1 mutations are highly heterogenous, and a fraction of NSCLCs harboring these mutations retain sensitivity to (ICI)-based regimens. We aimed to characterize the determinants of response to chemoimmunotherapy among these patients.

Methods: Clinicopathologic and genomic data were collected from patients with advanced NSCLC treated with chemoimmunotherapy and whose tumors underwent genomic profiling at three academic centers. Cox-proportional hazards models were used to understand outcomes to chemoimmunotherapy in the mutational NSCLC cohorts.

Results: Among 1492 patients with advanced NSCLC treated with chemoimmunotherapy, 329 (22.1%) and 246 (16.5%) harbored mutations in STK11 and KEAP1, respectively, and the objective response rates (ORR) were 28.3% and 30%, respectively. Among the 443 patients with metastatic NSCLCs with either STK11 and/or KEAP1 mutations, the median age was 68 (range 40-92), 96.6% had a history of tobacco use, 87.8% had adenocarcinoma histology, 86.5% had a ECOG performance status 0-1, the median PD-L1 was 0 (range 0-95), and 97.7% received chemoimmunotherapy in the first-line setting. In both STK11MUT and KEAP1MUT NSCLC, those with a tumor mutational burden (TMB) percentile ≥90% had a higher ORR, and longer median progression free survival (mPFS), and longer median overall survival (mOS) than those with a TMB percentile <90% (Table). In both mutational subgroups, absence of a concurrent mutation in KRAS was associated with a longer mPFS compared to those with a concurrent mutation in KRAS. In KEAP1MUT NSCLC, PD-L1 ≥1% was associated with a higher ORR and longer mPFS compared with a PD-L1 <1%; in STK11MUT NSCLC, there was no association between PD-L1 and response or survival to chemoimmunotherapy; however, these analyses may be limited by the overrepresentation of patients with low/negative PD-L1 levels in this cohort. NSCLCs harboring STK11 missense mutations had a longer mPFS and mOS compared to those with non-missense mutations; by contrast, there was no significant difference in mPFS or mOS in NSCLCs harboring KEAP1 missense vs non-missense mutations. Patients with mutations in STK11 or KEAP1 alone had a higher ORR and longer mPFS and mOS compared to those with concurrent mutations in STK11 and KEAP1 (Table).

Conclusions: Among NSCLCs with STK11 and/or KEAP1 mutations, various pathologic and genomic factors, including PD-L1 expression, TMB, KRAS status, and missense vs non-missense mutation subtype, impact the efficacy of chemoimmunotherapy.

Keywords: Immunotherapy, STK11 KEAP1, SMARCA4

P2.11B METASTATIC NON-SMALL CELL LUNG CANCER - IMMUNOTHERAPY - IMMUNORESISTANCE, SUNDAY, SEPTEMBER 8, 2024 - 18:15 - 19:45

P2.11B.03 Circulating Hallmarks of Hyperprogression in NSCLC upon 1st Line PD-(L)1 Inhibitors Alone or in Combination with Chemotherapy

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Introduction: Hyperprogressive disease (HPD) has been described in –14% of pretreated non-small cell lung cancer (NSCLC) patients upon single-agent PD-1/PD-L1 inhibitors (SA-ICI) and has not been reported upon platinum-based chemotherapy (PCT) and ICI combinations. So far, no predictive biomarkers are available for HPD early detection.

Methods: In NSCLC patients treated with 1st line single-agent ICI or PCT-ICI, HPD was defined as delta tumor growth rate (TGR) >50% and/or TGR ratio ≥2. Circulating low density neutrophils (LDNs) were assessed by flow cytometry on peripheral blood mononuclear cells (PMBCs). LDNs were defined as CD66b+CD15+ cells among CD11b+ PBMCs and immature subtypes as CD10- LDNs. The LDNs predictive role was assessed by Youden's test. Single-cell RNA-sequencing was performed on 14 PBMC samples (6 HPD, 8 PR) using Seurat and harmony R packages. Cell types were identified both though AUCell R package and manual curation. The differentiation in trajectories within the HPD cell dataset was described with Monocle3.

Results: 144 NSCLC patients were included: 75 treated with SA-ICI, 69 with PCT-ICI. In the SA-ICI cohort, HPD occurred in 8 (11%) patients. Immature circulating CD10- LDNs were significantly higher at baseline in HPD [median: 39.3, interquartile range (IQR): 28.7] compared to progressive disease [median: 7.4, IQR: 14.9, p<0.01] or partial response (PR) [median: 3.7, IQR: 12.6, p<0.01]. Circulating CD10- LDNs were associated with HPD [odds ratio (OR): 1.17, 95% CI: 1.06; 1.29], with a good prediction capability [cross-validated AUC 0.97 (95%CI: 0.94;1.00)]. A 30.5% cut-off value for CD10- LDNs was identified to discriminate HPD from others. In the PCT-ICI cohort, 14 patients had circulating CD10- LDNs ≥30.5%, being at high risk of HPD. However, no HPD was observed with PCT-ICI and dynamic evaluation in HPD high risk patients showed 52.3% (IQR: 28.4) reduction in CD10- LDNs upon PCT-ICI, suggesting that PCT prevents HPD by reducing immature LDNs. At a single-cell level, neutrophils from HPD patients had increased expression of IL-1 receptor type-II (IL1R2) compared to PR (log2FC=0.7, p<0.01), in line with an emergency granulopoiesis occurring in HPD. Furthermore, higher proportion of senescent T-cells was observed in HPD versus PR (log2FC=0.65, p<0.01), and genes associated with T-cells senescence were significantly modulated along the pseudotime trajectory (p<0.01) (Figure).

Conclusions: In HPD an opposite maturation drift occurs in circulating neutrophils compared to T-lymphocytes. In particular, immature neutrophils and senescent T-cells identify patients at high risk of HPD, who should be addressed to 1st line PCT-ICI combinations.

Keywords: Hyperprogressive disease, circulating biomarkers, immunotherapy

P2.11B METASTATIC NON-SMALL CELL LUNG CANCER - IMMUNOTHERAPY - IMMUNORESISTANCE, SUNDAY, SEPTEMBER 8, 2024 - 18:15 - 19:45

P2.11B.04 Chemotherapy Increases Acquired Resistance to Immunotherapy in NSCLC: A Metanalysis of Aggregate and Individual Patient Data

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Introduction: Acquired resistance (AR) has been defined as radiological progression after response to PD-1/PD-L1 inhibitors. Although the addition of platinum-based chemotherapy (PCT) to PD-1/PD-L1 inhibitors (ICI) is able to reduce primary resistance, the effect of PCT on AR is unclear.

Methods: Randomized clinical trials (RCTs) testing ICI alone (mono-ICI) or in combination with PCT (ICI+PCT), CTLA-4 inhibitors (combo-ICI) or both of them (combo-ICI+PCT) in metastatic NSCLC were searched in electronic databases (Medline, EMBASE, CENTRAL Cochrane) until 03/2024. RCTs with available Kaplan Meier (KM) curves of duration of response (DOR) and/or patients at risk at 12 months were eligible. AR rate was computed by patients at risk at 12 months from DOR curves. Primary endpoint was to indirectly compare the AR rate with PCT-containing versus PCT-free regimens. Aggregate data were reported with risk ratio (RR) and pooled by random effect model. Time to event outcomes were retrieved from KM curves through the individual patient data (IPD)-from-KM method and compared by log rank test.

Results: 16 RCTs (3915 patients, main characteristics and PD-L1 status in the Figure 1) were included. The addition of PCT significantly increased AR rate compared to PCT-free regimens both for ICI+PCT versus mono-ICI comparison (RR: 1.46, 95% CI 1.21-1.76) and for combo-ICI+PCT versus combo-ICI comparisons (RR: 1.48, 95% CI 1.07-2.05). Median DOR was significantly shorter with ICI+PCT compared to mono-ICI [11.8 months (95%CI 10.5-12.7) versus 16.2 months (95%CI 14.8-20.5), p=0.0001] and with combo-ICI+PCT compared to combo-ICI [11.6 months (95%CI 8.7-17.4) versus 18.4 months (95%CI 15.8-23.3), p=0.0005] (Figure 2).

Conclusions: In NSCLC the addition of PCT to immunotherapy (anti-PD-(L)-1 +/- anti-CTLA-4) significantly increases the rate of AR and reduces the DOR. These data highlight the need to identify biomarkers to better select patients who may benefit from a first-line PCT-sparing regimen, in order to reduce the risk of AR.

Keywords: acquired resistance, individual patient meta-analysis, immunotherapy

P2.11B METASTATIC NON-SMALL CELL LUNG CANCER - IMMUNOTHERAPY - IMMUNORESISTANCE, SUNDAY, SEPTEMBER 8, 2024 - 18:15 - 19:45

P2.11B.05 Effect of Dysbiosis-Inducing Drugs on the Response to Immune Checkpoint Inhibitors in Patients with NSCLC

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Introduction: Immune checkpoint inhibitors (ICIs) have significantly improved overall survival (OS) in patients with metastatic non-small cell lung cancer (NSCLC). However, only 30% of patients actually benefit from this costly treatment, which is not without side effects. Better patient selection prior to treatment is therefore essential. To this end, the search for new biomarkers more effective than PD-L1 expression is in progress. Among these, the composition of the gut microbiota appears to be closely correlated with response to ICIs. Many drugs can alter the composition of the microbiota and theoretically reduce therapeutic response of ICIs. In this study, we analyzed the impact of drug interactions in clinical practice.

Methods: We retrospectively collected clinical, biological and pharmacological data from ICI-treated patients with NSCLC followed at a university hospital between 2015 and 2022. Only resistant patients (progression-free survival (PFS)<3 months) and long responders (PFS>1 year) were included. Treatments associated with dysbiosis were systematically reviewed up to 90 days prior to ICI initiation. The treatments included were: corticosteroids >10mg/d, antibiotics (ATBs), proton pump inhibitors (PPIs), satins, non-steroidal anti-inflammatories, opioids, laxatives, metformin, anti-vitamin K, L-thyroxine, cholecalciferol, phloroglucinol, anti-H1 and H2, tricyclic antidepressants, serotonin reuptake inhibitors, antiarrhythmics and probiotics.

Results: This study included 369 patients, of whom 193 were resistant and 176 long-responders. Overall survival (OS) was significantly reduced in the corticosteroid group (p=0.0033; HR=2.4 (CI95% [1.1-5]), median OS 10.1 vs 29.2 months), PPI (p<0.0001; HR=2.6 (CI95% [1.7-4.1]), median OS 8.6 vs 36.4 months) and opioids (p=0.011; HR=1.7 (CI95% [1.1-2.6]), median OS 12.9 vs 30.4 months). PFS was negatively impacted in case of prescription of corticosteroid (p=0.0015, HR=2.7 (CI95% [1.1-6.7]), median PFS 1.6 vs 12.6 months), PPI (p<0.0001; HR=3.4 (CI95% [2-5-7]), median PFS 2.0 vs. 20.0 months), opioids (p=0.016; HR=1.8 (CI95% [1.1-3]), median PFS 2.4 vs. 13.9 months) and anti-H1 (p=0.014; HR=3.1 (CI95% [1.04-9.1]), median PFS 1.9 vs. 12.4 months). In multivariate analysis, only PPIs were associated with a reduction in OS (HR=3.5 (CI95% [2.1-5.9]) and PFS (HR=3.1 (CI95% [1.9-4.9])).

Conclusions: PPIs are associated with reduced efficacy of ICIs in NSCLC patients. The indication for gastric antisecretory agents should be reassessed before initiating immunotherapy.

Keywords: Immune Checkpoint Inhibitor, Proton Pump Inhibitor, Non Small-Cell Lung Cancer

P2.11B METASTATIC NON-SMALL CELL LUNG CANCER - IMMUNOTHERAPY - IMMUNORESISTANCE, SUNDAY, SEPTEMBER 8, 2024 - 18:15 - 19:45

P2.11B.06 BIRC5 Expression Correlated with Immunosuppressive Phenotype and Predicted Inferior Response to Immunotherapy in LUAD

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Introduction: BIRC5, also known as survivin, is the smallest but functionally most complex member of the inhibitor of apoptosis protein family. BIRC5 plays a pivotal role in shielding cells from both intrinsic and extrinsic apoptotic pathways, primarily by indirectly inhibiting caspase 9 activation and physically preventing direct interactions with apoptosis-promoting molecules.BIRC5 is highly expressed in most cancers and correlated with tumor growth, recurrence, chemotherapy resistance, and poor prognosis. However, a comprehensive analysis of BIRC5 expression in lung adenocarcinoma and its prognostic value for immunotherapy has not yet been investigated.

Methods: Clinical and transcriptomic data of 535 lung adenocarcinoma samples, 59 normal lung, and 54 patients with non-small cell lung cancer received immunotherapy were analyzed. Deconvolution analysis was conducted to uncover the relationship between tumor microenvironmental features and BIRC5 expression level. The predictive and prognostic values of BIRC5 was also evaluated with Log-rank test and Cox regression analysis.

Results: Lung adenocarcinoma had a significantly higher BIRC5 expression level than normal lung tissues. The elevated BIRC5 expression was markedly associated with unfavorable clinical outcomes. Transcriptomic and single-cell sequencing data analysis revealed that tumors

with high BIRC5 expression was correlated with multiple pathways' enrichment. Deconvolution analysis indicated a negative correlation between BIRC5 expression and infiltration levels of CD8+ T cells, dendritic cells, and NK cells in LUAD, but a positive correlation was observed between BIRC5 expression and regulatory T cells (Tregs) infiltrations. Importantly, lung adenocarcinoma patients received immunotherapy with high BIRC5 expression had dramatically shorter progression-free (1.2 vs. 4.5 months; P = 0.012) and overall survival (3.1 vs. 12.7 months; P = 0.005) than those with low BIRC5 expression.

Conclusions: These findings suggested that high BIRC5 expression was associated with DNA damage/repair, cell invasion and proliferation related pathways enrichment and increased Tregs infiltration, which would result in inferior outcomes in lung adenocarcinoma patients.

Keywords: lung cancer, bioinformatics, BIRC5

P2.11C METASTATIC NON-SMALL CELL LUNG CANCER - IMMUNOTHERAPY - IMMUNE ADVERSE EVENTS, SUNDAY, SEPTEMBER 8, 2024 - 18:15 - 19:45

P2.11C.01 With Eyes on the Future: Prospective Evaluation of Immune-Related Adverse Events in Patients with Lung Cancer

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Introduction: Immune checkpoint inhibitors (ICIs) bear unique, time-dependent immune-related adverse events (irAEs). However, limited data exist regarding tolerability in real-world populations. We report interim, non-sex stratified results of the first study prospectively evaluating ICI tolerability in patients with lung cancer (LC) in a real-world setting.

Methods: Recruitment began in July 2023 and is ongoing. The electronic Patient-Reported Outcomes version of the Common Terminology Criteria (PRO-CTCAE) was utilized to assess patients' irAEs. Patients (pts) complete up to 6 questionnaires throughout their treatment plus an end of treatment evaluation. Inclusion criteria includes pts ≥18 years, with LC stage I to IV, receiving single-agent ICI at Dana-Farber Cancer Institute. Descriptive statistics summarized patients' demographics, clinical characteristics, and symptoms.

Results: 36 pts were enrolled in the study as of January 23, 2024. 35 pts have completed their first PRO-CTCAE questionnaire; the median number of completed questionnaires was 2 (range: 1-6). Due to the current sample size, results reported reference pts' first PRO-CTCAE assessment. 53% of pts identified as female, 92% identified as White, and 6% as Black (Table 1). 56% of pts (19/34) reported having shortness of breath (SOB), most of whom (63%; 12/19) reported having moderate to severe SOB that often (somewhat to very much; 42%; 8/19) interfered with daily activities; 21% of them (4/19) stated that the SOB had worsened since starting ICIs. Similarly, of the 54% (19/35) with a cough, 42% (8/19) reported a moderate to very severe cough and 16% (3/19) reported its worsening since ICI initiation. 14 pts reported anorexia secondary to treatment, with most of them (57%; 8/14) reporting that it interfered with daily activities. Most pts (79%; 27/34) noted some degree of lack of energy. Rates of skin toxicity were low, with only 6% (2/35) experiencing a rash after beginning ICIs. Many pts did not experience nausea, abdominal pain, or unexpected sweating (80%; 28/35, 83%; 29/35, 77%; 27/35). However, of the pts reporting nausea and abdominal pain, high severity of these symptoms was noted (43%; 3/7, 50%; 3/6). Other low frequency irAEs included diarrhea, dry mouth, and dysgeusia.

Patient Characteristics

Total (n = 36), n (%)

≤ 50 years

3 (8)

Diagnosed in past 6 months

17 (47)

NSCLC

24 (67)

Pembrolizumab

18 (50)

Durvalumab

7 (19)

Nivolumab

2 (6)

Atezolizumab

1 (3)

Ipilimumab

1 (3)

Other ICI/do not know

7 (20)

Conclusions: SOB and cough were the most common symptoms experienced with high severity in this ongoing prospective evaluation of irAEs in pts with LC. Though nausea and abdominal pain were less common, when present, these symptoms were reported with high severity. Future data from this study will elucidate patient experiences with irAEs throughout their treatment course.

Keywords: immunotherapy, adverse events, treatment tolerability

P2.11C METASTATIC NON-SMALL CELL LUNG CANCER - IMMUNOTHERAPY - IMMUNE ADVERSE EVENTS, SUNDAY, SEPTEMBER 8, 2024 - 18:15 - 19:45

P2.11C.02 Incidence of Hematological Toxicity with Use of Immunotherapy and Chemotherapy in Advanced NSCLC: A Network Meta Analysis

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Introduction: Numerous randomized controlled trials (RCTs) have explored the effectiveness and safety of diverse treatments for advanced non-small cell lung cancer. However, the specific hematologic toxicity risks linked to these different therapies are still not well-defined.

Methods: We defined the primary outcome as the incidence of hematologic toxicity of ≥3 Grades, and the secondary outcomes included the incidence rates of all grades of hematologic toxicity events. Random-effects models were used for network meta-analysis, focusing on subgroup analyses for first-line/post-line treatments and different chemotherapy regimens. Besides, single-arm meta-analyses were performed for all interventions using a random-effects model.

Results: We reviewed 4657 articles and included 38 eligible RCTs involving 13 interventions and 24,951 patients. Compared with conventional chemotherapy, CTLA-4+Chemo (OR=1.68, 95%CI: 0.42, 6.68) increased the risk of ≥3 Grades anemia; PD-1+CTLA-4+Chemo (OR=1.33, 95%CI: 0.5, 3.55) and PD-1+Chemo (OR=1.13, 95%CI: 0.95, 1.35) increased the risk of ≥3 Grades decreased neutrophil count; PD-1+VEGF+Chemo (OR=2.18, 95%CI: 1.11, 4.3) and PD-1+Chemo (OR=1.34, 95%CI: 1.04, 1.81) increased the risk of ≥3 Grades decreased platelet count; PD-1+CTLA-4+Chemo (OR=2.72, 95%CI: 0.53, 24.08) increased the risk of ≥3 Grades decreased white blood cell count (Figure 1). Similar trends were observed in terms of overall hematologic toxicity of all grades. Subgroup analysis was consistent with the overall outcome. Figure 2 shows the incidence of hematologic toxicity across various interventions as determined by single-arm meta-analysis.

Conclusions: Our research indicates that combining immune checkpoint inhibitors with chemotherapy may increase the risk of hematologic toxicity beyond the levels seen with either treatment alone. This implies a multifaceted, synergistic interaction, potentially altering immune cell function, angiogenesis regulation, and the direct impact of chemotherapeutic agents on blood-forming cells. Further studies are needed to decipher the underlying molecular mechanisms and to identify risk factors and markers for this enhanced toxicity in combined Immunotherapy and Chemotherapy regimens.

Keywords: Immunotherapy, Hematological toxicity, Network meta-analysis

P2.11C METASTATIC NON-SMALL CELL LUNG CANCER - IMMUNOTHERAPY - IMMUNE ADVERSE EVENTS, SUNDAY, SEPTEMBER 8, 2024 - 18:15 - 19:45

P2.11C.03 Immune-Related Adverse Events are Associated with Survival in Chinese Lung Cancer Patients Treated With Immunotherapy

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Introduction: Patients receiving immune checkpoint inhibitors (ICIs) may develop immune-related adverse events (irAEs). While irAEs carry obvious risks for the patients, recent studies suggest a relationship with improved overall survival (OS) in patients experiencing irAEs. However, the association between specific irAEs and treatment benefit is not well understood. Here, we investigate the association of OS with immune-related pneumonitis (IRP) and immune-related hepatitis (IRH) - two common irAEs in Chinese lung cancer patients treated with ICIs.

Methods: A real-world retrospective cohort study design was conducted based on the Lung Cancer Tracking Cohort (LCTC) comprising EHR data from Hunan Cancer Hospital presenting between January 2018 to December 2023. Clinical data of 3,261 lung cancer patients treated with ICIs were included and analyzed. The relationship between IRP or IRH and survival was assessed using multivariate Cox-proportional hazard models with time-varying covariates and landmark analyses to address immortal time bias. The covariates that we adjusted for include gender, age, stage, smoking status, history of alcohol, line of therapy, treatment strategies, pathological type, ECOG score, local therapy, brain metastases and liver metastases.

Results: IRP and IRH were among the most prevalent irAEs observed. The median follow-up time of the 3261 patient cohort was 24.9 months (range from 0.2 - 90 months). Among all patients, 248 (7.6%) developed IRP, of which 23 (0.7%) experienced grade 3 or higher, and 380 (11.7%) developed IRH, of which 62 (1.9%) experienced grade 3 or higher. The median time to onset for IRP and IRH was 5.9 months and 2.1 months, respectively. We observed a significantly longer OS in patients developing IRH (HR = 0.76, 95%CI: 0.64 - 0.91, p = 0.002) in multivariate cox-proportional hazard models with time-varying covariates. However no such effect was found for IRP (HR = 1.10, 95%CI: 0.90 - 1.33, p = 0.325) and neither mild nor severe IRP showed an association with OS. When comparing the effect of mild (grade 1 or 2) and severe (grade 3 or higher) IRH on OS, mild IRH was significantly associated with longer OS (HR = 0.76, 95%CI: 0.63 - 0.91, p = 0.003). Severe IRH showed a similar though not significant association (HR = 0.79, 95%CI: 0.53-1.18, p = 0.262). Landmark analyses support these results.

Conclusions: This study, which to our knowledge is the largest analysis of specific irAEs and ICIs effectiveness in Chinese lung cancer patients and demonstrated a significant and positive association between IRH and longer OS. These findings highlight the importance of considering IRH as a potential indicator of better treatment outcomes in lung cancer patients. Additionally, this emphasizes the need to manage irAEs in order to optimize the benefit/risk balance for patients receiving ICIs. Further efforts are ongoing to assess the potential for genetic markers and/or signatures associated with the occurrence of IRH and IRP.

Keywords: Immune-related adverse events (irAEs), Overall Survival, Lung Cancer

P2.11C METASTATIC NON-SMALL CELL LUNG CANCER - IMMUNOTHERAPY - IMMUNE ADVERSE EVENTS, SUNDAY, SEPTEMBER 8, 2024 - 18:15 - 19:45

P2.11C.04 Enhancing Multidisciplinary Clinicians' Ability in Identifying and Managing irAEs in the Emergency Setting Through Online CME

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Introduction: Despite immune checkpoint inhibitors (ICIs) potential for generating durable responses and survival benefits, ICIs can induce a spectrum of immune-related adverse events (irAEs), ranging from mild to severe or life-threatening. Clinicians in the emergency department (ED) may be the first point of contact for patients with non-small cell lung cancer (NSCLC) experiencing an irAE, but may not have specialized training, thus demonstrating a need for collaborative workflows to reduce morbidity and mortality. The objective was to determine if online continuing medical education (CME) could improve ED physicians', oncologists', nurse practitioners' (NPs), and physician assistants' (PAs) ability to collaboratively treat irAEs in patients with NSCLC who present to the ED.

Methods: The educational initiative consisted of a 15-minute video discussion between two multidisciplinary faculty. Educational impact was measured with a repeated pre-/post-assessment including multiple choice competence questions and a 5-point Likert scale confidence question. Data from all ED physicians, oncologists, and NPs/PAs who completed pre- and/or post-education assessments were aggregated and stratified by learning theme and demographic question responses. Relative changes in percentage of correct responses and clinicians who were confident (value of 4 or 5) were used to measure improvement. A McNemar's test assessed significant levels of changes reported with P values <.05 considered statistically significant. The activity launched July 2023; data were collected until February 2024.

Results: ED physicians', oncologists', and NPs'/PAs' had statistically significant improvements in competence and confidence after education (N=38 to 64), including stratifications by practice setting and institutional protocol availability.

Conclusions: Participating clinicians realized statistically significant improvements in their ability to identify and treat irAEs in the ED. Clinicians' gains may correspond with real-world improvement in clinical care, thus enhancing patient outcomes and experiences. Findings suggest that additional educational activities can help address residual gaps and improve ability in this dynamic clinical setting.

Keywords: irAE, Emergency, CME

P2.11C METASTATIC NON-SMALL CELL LUNG CANCER - IMMUNOTHERAPY - IMMUNE ADVERSE EVENTS, SUNDAY, SEPTEMBER 8, 2024 - 18:15 - 19:45

P2.11C.05 Correlation Between Gut Microbiome and Immune-Related Adverse Reactions for Lung Cancer

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Introduction: As a new immunotherapy method, immune checkpoint inhibitors are currently a hot topic in the treatment of lung cancer. However, while immunotherapy brings curative effects, it also brings immune-related adverse reactions(irAEs). irAEs is the most common reason for the withdrawal of immunotherapy, which will undoubtedly affect the efficacy and quality of life of lung cancer patients. Therefore, reducing the occurrence of immune-related adverse reactions is an urgent problem to be solved. Gut microbiome plays an important role in maintaining the balance between human health and disease. Many studies have proved that gut microbiome can regulate human immunity, and thus play a certain role in the immunotherapy of lung cancer patients. The relationship between gut microbiome and irAEs is currently unclear.

Methods: We enrolled 16 NSCLC patients who developed irAEs during immunotherapy from May 1, 2021 to December 31, 2022. Collect baseline fecal samples from all patients (Q group) and fecal samples at the time of irAEs (H group), and perform metagenomic sequencing to compare differences in gut microbiome abundance and functional diversity between the two groups.

Results: Our analysis shows significant differences in the composition of gut microbiome between the two groups of patients. When irAEs occur, the abundance of Firmicutes and Proteobacteria in the patient's gut is higher, while the abundance of Bacteroidetes and Actinobacteria is lower. At the genus level, there was no significant change in the abundance of each dominant bacterial genus, but the abundance of Bacteroidetes and Prevotella in patients with irAEs was slightly lower than baseline. Compared to the baseline of irAEs patients, the most significantly associated bacterial species with irAEs are Ligilactobacillius_salivarius, Veillonella'atypoca, Veillonella_parvula, Veillonella_dispar, Streptococcus_parasanguinis. There were also significant differences in the gut microbiome function between the two groups of patients. When irAEs occur, the patient's gut microbiome plays a greater role in physiological functions such as nucleotide and lipid metabolism, intracellular trafficking, secretion, vesicular transport, and extracellular structure. In carbohydrate metabolism, when irAEs occur, the patient's gut microbiome plays a greater role in glycoside hydrolases.

Conclusions: This study suggests that lung cancer patients with irAEs have unique gut microbiome characteristics, which may serve as potential biomarkers for diagnosing and predicting irAEs.

Keywords: Gut Microbiome, Lung Cancer, Immune-Related Adverse Reactions

P2.14A MESOTHELIOMA, THYMOMA, AND OTHER THORACIC TUMORS - THYMUS AND OTHER CANCERS, SUNDAY, SEPTEMBER 8, 2024 - 18:15 - 19:45

P2.14A.01 Clinicopathological Characteristics and Treatment Outcomes of Patients with Advanced SMARCA4-Deficient Non-Small Cell Lung Cancer

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Introduction: SMARCA4/BRG1-deficient non-small lung cancer (SD-NSCLC) has distinct clinicopathological and genomic features from classical NSCLC with high invasiveness and poor prognosis, which is associated with primary resistance to standard treatment, especially in late-stage patients. Therefore, we designed this retrospective study focusing on stage III/IV and supposed to clarify the profiles and find the treatment response effects from immunotherapy and local treatment for these SD-NSCLC patients.

Methods: 53 SD-NSCLC patients in stage III/IV with follow-up time longer than 6 months from 110 consecutive patients diagnosed with SAMRCA4/BRG1 deficiency by immunohistochemistry at Sun Yat-sen University Cancer Centre from May 2019 to May 2023 were included in this study. We assessed the clinicopathological features of the patients and grouped them based on their treatments: ICIs (n=39) and non-ICIs(n=14), or with local treatment (including radiotherapy or surgery) (n=23) and without local treatment (n=30). Further, we conducted stratified analysis according to TNM stage to compare prognostic differences between groups.

Results: 94.3% (50/53) of the patients were male, with an average age of 59.3 years. 71.7% (38/53) of them had a smoking history, and 54.7% (29/53) were stage IV. Histologically, 84.9% (45/53) of the patients exhibited poorly differentiated carcinomas, 50.9% (27/53) were NSCLC not otherwise specified and 45.3% (24/53) were adenocarcinomas. 62.5% (20/32) of the patients had positive PD-L1 expression and 71.4% (15/21) had high tumor mutation burden (>=10 mut/Mb). Next-generation sequencing (NGS) was performed in 39.6% (21/53)of the patients. The most common mutations included TP53 (85.7%, 18/21), followed by SMARCA4(61.9%, 13/21), LPR1B (52.4%, 11/21), KEAP1 (23.8%, 5/21), STK11(19.0%, 4/21). Regimens containing ICIs significantly improved median progression-free survival (mPFS) than non-ICIs in

the stage IV SD-NSCLC patients (7 vs. 3 months, P=0.021), the median overall survival (mOS) also showed a longer trend (not reached vs. 15 months, P=0.107). While in stage III and overall patients, the mPFS and mOS did not differ significantly (P>0.05). Patients in stage III who received local treatment had a significantly longer mPFS than those who did not (9 vs. 2 months, P=0.012), although the difference in mOS did not reach significance (27 vs. 17 months, P=0.753). In stage IV and overall patients, local treatment did not markedly improve mPFS and mOS (P>0.05).

Conclusions: Combination therapy with ICIs may be an effective strategy for advanced SD-NSCLC patients and local treatment also has certain significance for locally advanced patients.

Keywords: SD-NSCLC, ICIs, local treatment

P2.14A MESOTHELIOMA, THYMOMA, AND OTHER THORACIC TUMORS - THYMUS AND OTHER CANCERS, SUNDAY, SEPTEMBER 8, 2024 - 18:15 - 19:45

P2.14A.02 Assessment of Immunohistochemical Panel Utilization in Thymic Carcinoma Diagnosis: Real World Experience Insights

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Introduction: Thymic tumors originate from the thymic epithelium and exhibit aggressive tumor invasiveness and a high potential for metastasis. These Thymic Epithelial Tumors (TETs) display distinct biological functions, histological findings, and genomic profiles. Thymic carcinomas represent approximately 20% of all TETs. Among the various histologic subtypes recognized by the World Health Organization (WHO), Thymic Squamous Cell Carcinoma (TSCC) is the most prevalent, accounting for 70-80% of cases. Despite advancements, the mortality rate of thymic cancer remains in the top 10 among chest tumors. Although clinical, radiological, and morphological features can aid in distinguishing between thymic carcinomas and Non-Small Cell Lung Cancers (NSCLCs), differentiation can sometimes pose challenges. Instances arise where shared histologic and radiological features blur the lines between NSCLC and thymic carcinoma. Surgical resection is the preferred treatment for TETs where feasible. However, inoperable cases necessitate accurate preoperative diagnosis for appropriate treatment decisions, such as chemotherapy. Immunohistochemistry (IHC) plays a crucial role in diagnosing small biopsied specimens, with the WHO recommending a specific IHC panel: Positive immunostaining for CD5, KIT (CD117), FOXN1, and/ or CD205. This study aims to explore the utilization of the recommended IHC panel by pathology departments across the Hospitals of the MedStar Network, considering that it is not routinely performed and is conducted only upon request from treating physicians.

Methods: Data collection for this study utilized the MedStar Georgetown Cancer Centre Network registry. Two Electronic Health Record (EHR) software platforms, namely MedConnect and Centricity, were employed to extract data. Initially, all patients diagnosed with thymic tumors between January 1, 2003, and December 31, 2023, were included. Subsequently, ICD-9 (164) and ICD-10 (C37) codes were utilized to identify cases of TSCC. Specific immuno-histochemical markers pertinent to TSCC, including CD-5, CD-117, p-63, and p-40, were further retrieved and subjected to analysis.

Results: A total of 364 cases of thymic tumors of any pathology were identified within the designated time frame using the MedStar Georgetown Cancer Centre Network registry database. Among these, only 29 patients received a confirmed diagnosis of TSCC. Notably, the IHC marker p-63 was tested in 21 out of 29 patients, CD-117 in 13 out of 18, CD-5 in 14 out of 20, and p-40 in 6 out of 16 cases of TSCC where testing was indicated. FOXN1 and CD 205 were not tested in any.

Conclusions: Despite WHO recommendations for testing all thymic carcinomas for specific IHC profiles, our study reveals that only a fraction of tumors undergo testing for these specific panels. Moreover, this testing is not standard practice among pathologists in our institutions and is conducted solely upon request from treating physicians. This practice may lead to misdiagnosis of lung cancer or missed diagnoses of thymic carcinoma, emphasizing the critical importance of accurate diagnosis due to the variability in treatment regimens for different cancers. Our next steps involve engaging with the pathology department to institute reflex testing based on suspicion of thymic cancer.

Keywords: thymic squamous cell carcinoma, immunohistochemical markers, diagnostic challenges

P2.14A MESOTHELIOMA, THYMOMA, AND OTHER THORACIC TUMORS - THYMUS AND OTHER CANCERS, SUNDAY, SEPTEMBER 8, 2024 - 18:15 - 19:45

P2.14A.03 Prediction of Post-Surgical Recurrence of Thymic Epithelial Tumours Using Clinicopathological Parameters Incorporating TNM9 Classification

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Introduction: 9th edition of TNM classification (TNM9) for thymic epithelial tumours has been proposed. The primary aim of this study is to develop a predictive model for post-surgical recurrence by incorporating routinely available clinicopathological parameters and TNM9. The secondary aim of the study is to identify a subpopulation of patients with very low risk of recurrence.

Methods: This is a single institutional, retrospective study including all thymic epithelial tumours underwent surgical resection with curative intent during a 31-year period (1991-2022), regardless of the resection status. Variables related to the clinical (age, sex), histopathological (histological subtype, lymphovascular invasion, tumour necrosis, resection status), staging (TNM9 final stage) and peri-operative treatment domains were retrieved from an institutional thymoma database. Survival analysis was performed using univariate and multivariate Cox regression, and variables predictive of recurrence with P<0.05 in univariate setting were included in multivariate analysis. Variables predictive with P<0.05 in multivariate analysis were used to develop a point-based predictive model, and the weight of each individual variable was based on its effect size in the former.

Results: This study includes a total of 436 cases, with a documented recurrence rate of 12.6% (55/436). Thymoma, thymic neuroendocrine tumour and thymic carcinoma comprise 90.8% (396/436), 3.4% (15/436), 5.7% (25/436) of cases respectively. In univariate setting, age (≤65 years), histological subtypes other than type A/AB/metaplastic or multinodular thymoma with lymphoid stroma (MNT), presence of lymphovascular invasion or tumour necrosis, TNM9 final stage II-IV, incomplete resection (R1/R2) and the administration of neoadjuvant or adjuvant therapy were associated with higher rates of recurrence. In multivariate setting, histological subtype, tumour necrosis, TNM9 final stage and resection status were independent predictors of recurrence. A four-tier recurrence risk group derived from these four independent variables stratified patients into very low (1.0%), low (6.7%), intermediate (28.1%) and high (44.1%) risks of recurrence, with AUC of 0.859 (95% CI 0.812-0.906, P<0.001). These risk groups also showed statistically significant associations with recurrence free survival. Patients with very low risk of recurrence represented just under half of the study population (47.5%), with estimated 5-year and 10-year recurrence free survival rates of 100% and 98.2% respectively.

Conclusions: In this study, we developed a practical predictive model of post-surgical recurrence for thymic epithelial tumours and refined the proposed TNM9 classification by identifying a very low risk group. This model permits risk-based patient stratification, post-surgical management and follow-up, and potentiates de-escalation strategies. Independent validation of our findings is warranted.

Keywords: Thymoma, Staging, Recurrence

P2.14A MESOTHELIOMA, THYMOMA, AND OTHER THORACIC TUMORS - THYMUS AND OTHER CANCERS, SUNDAY, SEPTEMBER 8, 2024 - 18:15 - 19:45

P2.14A.04 Mapping the Distribution of Ectopic Thymus Through Flow Cytometry Analysis of CD3mediumTCRvßmediumCD4+CD8+ T Cells

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Introduction: Accurately mapping the distribution of ectopic thymus (ET) is crucial for determining the appropriate extent of surgery for myasthenia gravis (MG). However, traditional histological methods for identifying ETs have significant limitations, including time-consuming procedures, inadequate specimen yield, and a risk of false negative results. This study aims to evaluate the effectiveness of flow cytometry in detecting ETs in patients undergoing total thymectomy.

Methods: A total of 864 samples from 103 patients were assessed at our center using flow cytometry analysis and Hematoxylin and eosin (H&E) staining. Tissues showing the presence of CD4+CD8+ T cells in flow cytometry or Hassall's corpuscles in H&E staining were considered ETs. We calculated the prevalence of ETs and conducted comparisons between different patient groups based on various clinical characteristics.

Results: In the discovery set, flow cytometry was able to identify ETs in 69.2% of samples, while standard histological methods only detected 23.6%. Our validation set revealed a higher incidence of ETs in MG patients compared to non-MG patients (73.5% vs. 58.0%, p < 0.0001), as well as in patients with thymic epithelial tumors compared to those with a normal thymus (68.1% vs 58.1%, p = 0.0088). We also found that MG patients had a higher prevalence of active ETs, characterized by a high proportion of CD4+CD8+ T cells indicating robust thymopoiesis. Furthermore, ETs were more frequently observed in the cervical region than the mediastinum region (75.0% vs. 60.8%, p = 0.0012), and in patients aged ≤ 40 years compared to those over 40 years old (73.0% vs. 60.6%, p = 0.0027).

Conclusions: Our findings emphasize the reliability of flow cytometry as an alternative method for detecting ETs, overcoming the limitations of traditional histological examination. Moreover, we provide a novel distribution map of ETs based on this approach, offering valuable insights to enhance surgical decision-making in MG treatment.

Keywords: Ectopic thymus, Myasthenia gravis, Flow cytometry

P2.14A MESOTHELIOMA, THYMOMA, AND OTHER THORACIC TUMORS - THYMUS AND OTHER CANCERS, SUNDAY, SEPTEMBER 8, 2024 - 18:15 - 19:45

P2.14A.05 Validity of Simple Thymomectomy for Clinical Stage I Thymoma without Myasthenia Gravis: A Propensity Score-Matched Analysis

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Introduction: Total thymectomy (TT) has been traditionally recommended as a standard mode of resection for thymic epithelial tumors. In recent years, simple thymomectomy (ST) has been growing trend in early-staged thymomas without myasthenia gravis (MG). However, due to no completed prospective trials, current international guidelines still recommend TT for all thymomas. The aim of this study is to access the surgical outcomes and the validity of ST in comparison with TT for clinical stage I non-myasthenic thymoma.

Methods: We conducted a retrospective analysis of clinicopathological data from 119 patients who underwent either ST or TT for non-myasthenic thymoma with clinical stage I disease (cT1N0M0 in the 8th edition of TNM staging system) between 2003 to 2018 at our institution. The mode of resection was determined by a multidisciplinary treatment board, with recent trend favoring ST for tumors measuring 5 cm or less. Surgical outcomes following each resection were evaluated, and a one-by-one propensity score (PS)-matched analysis was performed to reduce potential biases.

Results: Among the cohort, 50 patients (42%) underwent ST, while 69 patients (58%) underwent TT. The ST group more frequently received thoracoscopic approach (62% vs. 14%). Additionally, the ST group showed shorter operative times (median, 86 vs. 175 minutes) and lower rates of operative morbidity (CTCAE ≥grade 2, 2% vs. 9%) compared to the TT group. Median postoperative follow-up duration was 7.0 years (range, 0.1 to 19.2). Recurrence-free and overall survival (RFS and OS) did not significantly differ between the two groups (5-year RFS: 93.3% in ST and 95.2% in TT, p = 0.518; 5-year OS: 93.2% in ST and 98.5% in TT, p = 0.289). PS-matched analysis involving 40 patients in each group revealed comparable RFS (p = 0.342) and OS (p = 0.540) (Fig 1). Recurrence was observed in 3 patients from each group, and all of whom had tumor of ≥5 cm on preoperative CT scans. In the subgroup with tumor ≥5 cm tumor, the ST group had a higher recurrence rate (38% vs. 10% in the TT group). Postoperative autoimmune disease including MG did not occur in the ST group.

Conclusions: ST is less invasive alternative to TT and is deemed acceptable for clinical stage I thymoma without MG, considering both oncological and immunological aspects. However, caution should be exercised regarding the increased risk of recurrence in case of large tumors (>5cm) following ST. Further prospective studies are needed to confirm the present findings.

Keywords: thymoma, thymectomy, thymomectomy

P2.14A MESOTHELIOMA, THYMOMA, AND OTHER THORACIC TUMORS - THYMUS AND OTHER CANCERS, SUNDAY, SEPTEMBER 8, 2024 - 18:15 - 19:45

P2.14A.06 Diaphragmatic Plication in Surgery for Complex Mediastinal Tumor

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Introduction: Complex mediastinal tumor (CMT) referred to tumor that invades important mediastinal structures such as major blood vessels and nerves. In patients with CMT invading the phrenic nerve, some may present with preoperative diaphragmatic elevation, the other may suffer phrenic nerve damage during surgery, resulting in diaphragmatic elevation, which can lead to severe respiratory distress. For these patients, diaphragmatic plication can effectively lower the diaphragm.

Methods: We use endoscopic linear cutter stapler for diaphragmatic plication. First, we clamp the diaphragmatic apex to elevate it, and use another clamp to push down the abdominal contents. Following this, 6cm staplers are used for diaphragmatic plication, with a minimum width of 2cm and an average length of 10-20cm. For patients with thin diaphragms or oozing of blood, a 4-0 polypropylene suture is used for reinforcement.

Results: From 2020 to 2024, a total of 49 patients with CMT underwent intraoperative diaphragmatic plication by our team. There were 33 males and 16 females, with an average age of 49.9 years old. All patients underwent radical resection of mediastinal tumors. The main reason for intraoperative diaphragmatic plication was the inseparability or injury of the phrenic nerve, which accounted for 41 cases. Additionally, 13 patients had preoperative imaging findings of diaphragmatic elevation. Regarding the safety, no patient underwent reoperation during postoperative period. There were 6 postoperative deaths and 5 patients who experienced postoperative complications. The occurrence of postoperative complications and deaths was mainly associated with surgery for CMT, not with diaphragmatic plication. In terms of effectiveness, 11 patients with preexisting elevated diaphragm returned to normal. For other 34 patients, diaphragmatic plication was performed as a preventive measure due to the inseparability or injury of the phrenic nerve during surgery, and there was no postoperative diaphragmatic elevation observed. Therefore, a total of 45 patients were considered effective (91.8%). Among these 45 patients, 9 patients had recurrent diaphragmatic elevation during follow-up (20%). Furthermore, we performed remedial diaphragmatic plication for 3 patients with postoperative diaphragmatic elevation and respiratory distress followed by CMT surgery, and the effect was remarkable.

Conclusions: Diaphragmatic plication was safe and feasible for patients underwent surgery for CMT, although there was a certain chance of recurrence.

Patient Characteristics

Characteristics

All patients (n=49)

Preoperative

Gender

Male

33

Female

16

Age (y)

49.9

BMI

23.9

Pulmonary function

FVC (L)

2.98

FEV1 (L)

2.44

LVEF

65%

Neoadjuvant therapy

21

with MG

5

Tumor recurrence

3

Intraoperative

Incision

Clamshell

23

Median sternotomy

15

Subxiphoid

8

Others

3

Operative time (min)

258.3

Blood loss (ml)

631.3

Diaphragmatic plication

Left

25

Right

15

Bilateral

9

Postoperative

Pathology

Thymic squamous cell carcinoma

20

Thymoma

19

Others

10

Tumor size (cm)

8

VAS pain score

4.32

Chest tube drainage (ml)

2827.9

Chest tube duration (d)

7.67

Postoperative hospital stays (d)

8.87

Reoperation

0

Complication

5

Death

6

P2.14A MESOTHELIOMA, THYMOMA, AND OTHER THORACIC TUMORS - THYMUS AND OTHER CANCERS, SUNDAY, SEPTEMBER 8, 2024 - 18:15 - 19:45

P2.14A.07 Learning Curve Analysis of Near-Infrared Fluorescence-Guided Robotic-Assisted Minimally Invasive Esophagectomy with Indocyanine Green Dye

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Introduction: Robotic-Assisted Minimally Invasive Esophagectomy (RAMIE) using near-infrared fluorescence (NIF)-guided perfusion analysis with indocyanine green dye (ICG) is a novel technique for esophagectomy. We aimed to determine the number of cases required to reach technical proficiency at the first Canadian centre.

Methods: Patients with esophageal cancer who were candidates for esophagectomy were enrolled from 03/2022-03/2024 at one site in this prospective single-arm feasibility trial. Participants underwent RAMIE via a two-stage approach: abdominal stage via 5-port robotic approach, and thoracic stage via 5-port robotic approach. NIF-guided perfusion analysis with ICG was used to verify the course of the right gastro-epiploic artery in the abdominal stage, and to confirm the optimal location and perfusion state of the anastomosis in the thoracic stage. The anastomosis was constructed with a hand-sewn 2-layer technique. The learning curve was evaluated using the cumulative sum (CUSUM) method, with operative time as the quantitative metric.

Results: Of 18 patients enrolled, 11.11%(2/18) were withdrawn: one RAMIE was aborted due to hemodynamic instability; and the other due to conversion to laparotomy because of intra-abdominal adhesions. Median age was 68.5(IQR:58-71.5) and 93.75%(15/16) were men. Mean procedure time was 384.38(SD:57.10) minutes. ICG was used successfully in 100%(16/16) of cases: perfusion was detected with a green hue by NIF in both stages of the operation with clear identification of poorly perfused segments of the conduit. CUSUM analysis did not reveal an inflection point (Figure 1). Median length of stay was 8(IQR:7-11) days. Grade IVa complications occurred in 3 patients (3/16;18.75%): one patient experienced hemorrhagic shock; a second had a tracheoesophageal fistula within 90 days; and a third had an anastomotic leak requiring readmission to hospital.

Conclusions: CUSUM analysis of the first 16 cases did not reveal an inflection point, meaning the number of cases required to attain proficiency has not been reached yet.

Keywords: Learning Curve Analysis, Robotic-Assisted Minimally Invasive Esophagectomy, Indocyanine Green Dye

P2.14A MESOTHELIOMA, THYMOMA, AND OTHER THORACIC TUMORS - THYMUS AND OTHER CANCERS, SUNDAY, SEPTEMBER 8, 2024 - 18:15 - 19:45

P2.14A.08 Tyrosine Kinase Inhibitors (Alone or in Combination) for the Management of Advanced Thymic Epithelial Tumors (TETs) Among Hispanics

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Introduction: Thymic epithelial tumors (TETs) are rare malignant tumors with limited treatment options. No standard 2nd-line treatment is available following the preferred 1st-line chemotherapy, resulting in limited outcomes and poor prognosis. This study aimed to evaluate the efficacy of tyrosine kinase inhibitors (TKIs) in Latin America as well as some prognostic factors for advanced TETs.

Methods: A retrospective study was conducted using data from a CLICaP real-world database. Patient demographics, tumor genomics, and treatment outcomes were analyzed. Survival analyses were performed to assess progression-free survival (PFS) and overall survival (OS). Clinicobiological features and treatment outcomes with TKIs alone or in combination with immunotherapy were evaluated.

Results: 34 patients with confirmed histological diagnosis of thymic carcinoma were included. Median age at diagnosis was 52 years with a female representation of 35% (n=12). 32 patients (94%) presented symptoms at diagnosis with 6 (19%) experiencing myasthenia gravis. Furthermore, 20 individuals (59%) had familial history of cancer. With regards to staging, one patient (3%) was diagnosed at stage IIIB, 10 at IVA (29%) and the remainder at IVB (63%). Regarding pathological characteristics, CD117 immunohistochemistry was performed in 24

cases of which 16 (66%) were positive. Molecular characteristics revealed a mean TMB of 2.4 mut/Mb and PD-L1 expression >1% in 53% of cases. Mutations were identified in 24 cases. The most commonly mutated gene was TP53 in 16 (67%). Other mutations were identified in TET (n=2, 8%), PIK3CA (n=2, 8%) and KIT(n=2, 8%). CNV in the form of amplifications was found for CCND2 (n=2, 8%), AKT3 (n=2, 8%), and FGF (n=3,13%), whereas deletions were detected in MTAP (n=3,13%), and CDK4 (n=2, 8%). Considering treatment, Lenvatinib was administered to 21 patients (62%), sunitinib to 10 (24%), Lenvatinib pembrolizumab in 2 (6%), and everolimus to one (3%). TKI was offered as a second line in 21 patients (62%), a third in 7 (21%), and a fourth in 6 (17%). The best responses were partial in 5 patients, with an overall response rate of 15%. All responders were given TKIs as a second-line treatment. 19 achieved disease stabilization (56%). Regarding PFS, a median of 5.88 months (95%CI 4.73-7.47 months) was reached. Median OS was 53,7 months (95%CI 34 months-NR). Earlier treatment lines favored better PFS, with patients treated with TKI as a fourth line reaching a median of 1.28 months compared to 5.97 months as a second and 6.33 months as a third line (p<0.001).

Conclusions: These findings suggest that TKIs are efficacious as second or post-line treatments and represent a viable treatment option for Hispanic patients with advanced TETs.

Keywords: Thymic carcinoma, tyrosine kinase inhibitors, Latin America

P2.14A MESOTHELIOMA, THYMOMA, AND OTHER THORACIC TUMORS - THYMUS AND OTHER CANCERS, SUNDAY, SEPTEMBER 8, 2024 - 18:15 - 19:45

P2.14A.09 Adaptive Reprogramming of Arginine Biosynthesis is an Attractive Target for Modulating the Response to WEE1 Inhibition in Pleural Mesothelioma

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Introduction: Pleural mesothelioma is a rare but highly aggressive thoracic malignancy with an extreme shortage of treatment options. Platinum-based chemotherapy has long been the first-line therapy for patients with advanced pleural mesothelioma. Our previous study revealed that chemotherapy resistance in pleural mesothelioma is closely related to high WEE1 expression. Moreover, subsequent whole-genome CRISPR-Cas9 screening indicated that WEE1 may be a genetic vulnerability for pleural mesothelioma. However, our preliminary results revealed heterogeneity in the drug sensitivity of mesothelioma cell lines to WEE1 inhibitors, highlighting the importance of uncovering the underlying mechanisms of WEE1 inhibitor resistance.

Methods: In this study, we first selected pleural mesothelioma cell lines (H28 and MSTO-211H) sensitive to WEE1 inhibition based on a cell viability assay and induced drug resistance by chronic exposure to AZD1775 (MK-1775), a WEE1 kinase inhibitor, for 3 months. Moreover, unbiased transcriptomics and metabolomics profiling were applied to both parental and resistant mesothelioma cell lines. Furthermore, joint pathway analysis via transcriptomics and metabolomics assays was performed to decipher the molecular basis underlying WEE1 inhibitor resistance. In parallel, subsequent in vitro functional studies were performed to validate the biological function of the above-identified molecular alterations.

Results: Intriguingly, we showed that the adaptive reprogramming of arginine biosynthesis, a characteristic metabolic phenotype of pleural mesothelioma, is the major molecular alteration in resistant mesothelioma cells. Further exploration revealed that chronic exposure to a WEE1 inhibitor increased circulating arginine levels but was accompanied by significant downregulation of arginosuccinate synthase 1 (ASS1), which generally lacks the ability to convert citrulline back to arginine. Consistent with these findings, subsequent functional validation confirmed that the depletion of arginine in culture medium improved the drug response to WEE1 inhibition in mesothelioma cell lines through the induction of extensive DNA damage and apoptosis.

Conclusions: Our work thus provides the molecular basis for WEE1 inhibitor resistance while providing targetable metabolic vulnerability to enhance the antitumor response to WEE1 inhibition in patients with pleural mesothelioma.

P2.14A MESOTHELIOMA, THYMOMA, AND OTHER THORACIC TUMORS - THYMUS AND OTHER CANCERS, SUNDAY, SEPTEMBER 8, 2024 - 18:15 - 19:45

P2.14A.10 Real-World Evidence of Ipilimumab Plus Nivolumab Combination Therapy in Patients with Malignant Pleural Mesothelioma

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Introduction: Recent clinical studies have demonstrated the efficacy of immune checkpoint inhibitors (ICIs) for malignant pleural mesothelioma, and the ipilimumab plus nivolumab combination therapy was approved as standard therapy in Japan in 2021, following the approval of nivolumab in 2018. Thus, immune checkpoint inhibitors are expected to play a central role in the treatment of MPM. However, the safety and effectiveness in actual clinical practice consisting of many patients with poor tolerance to anticancer drugs, have not been fully investigated due to the limited number of the cases.

Methods: We retrospectively analyzed 55 patients with MPM who treated with ipilimumab plus nivolumab combination therapy at our institution from June 2021 to March 2023. Objective response rate (ORR) and disease control rate (DCR) were evaluated by modified RECIST ver 1.1. Survival curves were plotted with the Kaplan-Meier method and compared using the log-rank test. Adverse events were graded according to the CTC-AE ver 5.0.

Results: Patients' backgrounds were as follows: the median age was 72 years (range 45-88), the number of male/female was 42 / 13 and patients with ECOG performance status (PS) grade of 0-1 / ≥2 was 53 / 2. The respective number of the patients with epithelioid / sarcomatoid / biphasic / desmoplastic subtype was 35 / 13 / 6 / 1. Immune-related adverse events (irAEs) were observed in 38 patients. Regarding the effectiveness, the median progression free survival (PFS) was 12.4 months and overall survival (OS) was not reached to the median. ORR and DCR were 40.0% and 81.8% respectively. Regarding PFS of the patients, no significant difference was observed in ages (> 75 years old vs < 75 years old) and histological subtypes (epithelioid vs non-epithelioid). On the other hand, it was significantly longer in the patients with better PS (P≤0.0001) or in those who developed irAEs of any grade (P=0.01).

Conclusions: Ipilimumab plus nivolumab combination therapy was a safe and effective treatment for the entire patient population of MPM with good PS in real-world clinical practice.

Keywords: Malignant pleural mesothelioma, Ipilimumab plus nivolumab combination therapy, Real world evidence

P2.14A MESOTHELIOMA, THYMOMA, AND OTHER THORACIC TUMORS - THYMUS AND OTHER CANCERS, SUNDAY, SEPTEMBER 8, 2024 - 18:15 - 19:45

P2.14A.11 Real-World Immunotherapy Use in Pleural Mesothelioma: Insights & Immunological Landscape

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Introduction: Pleural mesothelioma (MPM), a malignancy arising from the pleural tissue, represents a rare yet aggressive tumor. While immunotherapy has shown considerable efficacy in this disease, its real-world utilization remains inadequately characterized. Moreover, there is a paucity of knowledge regarding the precise effects of immunotherapy on specific cellular subpopulations within the immune microenvironment.

Methods: We collected data from over 10 centers nationwide, comprising information from 287 patients, among whom 47 received either single-agent or combination immunotherapy. Clinical pathological information and survival data of malignant MPM patients undergoing immunotherapy were gathered. Immunological changes within the tumor tissues and normal pleura were assessed using multiplex immunofluorescence in 21 MPM patients, focusing on dendritic cells (DCs) , macrophages, lymphocytes, and immune checkpoints such as LAG3 and TIGIT. Additionally, single-cell sequencing was performed on tissue samples from three MPM patients before and after immunotherapy resistance.

Results: The median overall survival time for the 47 patients who received immunotherapy was 19.93 months, significantly higher than survival times reported in previous eras of chemotherapy (Figure 1). Additionally, we developed an organoid model to simulate immune resistance following immunotherapy (Figure 1). The number of DCs in the tumor microenvironment of MPM significantly decreased (P<0.05). Among them, ten patients had specific tissue samples before and after immunotherapy resistance, with multiplex immunofluorescence revealing a marked reduction in DCs and macrophages (P<0.05). Furthermore, comparative single-cell sequencing of tissue samples from three MPM patients before and after immunotherapy demonstrated a significant decrease in DCs and NKT following the development of resistance (P<0.05).

Conclusions: Hence, we consider the efficacy of immunotherapy in real-world settings for MPM patients satisfactory, recommending the proactive application of immunotherapeutic agents. During immunotherapy, DCs and other immune cells play crucial roles, warranting in-depth mechanistic research.

Keywords: Pleural mesothelioma, immunotherapy, organoid

P2.14A MESOTHELIOMA, THYMOMA, AND OTHER THORACIC TUMORS - THYMUS AND OTHER CANCERS, SUNDAY, SEPTEMBER 8, 2024 - 18:15 - 19:45

P2.14A.12 Unveiling COL17A1 as a Novel Cell Surface Target in Thymic Epithelial Tumors: A Target Discovery Pipeline Approach

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Introduction: Chemotherapy has been the standard of care for mTET in the past few decades. Herein, we aimed to develop a stepwise pipeline to identify potential cell surface targets suitable for immune-based therapy in mTETs.

Methods: From 2015 to 2020, 21 patients with stage IV TETs underwent clinical CLIA-based RNA sequencing (Discovery cohort). Using transcriptomic data from discovery cohort, we employed an integrated cell surface computational platform that predicts cell surface protein expression. To overcome the limitations of bioinformatic prediction, the expression of potential candidate proteins was validated through immunohistochemistry (IHC) in a tissue array of 97 mTETs and 35 normal tissues.

Results: Through RNA-Sequence of discovery cohort, we identified highly expressed transcripts in mTET. Among 60,908 transcriptomic pools screened, 10 potential targets were identified through a stepwise process. Final targets had expression in both thymoma and thymic carcinoma and no expression in vital organs in the proteomic database. In validation cohort, IHC of the targets, which included ABCG1, ANO9, CLDND1, COL17A1, and GRAMD1A revealed that COL17A1 had the highest protein expression in 66% of TETs and no significant expression in vital organs. Patients with COL17A1 expression had significantly worse overall survival compared to patients with negative TETs (n=90, HR 6.2, p<0.001). The spatindicatesriptomic analysis of a separate cohort showed moderate co-localization of T-cell markers with COL17A1 indicating the potential immunogenic nature of this protein.

Conclusions: We identified several highly expressed transcripts in mTET, among which COL17A1 protein stands out as a potential candidate. COL17A1 transcriptomic and proteomic profile, coupled with its impact in clinical outcome and immunogenicity makes it an attractive target candidate for therapeutic intervention.

Keywords: Thymic epithelial tumors, Cell surface target, immune-based therapy

P2.14A MESOTHELIOMA, THYMOMA, AND OTHER THORACIC TUMORS - THYMUS AND OTHER CANCERS, SUNDAY, SEPTEMBER 8, 2024 - 18:15 - 19:45

P2.14A.13 Discovery and Clinical Application of Potential Prognostic Genes for Clinical Outcome in Malignant Pleural Mesothelioma

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Introduction: Malignant pleural mesothelioma (MPM) is a disease with a very poor prognosis. Although we have experienced cases of long-term survival after surgery, some cases are difficult to treat surgically due to the large invasiveness. Recently, the results from the MARS 2 trial comparing the efficacy of surgery versus no surgery in the treatment of MPM were presented, and there was no significant difference in survival time between the two groups. Here, through comprehensive genetic analysis, we attempted to identify new prognosis-related genes to consider the indications for surgical treatment.

Methods: Gene expression and survival data of TCGA MPM dataset (n=85) were used. We applied a Cox proportional hazards model with overall survival and performed multiple testing (FDR 1%) on all 20,532 genes to obtain prognostic genes. Using the identified genes, we performed cluster analysis, Kaplan-Meier analysis, and gene ontology analysis to examine the clinicopathological significance of prognostic genes. To validate the relationship between selected gene expression and prognosis, we performed an immunohistochemical (IHC) analysis in 23 specimens from surgically treated patients with MPM who achieved macroscopic complete resection in our hospital.

Results: Cox multivariate analysis identified 1246 out of 20532 genes as prognostic genes. The 85 cases were divided into two clusters by consensus clustering based only on the expression level data of the above genes. Median survival times for each cluster were 31.2 and 12.7 months, with significant differences determined by log-rank test ($P < 0.001$). Comparison of histological subtypes between 2 groups revealed significant differences between groups ($P = 0.009$), however, the poor prognosis group also included many epithelial types. Analysis of the worse prognostic genes showed that the highest-ranked statistical enrichment was associated with the GO mitotic cell cycle ($Log10(P) = -67.03$). On the other hand, for the better prognostic genes, the terms list showed that the highest-ranked enrichment was associated with the GO defense response to the virus ($Log10(P) = -9.66$). From the comprehensive survival analysis, we identified CHST4 gene as a potential predictor of favorable overall survival for patients with MPM. We performed IHC using CHST4 for 23 MPM specimens and the median overall postoperative survival was 107.8 months in the high-expression-group and 38.0 months in the low-expression-group ($P = 0.044$, Figure)

Conclusions: Comprehensive analysis of TCGA MPM dataset made it possible to identify prognostic gene groups, suggesting the possibility of creating a new disease type classification and deciding the indication of surgical treatment.

Keywords: malignant pleural mesothelioma, CHST4, immunohistochemistry

P2.14A MESOTHELIOMA, THYMOMA, AND OTHER THORACIC TUMORS - THYMUS AND OTHER CANCERS, SUNDAY, SEPTEMBER 8, 2024 -

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P2.14A.14 A Real-World Multicenter Retrospective Study of Treatment Outcomes with Ipilimumab and Nivolumab in Mesothelioma

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Introduction: Studies have demonstrated survival benefit of immune checkpoint inhibition (ICI) compared to chemotherapy (chemo) for the management of unresectable mesothelioma. CheckMate 743 established ipilimumab/nivolumab (I/N) as the front-line standard of care. There is a need to integrate real-world data with clinical trial data to further understand patient outcomes outside of clinical trials.

Methods: We conducted a multi-center retrospective analysis of characteristics and outcomes of patients diagnosed with mesothelioma between 1/1 2016 - 8/30/2023 and treated with I/N in the front-line setting (FL) or after progression (PL). Clinical endpoints included progression free survival (PFS), overall survival (OS), overall response rate (ORR) and ICI related adverse events (IrAEs) defined using CTCAE 5.0.

Results: We identified 126 patients who received I/N (FL=90, PL=36). The median (m) age in the FL and PL groups was 73 yrs and 65 yrs respectively. Most patients were male (FL=81%, PL=69%), white (94%), and with an ECOG performance status of 0 or 1 (FL=83%, PL=97%). Most patients had pleural (FL=91%, PL= 75%) or peritoneal (FL= 8%, PL= 25%) mesothelioma. Histological subtypes were epithelioid (FL= 59%, PL= 83%), biphasic (FL=21%, PL=8%) and sarcomatoid (FL 19%, PL= 6%). BAP1 loss was identified by either IHC or NGS in 34% (FL) and 39% (PL) of patients. There was no significant difference in PFS between the two groups (mPFS, FL= 7.9 months (mos), PL= 8.4 mos; HR= 0.94; 95% CI, 0.59-1.5; p=0.67). No significant difference in OS between two groups was found (mOS, FL= 14.83 mos, PL= 28.90 mos; HR=0.51; 95% CI, 0.28-0.92; p=0.49). When comparing PFS of patients receiving 1st line chemo (n=33) to the FL group, no difference was noted (mPFS, chemo= 4.5 mos, FL= 7.9 mos; HR=0.31; 95% CI, 0.49-1.18; p=0.14). Among patients with evaluable responses, the ORR was 44% (35/80) and 42% (13/31) in the FL and PL groups respectively. IrAEs were observed in 44% and 56% of the FL and PL groups respectively. Grade 3/4 IrAEs accounted for 25% and 40% of toxicities in the FL and PL groups respectively. The treatment discontinuation rate due to IrAEs in the FL group was 21% and was 25% in the PL group.

Conclusions: No statistically significant differences in survival outcomes were noted between FL vs PL groups. However, more irAEs including grade 3 or 4 toxicities were noted in the PL group bringing to light the potential benefit of upfront I/N rather than upon progression on systemic chemo in-terms of tolerability. This is the first real world study conducted in the US evaluating the outcomes of patients with unresectable mesothelioma.

Keywords: survival, immunotherapy, multicenter

P2.14B MESOTHELIOMA, THYMOMA, AND OTHER THORACIC TUMORS - CLINICAL TRIALS IN PROGRESS, SUNDAY, SEPTEMBER 8, 2024 - 18:15 - 19:45

P2.14B.01 [DREAM] Double Lung Transplant Registry Aimed for Lung-limited Malignancies - A Prospective Registry Study for Medically Refractory Cancers

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Introduction: Adenocarcinoma in situ (AIS) and minimally invasive adenocarcinoma (MIA) are listed as 'special circumstances' for lung transplantation according to a consensus document from the International Society for Heart and Lung Transplantation (ISHLT). Five studies have reported on lung transplantation in carefully selected subsets of patients with multifocal lung adenocarcinoma. The 5-year survival rate of bilateral sequential lung transplantation was estimated at over 50% in patients with multifocal BAC, invasive adenocarcinoma, and NSCLC. Moreover, there is an unmet need for patients who have lung-limited metastasis after successful treatment for primary tumors such as sarcomas or colorectal cancer (CRC). As with liver transplantation for CRC patients who have liver-confined metastases, the applicability of lung transplantation in lung-limited metastatic patients should be explored. There is also an unmet need for patients with respiratory failure with a history of cancer in the last 5 years.

Methods: This is a prospective registration trial to evaluate outcomes of patients who undergo double lung transplantation for the treatment of the select groups of medically refractory cancers (primary lung cancers or metastatic cancers in lungs). Overall survival (OS), disease-free survival (DFS), allograft rejection (AR) and allograft survival (AS) as well as molecular and genetic biomarkers will be studied. The study duration will be 10 years including surveillance. The goal is to enroll 125 participants through the Northwestern Medicine Clinical Programs. Essential Criteria: 1. The tumor should be without any extrapulmonary metastasis as determined by standard of care diagnostic and staging workup. 2. All standard of care or experimental oncological treatments known to improve survival should have failed or deemed infeasible 3. Patients should meet the general criteria for lung transplant evaluation and listing Study cohorts: • Cohort A: Primary lung cancers - Examples include, but not limited to, invasive mucinous/non-mucinous non-small cell lung cancers and multifocal carcinomas. • Cohort B: Metastatic cancers to the lung only - Examples include, but not limited to, germ cell tumors, head & neck tumors, colorectal tumors, renal cell tumors, testicular cancers. • Cohort C: Respiratory failure with a history of cancer in the last 5 years- Examples include, but not limited to interstitial lung disease (ILD), pulmonary fibrosis (idiopathic or secondary), advanced chronic

obstructive pulmonary disease (COPD), bronchiectasis, emphysema, cystic fibrosis (CF), emphysema due to alpha-1 antitrypsin deficiency, and pulmonary arterial hypertension (PAH) Clinical trial registry number : NCT05671887. Enrollment began November 16, 2022. Trial is open and continues to enroll participants as of April 5, 2024.

Keywords: Lung Cancer, Double Lung Transplantation, Lung Transplantation

P2.14B MESOTHELIOMA, THYMOMA, AND OTHER THORACIC TUMORS - CLINICAL TRIALS IN PROGRESS, SUNDAY, SEPTEMBER 8, 2024 - 18:15 - 19:45

P2.14B.02 Application of Chemokine Receptor 4 Targeted 68Ga Pentixafor in Evaluation of Thymic Epithelial Tumors (TETs): A Prospective Study

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Introduction: Recently the correlation between C-X-C chemokine receptor 4 (CXCR4) overexpression with poor prognosis in thymic epithelial tumors (TETs) with myasthenia gravis has been reported. This pilot study was designed to evaluate the use of 68Ga-Pentixafor PET/CT, which targets CXCR4, in the non-invasive diagnosis of TETs.

Methods: With institutional review board approval and informed consent (NCT06086327), a total of 22 patients with suspected TETs (mean age ± SD, 53 ± 12.8 y; 8 men) were enrolled in this prospective pilot study up to now. All patients underwent 68Ga-Pentixafor PET/CT scans at 37 ± 9.5 minutes after injection of approximately 3.7 ± 0.8 mCi of 68Ga-Pentixafor, and the PET/CT outcomes were compared with operation pathology. The expression level of CXCR4 gene was analyzed using bulk RNA-seq in TETs and normal thymus tissues. Cellular localization of CXCR4 was evaluated using single nuclei RNA sequencing (snRNA-seq) analysis.

Results: 21 patients underwent surgery and one patient was followed up after PET/CT scan. 11 patients were diagnosed with TETs (4 Type AB, 1 Type B1, 3 Type B2, 1 Type B3, 1 MNT, and 1 thymic carcinoma) and 11 patients were diagnosed with other tumors (6 thymic cysts, 1 MALT, 1 bronchogenic cyst, 1 pulmonary cyst, 1 haemangioma and 1 mature teratoma). 68Ga-Pentixafor identified all patients with TETs (11/11, 100%), and the mean SUVmax uptake value in all 11 lesions of TETs was 13.9 ± 9.0, which was significantly higher than that in non-TETs (2.2 ± 0.7) ($p < 0.001$). Bulk RNA-seq analysis of 6 TETs and 6 normal thymic tissues reveal that the gene expression of CXCR4 was elevated significantly. Single-cell analysis demonstrated CXCR4 was mainly distributed in immune cells including T_NK cell, B cell, proliferating B cell, plasma, and Macrophage. The distribution of CXCR4 positive cell demonstrated the uptake of CXCR4 targeted 68Ga-Pentixafor mainly enriched in the stroma region of TETs.

Conclusions: The preliminary study indicates the diagnostic utility of 68Ga-Pentixafor in TETs and the differential diagnostic ability of 68Ga-Pentixafor in TETs. Further investigation of the value of differentiating subtypes of TETs and predicting prognosis using 68Ga-Pentixafor in larger clinical trials is warranted.

Keywords: thymic epithelial tumors (TETs), C-X-C chemokine receptor 4 (CXCR4), 68Ga-Pentixafor PET/CT

P2.14B MESOTHELIOMA, THYMOMA, AND OTHER THORACIC TUMORS - CLINICAL TRIALS IN PROGRESS, SUNDAY, SEPTEMBER 8, 2024 - 18:15 - 19:45

P2.14B.03 A Phase II Parallel Arm Study of Sacituzumab Govitecan-Hziy in Patients with Advanced Thymoma and Thymic Carcinoma

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Introduction: Thymic epithelial tumors (TETs), including thymoma and thymic carcinoma, are rare thoracic tumors of the anterior mediastinum. For those with advanced disease, platinum-based chemotherapy is used as first-line treatment. However, there is no standard regimen established for TET at progression after initial therapy, and treatment options for advanced/recurrent TETs are limited. Trop-2, a transmembrane glycoprotein, is overexpressed in solid tumors including thymomas and thymic carcinomas. Sacituzumab govitecan-hziy, a Trop-2-directed antibody-drug conjugate, has shown efficacy and safety in several tumors including breast cancer and urothelial cancer. The overexpression of Trop-2 in TETs and the clinical efficacy in other malignancies provide rationale for exploring its use in thymoma and thymic carcinoma.

Methods: This open-label, single-arm, parallel cohort, multi-center study assesses the safety and efficacy of sacituzumab govitecan-hziy in patients with advanced thymoma (cohort A) and thymic carcinoma (cohort B) who have received at least one prior line of systemic

therapy. The study employs a Simon optimal two-stage design, enrolling patients with adequate performance status, measurable disease, and adequate organ function. Sacituzumab govitecan-hziy is administered at a fixed dose of 10 mg/kg weekly on Days 1 and 8 of 21-day cycles until disease progression or unacceptable toxicity. Follow-up continues every 6 months for 2 years post-discontinuation. Archival tissue is obtained prior to initiation of study treatment with an optional biopsy at the time of progression. In cases where archival tissue is not available, a fresh biopsy is obtained at baseline. Blood samples for correlative studies are collected at baseline, on day 1 of cycle 3, and at the time of progression. The primary endpoint is investigator-assessed response using Response Evaluation Criteria in Solid Tumors v1.1 criteria, with tumor imaging assessments every 2 cycles during the first 3 months and every 3 cycles thereafter. Secondary endpoints comprise adverse events by Common Terminology Criteria for Adverse Events v5.0, median and 6-month progression-free survival, duration of response, and overall survival. For each cohort, 9 patients will be enrolled. If 0 of the 9 achieve a response, no further patients will be enrolled in that cohort. If 1 or more of the first 9 patients has a response, accrual will continue until a total of 17 patients have been enrolled in that cohort.

Results: Not applicable

Conclusions: Not applicable

Keywords: Thymoma, Thymic Carcinoma, Trop-2

P2.14B MESOTHELIOMA, THYMOMA, AND OTHER THORACIC TUMORS - CLINICAL TRIALS IN PROGRESS, SUNDAY, SEPTEMBER 8, 2024 - 18:15 - 19:45

P2.14B.04 Tislelizumab Plus Standard Chemotherapy as First-Line Treatment in Advanced Thymic Epithelial Tumors(TETs): A Prospective, Single-Arm Trial

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Introduction: Thymic epithelial tumors (TETs) ,classified as either thymoma (T) or thymic carcinoma (TC), have a poor prognosis, and treatment options are limited. Chemotherapy remains the standard treatment for advanced TETs. However, Chemotherapy yielded limited benefits with response rates of 20%-30% reported in previous clinical trials. With the exploration of Immunotherapy, PD-1 and PD-L1 inhibitors are gaining momentum as new options for various malignancies. High PD-L1 expression on TETs suggests that anti PD-1/PD-L1 agents could be a promising alternative treatment option for these tumors. Completed clinical trials have shown an encouraging efficacy of Pembrolizumab as a second-line therapeutic strategy for TETs ,despite the high rate of immune-related adverse events(irAEs). Notably, irAEs seem more common in patients with thymoma (T). Therefore, Immunotherapy for TETs is highly controversial. More safety and effective treatment options for TETs need to be explored. There is increasing evidence suggesting that compared with a PD-(L)1 inhibitor alone, a combination with chemotherapy for the first-line treatment may decrease the rates of most irAEs. Tislelizumab is a novel engineered anti-PD-1 monoclonal antibody with high affinity , which was specifically engineered to minimize Fc-–receptor (Fc–R) macrophages binding in order to avoid antibody-dependent phagocytosis. Tislelizumab has shown preliminary anti-tumor effects in various solid tumors. Here, We initiate a prospective trial to explore the feasibility, efficacy and safety of Tislelizumab plus standard Chemotherapy as first-line therapy in unresectable or recurrent TETs.

Methods: Eligible participants must be age ≥18 years with histologically confirmed T or TC not amenable to potentially curative treatments or recurrence after operation; have an Eastern Cooperative Oncology Group (ECOG) performance status of ≥1; and without prior system anticancer therapy after diagnosed with this disease. Key exclusion criteria include patients with immunosuppression, active autoimmune disease or documented history of clinically severe autoimmune disease. Patients with Thymoma will receive Tislelizumab(200mg,d1) in combination with standard Chemotherapy (Cisplatin 50 mg/m2,day1 and Doxorubicin 50 mg/m2 day1 and Cyclophosphamide 500 mg/m2 day1) ,q3w,for 4-6 cycles. Patients with Thymic carcinoma will receive Tislelizumab(200mg,d1) in combination with paclitaxel(200mg,d1) and Carboplatin (AUC=5,d1) ,q3w,for 4-6 cycles. Tislelizumab was administered intravenously at a fixed dose of 200 mg every 3 weeks until disease progression, death, unacceptable toxicity, withdrawal of consent, or at the discretion of the investigators. The survival outcomes, efficacy and safety profile will be investigated. Primary outcome measures will be the overall response rate (ORR) and progression-free survival (PFS). Secondary measures will explore overall survival (OS), duration of response (DOR) ,disease control rate(DCR) and safety. This study is registered with chinadrugtrials.org.cn, ChiCTR2400081177.

Results: From October 2023 to April 2024, this study has enrolled 8 TETs patients(5 with TC and 3 with T) .Median age was 61 years(range: 54-72) and 50% were male. By the cutoff day (April 5th,2024), none of them developed disease progression and 5 patients can be evaluated. Confirmed partial response (PR) were achieved in 2 patients and Stable disease (SD) in 3 patients, resulting in DCR of 100%. The PFS and OS were not reached. One enrolled patient was diagnosed with type A Thymoma with malignant lesions involved the superior vena cava and right atrium. The edema caused by superior vena cava syndrome significantly reduced after systemic treatment. Of the 8 enrolled patients, the most frequently observed adverse events of any grade, regardless of their causality to Tislelizumab, was myelosuppression (5/8). One patient with Thymoma (1/8) experienced immune-related adverse events(irAEs) grade 3 immune-related pneumonia. No immune-related Grade 4-5 AEs were reported and all AEs were manageable with supportive measures.

Conclusions: Tislelizumab plus standard Chemotherapy as first-line treatment showed encouraging antitumor activity and tolerable safety profile.Larger prospective randomized studies are warranted.This study is ongoing and more data will be released. Further ploration of biomarkers is also underway to identify potential benefit populations.

Keywords: Tislelizumab, Thymic epithelial tumor, First-line treatment

P2.14B MESOTHELIOMA, THYMOMA, AND OTHER THORACIC TUMORS - CLINICAL TRIALS IN PROGRESS, SUNDAY, SEPTEMBER 8, 2024 - 18:15 - 19:45

P2.14B.05 eVOLVE-Meso: A Global Phase 3 Study of First-Line Volrustomig Plus Chemotherapy in Unresectable Pleural Mesothelioma

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Introduction: Recent phase 3 studies in patients with unresectable pleural mesothelioma (PM) have demonstrated a significant improvement in median overall survival (OS) for anti-programmed cell death-1 (PD-1) antibodies in combination with standard chemotherapy (CCTG IND.227) or cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) inhibition (CheckMate 743). No trials to date have investigated the treatment of PM using a combination of chemotherapy with inhibition of both PD-1 and CTLA4 using immunotherapy, in comparison to standard-of-care dual immunotherapy alone or chemotherapy alone (depending on histology). Volrustomig (MEDI5752) is a monovalent, PD-1/CTLA-4 bispecific, humanized IgG1 monoclonal antibody engineered to specifically inhibit PD-1, with increased CTLA-4 blockade on PD-1+ activated T cells compared to PD-1- resting peripheral T cells. This mechanism of action may allow enhanced CTLA-4 blockade at tolerable doses beyond those achieved with current PD-1/CTLA-4 combinations. In a first-in-human phase 1/2 study (NCT03530397), first-line volrustomig + carboplatin + pemetrexed showed promising efficacy with acceptable tolerability in non-small-cell lung cancer. Building upon these findings, the phase 3, open-label, multicenter, global eVOLVE-Meso study will evaluate whether first-line volrustomig in combination with chemotherapy improves efficacy compared with current standard-of-care regimens in patients with unresectable PM (NCT06097728).

Methods: Key eligibility criteria include age ≥18 years, WHO/ECOG PS of 0 or 1, adequate organ and bone marrow function, PM with known histology (epithelioid or non-epithelioid including biphasic or sarcomatoid), no prior systemic therapy for PM, and no active or prior autoimmune or inflammatory disorders (Figure). Approximately 600 patients will be randomized in a 1:1 ratio to volrustomig + carboplatin + pemetrexed; or investigator's choice of (a) nivolumab + ipilimumab until PD, unacceptable toxicity or for up to 2 years, or (b) for epithelioid histologies only, pemetrexed + carboplatin or cisplatin. Randomization will be stratified according to tumor histology (epithelioid vs non-epithelioid), sex (male vs female), region (Americas vs Europe vs Asia), and investigator's choice of planned regimen (nivolumab + ipilimumab vs platinum + pemetrexed). The primary endpoint is OS in patients with epithelioid histology. Secondary endpoints include OS in all randomized patients; investigator-assessed progression-free survival in patients with epithelioid histology and in all randomized patients, objective response rate, and duration of response determined by modified RECIST 1.1; time to second progression or death; and safety. Pharmacokinetic and exploratory biomarker analyses will also be conducted. Enrollment opened in November, 2023.

Keywords: Bispecific antibody, Pleural mesothelioma, Immunotherapy

P2.16A PATIENT ADVOCACY - BIOMARKERS, SUNDAY, SEPTEMBER 8, 2024 - 18:15 - 19:45

P2.16A.01 Actionable Alterations Identification in NSCLC by Comprehensive Genomic Profiling for Clinical Trial Enrollment: EPROPA

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Introduction: To reduce the gap about the relevant heterogeneity of molecular testing and cancer care across Europe, Women Against Lung Cancer in Europe (WALCE) promoted the European Program for ROutine testing of Patients with Advanced lung cancer (EPROPA) and providing a free-of-charge molecular profiling platform for non-small cell lung cancer sample characterization with the aim of increasing the detection of targetable drivers and improving patients' access to clinical trials.

Methods: From January 2021 to December 2023, 20 centres located at 5 different European countries (Greece, Slovenia, Romania, Albania and Italy) joined EPROPA, with 555 advanced NSCLC patients registered into the program. Anonymized patients' clinical-pathological data were shared through the EPROPA web platform and tissue samples were collected to the Molecular Pathology Unit of the Reference Center (University of Turin) for molecular analyses. A comprehensive genomic profiling by targeted next-generation sequencing approach has been performed and molecular reports have been discussed within the molecular tumour board (MTB) in order to assess patients' eligibility for clinical trials.

Results: The average turnaround time was 8 days, with only 30 out of 555 (6%) tissue samples not suitable for molecular analysis. Among the 525 analyzed samples, a total of 570 molecular alterations have been identified, including 264 pathogenic targetable oncogenic alterations and 113 cases with co-occurring mutations, while no molecular alterations have been detected in 41/525 (8%) of cases. A total of 18 molecular alterations with potential germline and hereditary cancer syndrome implications have been reported. The identification of a clinical trial was considered for 205 patients. After MTB discussion, 30 patients were enrolled and treated in clinical studies available in Europe; no clinical trials were available for 122 patients while 53 patients were not clinically eligible.

Conclusions: This data confirmed the feasibility and usefulness of the program in the real-world practice scenario, supporting the implementation of NGS-based molecular characterization of advanced NSCLC samples, in order to reduce the unequal access to tests, drugs and clinical trials in Europe.

Keywords: Precision medicine, lung cancer, molecular biomarkers

P2.16A PATIENT ADVOCACY - BIOMARKERS, SUNDAY, SEPTEMBER 8, 2024 - 18:15 - 19:45

P2.16A.02 Improving Patients' Awareness of Biomarker Test Timing and Purpose with 4R Oncology Intervention

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Introduction: Patients' awareness of timing and purpose of biomarker testing is critical for their engagement in care but is challenging to achieve (Martin 2022). The 4R Oncology model of patient self-management and timely care delivery has shown improvements in patient knowledge of care timing/sequence (Trosman 2021, Liu 2023) but has not been studied in NSCLC specific to biomarker testing. 4R is Right Info/Care/Patient/Time. A central 4R tool is Care Sequence, a patient-facing care plan describing the course and timing/sequence of care. We implemented 4R in NSCLC at 8 centers (4-community, 3-academic, 1-VA) in 2022-2023 and assessed its impact on patients' awareness of biomarker testing timing and purpose.

Methods: We refined Care Sequences to emphasize biomarker timing versus treatment decisions, and to recommend patient actions while waiting for results, including obtaining supportive, social and health maintenance care. The intervention (4R) patient cohort received Care Sequences at care planning appointments, accompanied by patient-provider discussion. We compared survey results from the 4R cohort with historical control cohort of patients who received care pre-4R. See Table for metrics.

Results: Survey response rates: 4R cohort 67% (61/91), control cohort 66% (112/170). Respondents in 4R cohort/control cohort respectively were: 62%/46% black, 64%/48% high school educated or less, 64%/55%with annual income <$30,000, 54%/58% NSCLC Stage IV. Implementing 4R resulted in significant improvement in all 11 metrics between control and 4R cohorts (Table). In addition to improving patient awareness of biomarker test timing, the use of 4R was associated with higher rate of patients willing to wait for test results before treatment and patients understanding how they can be active with there are while waiting.

Conclusions: Utilizing 4R Oncology significantly improved patients' understanding of biomarker test timing versus treatment decisions and increased patients' willingness to wait for results before starting treatment. 4R broad national rollout is underway.

Patient input on biomarker and other test* timing and purpose

Metrics: Patient input on biomarker and other test* timing and purpose

4R cohort patients

Control cohort patients

Pvalue

Questions asked of all patients, 4R cohort N=61; control cohort N=112

I received biomarker testing

70%

47%

.003

I knew WHY I needed to wait for biomarker or other test results to start therapy

82%

55%

.0003

I knew how long test results will take

93%

53%

.0001

Providers told me I need to wait for biomarker or other test results before starting therapy

77%

30%

.0001

I was OK waiting for biomarker or other test results before starting therapy

95%

77%

.001

I knew what I could do to stay as healthy as possible while waiting for test results

93%

71%

.0003

I knew what help I could get for my financial, family, or practical needs while waiting for test results

90%

53%

.0001

Questions asked of patients who received biomarker testing, 4R sub-cohort n = 43; control sub-cohort n=53

Providers discussed biomarker results with me

95%

77%

.01

Providers discussed with me how biomarker results impacted my therapy selection

98%

83%

.02

Biomarker results were clear to me

91%

43%

.0001

I was clear WHY my therapy was selected

95%

60%

.0001

*We included other testing because not all patients might have received biomarker testing. For these patients, understanding of timing and purpose of other tests that inform treatment decisions serve as a proxy for timing and purpose of biomarker testing.

Keywords: Biomarker, testing, timing

P2.16B PATIENT ADVOCACY - CLINICAL COMMUNICATION, SUNDAY, SEPTEMBER 8, 2024 - 18:15 - 19:45

P2.16B.01 Attributes that Impact Patient and Physician Preferences for Maintenance Treatment in Advanced/metastatic NSCLC

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Introduction: Patients with advanced/metastatic non-small cell lung cancer (a/mNSCLC) and treating physicians may have different perspectives on maintenance therapy. It is important to identify what treatment attributes are important for both patients and physicians as they may significantly affect treatment selection. This study investigated treatment attribute preferences of patients and physicians in the maintenance therapy setting after first-line (1L) treatment for a/mNSCLC.

Methods: This survey-based study, conducted alongside a discrete choice experiment, included patients and physicians in the US and UK. Eligible patients (aged ≥18 y) had an a/mNSCLC diagnosis and had completed 1L treatment. Physicians were licensed oncologists with ≥5 years' experience in a/mNSCLC treatment and had treated ≥20 such patients in the past year. Data were collected using choice cards, designed to capture treatment attribute preferences, including efficacy (overall survival [OS] and progression-free survival [PFS]), chance of new brain metastasis, and adverse events. Attributes related to quality of life were not specifically included because of their high correlations with the selected efficacy and safety attributes.

Results: Among 82 patients (34 UK, 48 US), the 3 most important treatment attributes were chance of new brain metastasis, OS, and risk of severe neutropenia (Table). The least important treatment attributes for patients were risks of severe nausea and severe vomiting. Among 101 physicians (51 UK, 50 US), the 3 most important treatment attributes were OS, chance of developing new brain metastasis, and PFS (Table). Risks of experiencing severe nausea or vomiting were the least important attributes to physicians.

Conclusions: In this real-world study, concordance was seen between patients with a/mNSCLC and treating physicians on the importance of certain treatment attributes. OS and the chance of developing new brain metastasis were among the top 2 most important treatment attributes for physicians and for patients with a/mNSCLC; however, OS and PFS were rated at a greater relative importance, and chance of new brain metastasis was rated at a lesser relative importance, for physicians than patients. These attributes will be important to consider when selecting maintenance therapy treatment following 1L therapy.

Keywords: metastatic NSCLC, Maintenance treatment, Patient preferences

P2.16C PATIENT ADVOCACY - DISPARITIES, SUNDAY, SEPTEMBER 8, 2024 - 18:15 - 19:45

P2.16C.01 Awareness, Stigma, and Fatalism Towards Cancer Clinical Trials Among Black Individuals Diagnosed with Lung Cancer

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Introduction: Only about 8% of people with cancer in the USA participate in clinical trials. Participation is even lower among racial and ethnic minority groups, including Black persons diagnosed with cancer who comprise about 6% of trial participants. The STRIDES (Studying

Trial Determinants of Success) study utilized patient-reported data to examine barriers and facilitators to trial participation among Black individuals diagnosed with lung cancer.

Methods: Individuals over the age of 18, previously diagnosed with lung cancer, and who identified as "all or part Black, African American, or African" were invited to respond to a survey on experiences and preferences around lung cancer clinical trials. Participants were required to have received lung cancer care within 5 years of study enrollment at one of three institutions in the Southeastern USA: University of Alabama at Birmingham, Vanderbilt University Medical Center, or INOVA Schar Cancer Institute. Surveys included demographic items and validated scales assessing experiences of stigma and cancer fatalism as well as trial knowledge. Recruitment methods were decided locally based on best practices at each participating site. Survey data, collected at each institution, were pooled, cleaned, and evaluated using descriptive statistics and bivariate analyses.

Results: 61 people with lung cancer responded to the survey (average age: 65 years; 58% female). Among respondents who were willing to provide a response (N=57), 68% reported a household income under $50,000 US dollars in the past 12 months and all currently had health insurance. The Cancer Fatalism survey (derived from Powe) and Lung Cancer Stigma Inventory were administered, and responses indicated low levels. For instance, when asked "if someone has cancer, it is already too late to get treated", 91.8% disagreed and when asked "It has been hard to tell people that I have lung cancer", 70.4% disagreed. Most participants (55%) reported that no one had discussed clinical trials with them. Among respondents who reported having trial discussions, the majority occurred at the time of diagnosis (59%), most commonly with their primary oncologist (50%). These discussions were rated on average as helpful and understandable (average 4.18 and 4.31 respectively on a 5-point Likert scale). The preferred format of clinical trials education varied among STRIDES participants, but the most frequently preferred source of clinical trials information (reported by 44% of respondents) was the primary oncologist.

Conclusions: Over half (55%) of STRIDES participants reported having had no conversations about clinical trials with a member of their clinical care team. Other studies have indicated marginalized populations are interested in trial enrollment if offered. Considering this and that we observed a large population not having trial discussions in STRIDES, increasing the frequency and modality of trial conversations could be key to increasing enrollment of underrepresented Black individuals in clinical trials. The preferred source of trial information in STRIDES was the primary oncologist, highlighting implications for practice patterns in trial enrollment and underscoring the physicians' role in addressing trial participation gaps. This data provides important information for cancer centers developing strategies to increase clinical trials diversity.

Keywords: Clinical Trials, Cancer Disparities, Health Equity

P2.16C PATIENT ADVOCACY - DISPARITIES, SUNDAY, SEPTEMBER 8, 2024 - 18:15 - 19:45

P2.16C.02 Development of a Framework to Address Lung Cancer Health Disparities: One Organization's Experience

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Introduction: Lung cancer remains the leading cause of cancer deaths in the United States and the developed world. Great advances, including screening implementation and innovative treatments, are being developed at a rapid rate. However, lack of access and social/structural challenges continue to have a negative impact on marginalized communities, which may be at greater risk for lung cancer and have less access to new treatment advancements. While a fair amount has been written on inequities in lung cancer care in the United States, our goal was to create a centralized repository of lung cancer disparities data, and then to use this data to create a strategic framework to target those most in need for our outreach efforts.

Methods: First, a literature review was conducted using five databases with the following inclusion criteria: (I) peer-reviewed academic journals published in English between the years 2000 and 2022; (II) research that focused on disparities across the lung cancer continuum; and (III) research articles addressing social and structural barriers to lung cancer health care access. A total of 95 articles and 24 reports were used for this narrative review. The review analyzed 10 populations: Black/African American; American Indian/Alaska Native; Hispanic/Latinx; Asian American/Pacific Islander; low income; rural; LGBTQIA+; women; active duty military and Veterans; and those at risk and diagnosed with small cell lung cancer. Those results were published in 2023. To develop the framework, a 15-week process was used to identify priority populations. First, internal interviews and an external landscape analysis were conducted. Next, findings were presented, and staff were engaged in visioning exercises to map the organizations' health equity aspirations and identify opportunities. An initial framework and strategy options were drafted and continually refined through additional interviews and focus groups. The final framework was then presented to all staff for finalization.

Results: The top priority groups were identified as those at risk and living with lung cancer who are Black/ African American, those living in rural areas, and those of lower socioeconomic status. Secondary priority populations of importance include Veterans, Hispanic/Latinos, and women. Each department with GO2 for Lung Cancer was then assisted in identifying up to three strategies for 2024 to begin to address health disparities.

Conclusions: Future studies are needed to further develop meaningful solutions to disparities in health outcomes and access for those who are at risk, diagnosed with, or surviving lung cancer from marginalized populations.

Keywords: lung cancer, health disparities, marginalized populations

P2.16D PATIENT ADVOCACY - LUNG CANCER EDUCATION, SUNDAY, SEPTEMBER 8, 2024 - 18:15 - 19:45

P2.16D.01 Changes in Students' Perceptions of Cancer Through Cancer Education and Lectures by External Instructors with Cancer Experience

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Introduction: The fourth phase of the Basic Plan for Cancer Control also emphasizes the importance of cancer education and the dissemination of knowledge about cancer. The purpose of this study is to investigate how students' perceptions of cancer change through lectures by external instructors with cancer experience and to verify the effectiveness of cancer education conducted by those who have experienced cancer.

Methods: The Kanagawa Prefecture Cancer Patient Organizations conducted pre- and post-cancer education surveys from 2020 to 2022 under the framework of the Kanagawa Voluntary Activity Promotion Fund 21 Project. The survey targeted 29 schools (14 high schools, 11 middle schools, and 4 by academic year), with a total of 1485 students participating in the pre-survey and 1375 students in the post-survey. The main focus of the analysis was on the changes in students' perceptions of cancer. The data from the pre- and post-surveys were compared to quantitatively analyze the changes in cancer perceptions. Specifically, the differences in the statistical proportions before and after for each item were analyzed.

Results: Perception of being bedridden or in the hospital: "Yes" responses significantly decreased from 50.1% before to 31.6% after. (p = 0.0251) Thinking that nothing special changes just because it's cancer: "Yes" responses significantly increased from 22.2% before to 45.1% after. (p = 0.0297) Feeling pity: "Yes" responses decreased from 46.5% before to 29.7% after, showing a significant trend. (p = 0.0545) Associating cancer with excessive smoking or drinking: "Yes" responses decreased from 26.6% before to 21.3% after, showing a significant trend. (p = 0.0911) Thinking the person looks pale and thin: "Yes" responses decreased from 27.5% before to 15.2% after. (p = 0.184) Thinking the person is always depressed: "Yes" responses increased slightly from 10.7% before to 11.5% after. (p = 0.314) Believing that the person can work: "Yes" responses increased from 6.8% before to 25.5% after. (p = 0.319) Thinking the person can enjoy life: "Yes" responses increased from 4.7% before to 29.7% after. (p = 0.433)

Conclusions: Changes were observed in students' perceptions of cancer, particularly in the beliefs that people with cancer are bedridden or in the hospital and that having cancer does not significantly change things. It is believed that the presence of external instructors with cancer experience delivering the lectures had an impact. Although there was no significant difference regarding the belief that cancer is caused by excessive smoking or drinking, a significant trend was observed. This suggests a reduction in the prejudice that cancer patients acquire the disease due to poor lifestyle habits.

Keywords: Stigma, Cancer Education

P2.16E PATIENT ADVOCACY - NEEDS OF PATIENTS AND CAREGIVERS, SUNDAY, SEPTEMBER 8, 2024 - 18:15 - 19:45

P2.16E.01 Lung Cancer Patients' Support Preferences: Insights from a Global Patient Experience Survey

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Introduction: The Global Lung Cancer Coalition (GLCC), a partnership of 43 patient organisations across 30 nations, reaffirms in its charter the right of all lung cancer patients to be treated with dignity and respect and to have informed self-determination. Understanding lung cancer patients' experience and what support they need to help them cope with their condition is an important aspect of the GLCC's work. This survey therefore sought to better understand the support preferences of lung cancer patients around the world.

Methods: In the GLCC's fifth annual survey, the coalition commissioned Censuswide to conduct a global survey of lung cancer patients. The survey is currently in the field across 18 countries (Australia, Argentina, Bulgaria, Canada, Denmark, Greece, Ireland, Israel, Italy, Japan, Mexico, Portugal, Netherlands, South Africa, Spain, Taiwan, UK, USA). As part of this survey, the GLCC included questions about where respondents currently seek help in coping with their condition and where they would like to receive help.

Results: 67% (602/905) of respondents reported receiving support from healthcare professionals to cope with their disease, followed by 62% (559/905) of respondents who reported receiving support from family and friends. Other prominent modes of support include in-person support groups (29%), online support groups (25%), social media communities (21%) and counselling/therapy (19%).

When asked what support they would like to receive to help them cope with their disease, answers were broadly aligned with what support is already being accessed. Although there was a greater desire for counselling or therapy (23% v 19%), as well as a desire for greater

support from spiritual or religious communities (11% v 7%) and work colleagues (7% v 4%).

Conclusions: By identifying where patients seek help and their preferences for receiving support, from family and friends to online communities and professional services, patient organisations and providers can tailor their assistance, support services, and interventions to better meet patients' needs, thus upholding their integrity and dignity.

Keywords: lung cancer, patient experience, support preferences

P2.16E PATIENT ADVOCACY - NEEDS OF PATIENTS AND CAREGIVERS, SUNDAY, SEPTEMBER 8, 2024 - 18:15 - 19:45

P2.16E.02 Emotional Support Resource Access and Utilization Among People with Lung Cancer

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Introduction: A systematic review conducted by Rajapakse in 2021 found that up to 80% of people with lung cancer experience psychological distress, including depression, which is three times higher than other types of cancer. Despite this, mental health services are generally underutilized. Given these challenges, we examined patterns of underutilization using data from a real-world patient-reported data registry.

Methods: The Lung Cancer Registry (lungcancerregistry.org) from GO2 for Lung Cancer is an online collection of surveys for people with lung cancer to provide treatment information and disease status updates. From the annual questionnaire data collected from 2019-2023, we included US-based participants who had indicated any level of depression (at least "a little bit" depressed) when responding to "Did you feel depressed?" on the EORTC Core Quality of Life questionnaire, and then evaluated whether they had utilized emotional support resources (i.e. support group and/or counseling). In the subset of participants who reported any level of depression, our objective was to describe the demographics and disease-related characteristics of the group who reported utilizing emotional support resources, as compared to those who did not. To determine access to emotional support resources, we looked at travel time to clinic and the participant's distance from the nearest NCI-Designated Cancer Center. Associations between categorical groupings were evaluated for statistical significance using chi-square tests of association or Fishers exact test as appropriate. Distributions of continuous variables (domain scores, age, and time from diagnosis) were compared using a Wilcoxon rank-sum test.

Results: Of the 82 participants who indicated at least "a little bit" depression and may have particularly benefited from support resources of counseling or support groups, only 36 (43.9%) reported receiving such support. Furthermore, a greater percentage of participants who reported travel time to clinic of less than one hour did access a resource, as compared to those who reported longer travel times (54% versus 32%), although the association was not significant (p=0.12). The distance between the participant's residence and the nearest NCI-Designated Cancer Center was significantly lower in those who utilized resources (mean of 30 miles versus 54 miles, p=0.007). Other characteristics (demographics, stage of disease, physical function, and global health) were essentially the same across the two groups.

Conclusions: In this study, we sought to determine whether people with lung cancer who experience depression have access to and receive the emotional support resources they need. While we found a correlation between distance to NCI-Designated Cancer Center and receipt of emotional support resources, we did not collect information on whether the support groups and counseling sessions were conducted in-person or virtual. Further analysis with larger sample sizes is needed to determine the barriers to receiving emotional support among those who report depression. Regardless, these findings suggest that collaboration between health care teams and advocacy or cancer organizations is warranted in increasing access to emotional support programs for people with lung cancer.

Keywords: emotional support, depression, quality of life

P2.16F PATIENT ADVOCACY - PATIENT-RESEARCHER PARTNERSHIP, SUNDAY, SEPTEMBER 8, 2024 - 18:15 - 19:45

P2.16F.01 Patient-Led Oncogene-Driven Lung Cancer Translational Research to Expedite Therapeutic Development

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Introduction: Oncogene-driven lung cancers (LCs) arise in people from all walks of life. Therefore, it is no surprise that ALK Positive Inc. (API), a nonprofit patient advocacy organization, has formed Medical Committees comprised of patients and caregivers with experience in medicine, research, pharma, biotech, business, and finance. The API Medical Committees are dedicated to advancing new therapies for ALK+ cancers that will convert these lethal cancers into chronic and curable diseases. The primary goal of these patient-driven analyses of ALK+ tumor gene expression is to nominate candidate targets for new therapies and biomarkers of tumor treatment response.

Methods: We have utilized publicly available single cell RNA (scRNA) sequence data to analyze expression of over 18,000 protein-coding genes among 61 cell types defined within a human lung cell atlas from Sikkema et al 2023. Raw data were from Kim et al 2020, Laughney et

al 2020, Maynard et al 2020, Bischoff et al 2021 and Wu et al 2021. EirClin utilized an scRNASequest (Li et al 2023) computational workflow, including but not limited to Harmony, Azimuth, Seurat, Scanpy and Nebula, to perform data harmonization, reference-based cell type annotation and differential analysis. Single cell expression profiles were visualized with CellXGene VIP software (Li et al 2020) to create trackplots (Figure 1) in which each vertical line represents a single tumor cell.

Results: We characterized scRNA expression profiles in 64 LC patients, including ALK+, BRAF+, EGFR+, HER2+, KRAS+, MET+ and ROS1+ patients. Our analysis identified targets expressed among multiple oncogenic drivers. The figure below visualizes expression profiles for 12 representative target genes among these 64 LC patients. Understanding expression profiles among drivers can inform clinical trial design by enabling inclusion of driver subpopulations that express of a particular therapeutic target, and facilitate faster trial enrollment by including all driver subpopulations likely to benefit from a given therapeutic intervention.

Conclusions: Our goals are to enable faster, more effective clinical trials to improve treatment responses in oncogene-driven lung cancers. We are open to collaborating with other advocacy groups to expand datasets across multiple drivers. Our study demonstrates that patients and caregivers have the capacity and can acquire funding to undertake independent, patient-centric research that will advance personalized treatments and facilitate transformation of oncogene-driven cancers into chronic and curable diseases.

Keywords: ALK, Patient advocacy, Single cell RNA sequencing

P2.16F PATIENT ADVOCACY - PATIENT-RESEARCHER PARTNERSHIP, SUNDAY, SEPTEMBER 8, 2024 - 18:15 - 19:45

P2.16F.02 LIFE Project: Lung Cancer Patients' Involvement in Research Fostering Their Empowerment

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Introduction: The LIFE project aims to strengthen patient-centered clinical research by empowering lung cancer patients through their active participation in the research process. While addressing the current gaps in patient engagement, the project's primary focus is upon designing a framework that would facilitate collaboration between patients and healthcare professionals to ensure that the clinical research conducted is both ethical, relevant, and meaningful for all stakeholders involved.

Methods: The study utilized a qualitative research method that incorporated Metaplan technique workshops with lung cancer patients and healthcare professionals from the Catalan Institute of Oncology (ICO). These workshops aimed to explore the benefits of patient involvement in research, address concerns from both patients and professionals about such involvement, and identify the necessary skills and knowledge required for patients to participate effectively.Two exploratory workshops were executed. The first included eight patients (6 women and 2 men), while the second was attended by seven health-professionals (4 medical oncologists, 1 radiation oncologist, and 2 advanced practice nurses) from the Thoracic Cancer Unit at ICO.To conclude the qualitative research project, the final exploratory phase, which involved the focus group's exploration and consensus phase, was conducted. A workshop was organized, where 7 patients and a family member, along with the seven healthcare-professionals, collaboratively reviewed the outcomes of the previous workshops.At the conclusion of the workshop, a prioritization exercise was conducted to assess various proposed areas concerning the skills and knowledge that patients need to enhance. This assessment focused on the significance of each skill/competence and its feasibility, using a simple priority matrix, which aligns with the main goal of the LIFE project. The prioritization process involved scoring each identified element on a scale from 0 to 10, based on the consensus reached between patients and professionals.

Results: The study successfully identified key areas of cooperation between patients and professionals that contribute to strengthening research. These areas include research design, informed consent, and the dissemination of results. The primary concerns raised encompassed meeting patients' expectations, ethical considerations, and practical issues. Additionally, the study highlighted the necessary skills for patients, with a focus on research literacy and effective interpersonal communication. An analysis comparing the average results from patients and professionals revealed no statistically significant differences. "Knowledge training" emerged as the top priority among the necessary skills for patients. The essential areas where training is considered necessary include knowledge of the disease and treatment options, understanding of the entire clinical research process, communication skills, and teamwork.

Conclusions: The findings of the LIFE project demonstrate the vast potential of patient involvement in lung cancer research and the mutual benefit of patient-professional cooperation in clinical trials. By including patients in the clinical research process from start to end, the project enables the development of more ethical and relevant patient-centered clinical studies. Future research should engage in addressing the presented concerns, enhancing patient literacy, and supporting patient leadership in clinical studies. The results clearly support the shift to more participative patient-oriented research methodology in lung cancer studies and, probably, in patient care practice.

Keywords: patient empowerment, lung cancer, clinical trials

P2.16F PATIENT ADVOCACY - PATIENT-RESEARCHER PARTNERSHIP, SUNDAY, SEPTEMBER 8, 2024 - 18:15 - 19:45

P2.16F.03 Development of a Patient-Friendly Lung Cancer Lexicon

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Introduction: The IASLC Language Guide was published in 2021, promoting the adoption of preferred language and phrasing in oral and written communication that is person centered, eliminates blame, ends stigma, and is equitable. Although recent trends in the scientific literature point to increasing use of patient-centric titles, some language used in scientific publications, including those meant for lay audiences, continues to be overwhelming and overly technical for patients and caregivers; commonly used terms are sometimes not inclusive or empathetic to the patient's lived experience. This project aimed to expand on the IASLC guide by developing a patient-friendly lexicon for lung cancer communications and is intended for adoption within a major pharmaceutical company.

Methods: Development of this lexicon involved a multistep process. The unmet need was examined through social media analysis of lung cancer conversations and literature analysis of terms currently used in lung cancer plain language summaries. Additional insights into existing language barriers and complex concepts in the lung cancer space were elucidated via an advisory board and multiple stakeholder interviews of experts, including lung cancer healthcare providers, patients, and patient advocates. A set of commonly used complex or noninclusive scientific terms was discussed, and alternative simplified and/or more inclusive terms or phrases were suggested. Further validation and refinement of the patient-friendly lexicon was conducted with a team of pharmaceutical company lung cancer researchers and a lung cancer patient/advocate.

Results: Social media listening analysis revealed that online communities discussing lung cancer often could not interpret or understand medical terminology used in clinical trial summaries, healthcare provider conversations, and online resources from medical associations or pharmaceutical companies. Results of the literature analysis showed that lung cancer plain language summaries do not utilize consistent or standardized language when describing concepts involving disease state, treatment descriptions (eg, how targeted treatments work), and treatment outcomes. Insights gathered from lung cancer experts found that many common terms used to describe treatment outcomes were not patient-centric (eg, describing a safety profile as "tolerable" when not reported as such by patients) and/or challenging for patients to understand and/or for providers to explain (eg, "median"). Alternative patient-friendly terms or explanations were proposed and pressure tested to be empathetic, clear, and easily understood. The final set of validated patient-friendly lexicon terms was divided into three categories: safety, efficacy, and other. In addition, use cases were assigned such that the lexicon terms could be appropriately used in either low complexity cases (eg, plain language summaries), high complexity cases (eg, professional congress abstracts), or both. For example, the term "side effect" was included in the lexicon as a simpler alternative to "adverse event" but may only be appropriate in low complexity cases. The entire lexicon will be shared in the presentation.

Conclusions: Some commonly used terms in lung cancer research can be simplified to be more patient-centric, empathetic, and inclusive. The patient-friendly lung cancer lexicon was developed with the hope that widespread adoption in medical communications could help advances in lung cancer research be more easily understood among patients and caregivers.

Keywords: patient-centric, lexicon

P2.16G PATIENT ADVOCACY - SCREENING, SUNDAY, SEPTEMBER 8, 2024 - 18:15 - 19:45

P2.16G.01 Annual Lung Cancer Screening Day in the United States- Year Two

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Introduction: The American Cancer Society National Lung Cancer Roundtable, American College of Radiology, and Radiology Health Equity Coalition, partnered again for the second annual National Lung Cancer Screening Day on Saturday, November 11, 2023, as an important part of Lung Cancer Awareness Month. In acknowledgment of National LCS Day falling on Veterans Day, the ACS NLCRT, ACR, and RHEC partnered with the Veterans Health Administration on this campaign to salute our Veterans by increasing outreach and awareness to our veteran population, in turn saving more lives. The LCS day campaign asks facilities to open their doors on the second Saturday in November to offer lung cancer CT screening. Opening on a Saturday increases access to lung cancer screening particularly for individuals who may not be able to take time off work Monday through Friday. National LCS Day serves as a catalyst for lung cancer screening, increasing the profile of this life saving test among health care providers and in the community, with the goal of increasing community and patient education and increasing lung screening as a year-round priority.

Methods: Marketing for National Lung Cancer Screening Day began in July, a shift from the previous year when it started in September. Facilities sign up on a website (https://nlcrt.org/lung-cancer-screening-day) which provided access to complementary marketing and instructional materials with patient- friendly videos to facilitate opening their doors to patients on Saturday, November 11, 2023. Resources included promotional flyers for patients in English and Spanish, a logistics guide for opening a screening center on a Saturday, a patient-centered marketing email template, a sample press release for facilities to engage their local news platforms, and an order form for white ribbon lapel pins. A post-survey was sent to participating facilities to collect information on patients screened and perceptions of event success.

Results: There was a significant steady increase in registered facilities in 2023 compared to 2022, with 759 facilities in 47 states and Puerto Rico in 2023 as illustrated in Figure 1, compared to 328 facilities in 2022 Among the 2023 facilities, 74% were new to LCS Day and 26% had participated in the inaugural 2022 LCS day. Facilities that were already open on Saturday made up 41% of the facilities of which 31% opened specifically for LCS Day, and 28% were advocacy organizations

Conclusions: The second National Lung Cancer Screening Day was successfully held at facilities in 97% of states across the U.S., an increase from 75% from the prior year, increasing patients screened and awareness about LCS in their communities. The participation of both screening facilities and LCS advocacy organizations demonstrates commitment to use NLCSD as a way to educate patients and communities to reduce lung cancer deaths through this life saving screening exam.

Keywords: Screening, Early Detection, Patient Outreach

P2.16G PATIENT ADVOCACY - SCREENING, SUNDAY, SEPTEMBER 8, 2024 - 18:15 - 19:45

P2.16G.02 “It’s Like A Donut!”- Veteran Perspectives of Lung Cancer Screening with Low Dose CT

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Introduction: Screening with low dose computed tomography (LDCT) reduces mortality from lung cancer. However, LDCT utilization is low in clinical practice, including in the United States Veterans Health Administration. We explored Veteran experiences with lung cancer screening and perceived barriers to receiving LDCT screenings and opportunities for improving lung cancer screening at Veterans Affairs Medical Centers (VAMCs).

Methods: We conducted a cross-sectional, qualitative study of Veterans at a single VAMC between January 1, 2021 and August 6, 2021. Our research team led semi-structured telephone interviews with Veterans after they were referred to the VAMC’s Lung Cancer Screening Program, including those who agreed or declined to enroll. We utilized the Socioecological Model as a framework for data analysis. This model includes four domains: Organizational, Interpersonal, Individual and Societal. The qualitative data were analyzed using an iterative inductive-deductive approach to identify themes and relationships between themes.

Results: A total of 34 interviews (20 with Veterans who enrolled in the lung screening program and 14 with Veterans who did not enroll) were conducted and included in the final analytic sample. The strongest factor associated with Veterans’ decision to pursue lung cancer screening was their level of personal education and awareness about this early detection test (individual, interpersonal and organizational domains of socioecological model). Veterans indicated a lack of understanding of the steps involved in LDCT screening would make them less likely to enroll. Veterans reported not understanding that lung cancer screening is an imaging-based study. Another common theme included rural factors include location and societal norms (societal domain) and access to care (organizational domain) as barriers influencing the decision to undergo LDCT. Organizational suggestions for improvement included developing accessible Veteran-centric educational materials on what a CT scanner looks like and sounds like, and the duration of LDCT examination (less than 1 minute). Regarding the LDCT scan, one participant stated “it’s like a donut!”, indicating that if others understood the simplicity of the exam, they too may be more likely to participate. Societal suggestions from Veterans for improvement included implementing mobile screening units, broadening education and awareness, and improving the overall personal screening experience.

Conclusions: Veterans interviewed relayed a lack of clarity on the process and duration of lung cancer screening, negatively influencing decisions to pursue lung cancer screening. Interview participants offered a variety of solutions that were specifically tailored to address educational barriers and increase LDCT screening in the Veteran population, including the use of mobile screening units and improved, Veteran-centric education. Future studies are warranted to test the effectiveness and acceptability of these recommended strategies aiming to increase LDCT utilization in the Veterans Health Administration.

Keywords: Lung cancer screening, Veterans, socioecological model

P2.17A GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS - CLINICAL MANAGEMENT, SUNDAY, SEPTEMBER 8, 2024 - 18:15 - 19:45

P2.17A.01 Treatment Outcomes after Access to Broad Molecular Tests, Targeted Agents and Immunotherapy in NSCLC Patients from Brazil

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Introduction: Tailored management of metastatic NSCLC demands access to broad NGS panels and PDL1 expression in a timely manner

for first-line treatment selection. In Brazil, patient support programs sponsored by pharma give access to molecular diagnostic assays since 2017, with broad NGS covered since 2020. We aimed to evaluate the real-world Overall Survival (rwOS) after first-line palliative treatment modality with tyrosine kinase inhibitors (TKIs), and immunotherapy (IO).

Methods: Between jan/2017 and sep/2023, data from all patients diagnosed with metastatic NSCLC were retrieved from the Oncoclínicas datalake (largest Brazilian private oncology institution). Epidemiological characteristics, treatment details, and survival outcomes were extracted from structured fields of EHRs combined with elements from unstructured sources using technology-based abstraction techniques and human curation. Biomarker data was available for a subset of patients tested at internal Oncoclínicas Precision Medicine lab. rwOS was calculated from start of first treatment regimen until death or last follow-up with Kaplan Meier method. Study was approved by Reseach Ethics Committee (CAAE 75373323.5.0000.0047).

Results: Median age was 71 years (range 22-101), 51% were male, and 67% were from southeast region of the country. In 782 cases with comprehensive molecular data, the most common alterations were KRAS mut (28.4%, KRASG12C in 9.7%), followed by EGFR mut (23.6%, exon 20 ins in 2.9%), ALK fusions (6.4%), MET exon 14 skipping (4.4%), ERBB2 mut (3.4%), ROS1 fusions (3.1%), and BRAFV600E mut (1.9%). Overall, high PD-L1 expression (>=50%) was found in 12.3% of the samples. Over the seven years period, we observed a major decrease in the use of chemotherapy (CT) alone (from 76% in 2017 to 29% in 2023) accompanied by an increase in the use of combination of IO + CT (from 2% in 2018 to 43% in 2023). Meanwhile, TKI (EGFR, ALK and ROS1) and IO single-agent increased gradually over time. With median follow-up of 12 months, rwOS was 26.5 months (CI95% 20.3-46.7) for patients who had TKI in first-line, 15.7 months (CI95% 13-17.8) for patients with IO and 15.5 months (CI95% 12.17-19.3) for patients with IO + CT.

Conclusions: Targeted therapies have been associated with better outcomes in our real-world cohort of patients. Access to comprehensive molecular profiling has expanded the application of precision medicine to greater proportion of patients in recent years.

Keywords: non-small cell lung cancer, access, next-generation sequencing

P2.17A GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS - CLINICAL MANAGEMENT, SUNDAY, SEPTEMBER 8, 2024 - 18:15 - 19:45

P2.17A.02 Cost-Efficiency Modeling of Conversion to Biosimilar Bevacizumab-bvzr in Metastatic Non-Small Cell Lung Cancer in Medicare

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Introduction: Biosimilars to originator bevacizumab (Avastin®), such as bevacizumab-bvzr (Zirabev®), can deliver substantial savings and/or expanded access to biologic therapy for patients with metastatic non-squamous non-small cell lung cancer (mNSCLC). The objective of this study is to explore the cost-efficiency and budget-neutral expanded access of bevacizumab-bvzr in mNSCLC in Medicare.

Methods: We developed a Medicare payer perspective simulation model of patients treated for mNSCLC to estimate cost-savings from converting bevacizumab (originator) to bevacizumab-bvzr. The target patient population receiving annual first line systemic therapy for non-squamous mNSCLC treatment in Medicare (n=26,370) was calculated using Medicare enrollment data, SEER incidence rates for distant adenocarcinoma & large cell carcinoma among those age ≥65, and an assumption that 11% of new diagnoses receive bevacizumab-based treatment based on recent evidence from Voruganti et al. (2023). We modeled combination therapy with paclitaxel + carboplatin—a common U.S. clinical guideline-recommended regimen in non-squamous mNSCLC. Costs were derived from 2024 Average Sales Price (ASP). Results include per-patient per-month (PPPM) cost savings (vs. originator), total monthly savings in the cohort, and number needed to convert (NNC) to biosimilar to fund treatment of an additional 100 patients.

Results: PPPM savings from conversion to bevacizumab-bvzr were $8,410. In 50% (n=1,947) and 100% (n=3,894) conversion scenarios mean PPPM savings were $4,205 and $8,410, and full cohort monthly savings were $16,374,114 and $32,748,228 respectively. These savings represent 35% and 70% reductions in cost vs. originator-based treatment, respectively, and exceed savings from conversion to alternative biosimilars bevacizumab-adcd, -awwb, or -maly (See Table). At 100% conversion, monthly savings from biosimilar conversion could fund up to 8,460 additional patient-months of treatment with bevacizumab-bvzr + paclitaxel + carboplatin. The NNC was 43 to treat an additional 100 patients with bevacizumab-bvzr + paclitaxel + carboplatin and ranged from 55 to 4,422 with alternative biosimilars (See Table).

Conclusions: In the first cost-efficiency and expanded access study of biosimilar bevacizumab in mNSCLC, we find that bevacizumab-bvzr + paclitaxel + carboplatin can result in substantial cost savings relative to originator-based first line treatment of patients with non-squamous mNSCLC in Medicare. These cost savings could be reinvested to treat a substantial number of additional patients with mNSCLC, or fund other costs of care in Medicare, on a budget-neutral basis.

Table 1: Summary Results

Drug Name

Monthly Cost with Paclitaxel + Carboplatin Based on ASP

Per-Patient Per-Month Savings vs. Originator

Number Needed to Convert to Biosimilar to Fund Treatment of 100 Patients

Bevacizumab (Originator)

$12,017

Reference

Reference

Bevacizumab-bvzr

$3,607

$8,410

43

Bevacizumab-awwb

$4,265

$7,752

55

Bevacizumab-maly

$9,859

$2,158

457

Bevacizumab-adcd

$11,752

$266

4,422

Keywords: Biosimilar, Bevacizumab, Health Economics

P2.17A GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS - CLINICAL MANAGEMENT, SUNDAY, SEPTEMBER 8, 2024 - 18:15 - 19:45

P2.17A.03 Preoperative Anxiety in Patients Undergoing Video-Assisted Thoracoscopic Surgery: Predictive Factors and Specific Concerns and Fears

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Introduction: Preoperative anxiety is a common reaction of patients admitted for surgery, which constitutes a bad emotional experience for surgical patients. The prevalence and influencing factors of preoperative anxiety in patients undergoing video-assisted thoracoscopic surgery remain unclear. The study aims to explore the independent predictive factors for preoperative anxiety in patients undergoing video-assisted thoracoscopic surgery and to analyze the specific concerns and fears faced by patients.

Methods: Study participants included patients scheduled for video-assisted thoracoscopic surgery intervention who underwent preoperative anxiety assessments using interview-based questionnaires. Demographic, clinical, and surgical variables were collected. The interview questionnaire included the anxiety component of the Hospital Anxiety and Depression Scale. The prevalence and intensity of anxiety were primarily analyzed descriptively. Univariate and multivariate logistic regression analyses were conducted to identify independent risk factors and to establish a risk scoring model.

Results: A total of 540 patients (57% female) were enrolled. According to the Hospital Anxiety and Depression Scale score composition, 22.4% exhibited preoperative anxiety (score ≥ 8 points). The prediction model had good discrimination, with an area under the receiver operator characteristic curve (AUC) of 0.760 (95% CI = 0.711-0.809) . The predictive variables included in the final clinical model were an age of <60 years (OR = 3.257; 95% CI = 1.791-5.924), body mass index of <25 kg/m2 (OR = 2.266; 95% CI = 1.302-3.946), lung nodule diameter of >1 cm (OR =3.071; 95% CI = 1.826-5.164), lung nodule observation time of >1 month (OR = 2.644; 95% CI = 1.511-4.627), preoperative comorbidities (OR = 2.356; 95% CI = 1.451-3.827), and marital status (divorced vs. married) (OR = 4.842; 95% CI = 2.333-10.049). The primary concerns and fears reported by patients undergoing minimally invasive thoracoscopic surgery encompassed long-term prognosis, postoperative complications, and postoperative discomfort. Surgical patients exhibit varying degrees of concerns and fears, with notable differences observed among individuals based on their levels of anxiety, gender, and age.

Conclusions: Preoperative anxiety remains common in patients planning to undergo video-assisted thoracoscopic surgery. The nomogram demonstrated good predictive performance for preoperative anxiety in patients undergoing video-assisted thoracoscopic surgery. Using this nomogram can help to identify patients with preoperative anxiety, enabling the provision of more personalized support to these individuals to help them cope with their preoperative anxiety.

Keywords: Preoperative Anxiety, Hospital Anxiety and Depression Scale, Risk Factors

P2.17A GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS - CLINICAL MANAGEMENT, SUNDAY, SEPTEMBER 8, 2024 - 18:15 - 19:45

P2.17A.04 Cost Effectiveness of a System-Level Precision Medicine Intervention for Stage IV Non-Small Cell Lung Cancer Patients

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Introduction: We modeled four scenarios for implementation of a system-level precision medicine intervention to increase the effective use of next generation sequencing (NGS) in newly diagnosed stage IV non-small cell lung cancer (NSCLC) patients.

Methods: The intervention modeled was based on the PREcision meDICine Thoracic (PREDICT) service in place at our institution, consisting of system-wide reflex testing of newly diagnosed stage IV NSCLC patients by an in-house solid tumor focused assay (hybrid DNA/RNA NGS panel) and PD-L1 testing; a PREDICT navigator; a molecular tumor board (MTB); and an integrated information portal for real-time updates on sample processing, results, and MTB recommendations. Using a decision tree model, we examined four implementation scenarios: 1) send-out sequencing and PD-L1 testing for all newly diagnosed Stage IV NSCLC patients, 2) PREDICT for all newly diagnosed patients, 3) send-out NGS for patients with non-squamous disease (plus PD-L1 regardless of histology), and 4) PREDICT for those with non-squamous disease (those with squamous histology receive only PD-L1 testing). Based on the literature, we assumed 79.9% of patients undergoing send-out NGS would receive usable results; from experience, we assumed 97% of patients in the PREDICT groups would receive usable results. Epidemiologic parameters describing the distribution of stage IV NSCLC by histology, specific actionable genomic alterations, and PD-L1 expression were derived from the literature, as were estimates for survival, cost, and health-state utilities under indicated scenarios of first-, second-, and third-line treatment with targeted therapies, checkpoint inhibitors, and chemotherapy. We examined costs (in 2023 US dollars) from the health system perspective. For purposes of spreading fixed costs, we assumed 500 stage IV NSCLC lung cancer patients per year at a hypothetical institution. Costs and QALY's were discounted at a standard 3%.

Results: Table 1 lists the predicted costs and QALYs gained per patient for each scenario as well as the proportions of patients receiving targeted therapy and chemotherapy as part of first-line treatment. Scenarios 1 and 2 were each more costly and less effective than alternatives and were thus eliminated from the cost-effectiveness analysis. The incremental cost-effectiveness ratio (ICER) for moving from the less costly but less effective strategy 3 to strategy 4 was $242,139 per QALY gained.

Conclusions: Implementing a comprehensive precision medicine intervention centered around in-house NGS for non-squamous stage IV NSCLC patients spared a high proportion of patients chemotherapy in first-line treatment but cost $242,139 per QALY gained compared to a more conventional strategy.

Keywords: cost-effectiveness, precision medicine, non-small cell lung cancer

P2.17A GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS - CLINICAL MANAGEMENT, SUNDAY, SEPTEMBER 8, 2024 - 18:15 - 19:45

P2.17A.05 Racial and Gender Disparities in Immune-Related Adverse Effects: A Nationwide Inpatient Sample Database Analysis

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Introduction: Immune checkpoint inhibitors (ICIs) have revolutionized the treatment of several solid tumors and has led to an improvement in 5-year-survival of these patients. However, they cause various immune-related adverse events (irAEs). Across clinical trials, incidence of irAEs varies between different cancer subtypes, treatment combinations and study settings. There is a lack of validated predictive biomarkers for irAEs. This study aims to evaluate an association between the occurrence of irAEs and patient demographics, in particular race and gender of the patient.

Methods: We analyzed data from the National Inpatient Sample (NIS) database of 2016-2020, of the Agency of Healthcare Research and Quality (AHRQ) focusing on all cancer patients hospitalized between 2016-2020. Using ICD-10 codes, database was queried for patients who had received immune checkpoint inhibitors and developed irAEs. Characteristics including demographics, comorbidities; and AEs were studied using chi-square for categorical or ANOVA for continuous data (statistical significance p-value < 0.05) and results were stratified

based on patient's races and gender.

Results: A total of 25,814 patients receiving immune checkpoint inhibitors were identified of which 58.58% (15,124) were male and 41.41% (10,690) female. The ethnic background information was available for 24,775 patients; of which 63.9% (15835) were White, 7.12% (1765) African American, 12.43% (3080) Hispanic, 4.37% (1085) Asian/Pacific Islander, 0.42% (105) Native American, and 11.72% (2905) belonged to other races. Majority (42.4%) of the African American patients belonged to the lowest income quartile while majority (59.4%) of Asian/Pacific Islander patients belonged to the highest income quartile. The proportion of patients with commercial/private health insurance was higher in the White (51.7%), African American (37.4%), Asian/Pacific Islander (47%) and Native American (42.9%) subgroups. In contrast, 39.1% of the Hispanic patients had Medicaid. irAEs were most prevalent in Asian/Pacific Islander patients (12%) followed by African American patients (11.9%), and White patients (11%). The adjusted odds ratio (aOR) of irAEs was lower in Hispanic patients as compared to White patients (aOR 0.61, 95% CI 0.44-0.84, p 0.003). Females had higher aOR of irAEs (1.27, 95% CI 1.06-1.53, p 0.009) as compared to males.

Conclusions: This study underscores the demographic influence on irAEs among patients receiving immune checkpoint inhibitors; including race and ethnicity, given the lower odds in Hispanic and Asian/Pacific Islander subgroups as compared to White patients. Moreover, females had higher incidence and odds of irAEs as compared to males. Understanding these disparities is critical to facilitate equitable healthcare for all cancer patients.

P2.17A GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS - CLINICAL MANAGEMENT, SUNDAY, SEPTEMBER 8, 2024 - 18:15 - 19:45

P2.17A.06 Impact of COVID-19 Diagnosis and Treatment for Lung Cancer in the US National Cancer Database (NCDB) from 2014 To 2021

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Introduction: The COVID-19 pandemic impacted healthcare services, including cancer diagnostics and management. This study analyzes the effects of COVID-19 on staging at diagnosis, first treatment performed, and mean time to treatment initiation (TTI) for non-small cell lung cancer (NSCLC).

Methods: Retrospective cohort analysis of all individuals registered with NSCLC in the US National Cancer Data Base (NCDB) from 2014 to 2021. Individuals with missing data for TTI or clinical stage were excluded. ANOVA, Chi-square, and t-tests were used to compare the pre-COVID (2014-2019) to-COVID (2020-2021) periods.

Results: 767,101 individuals were included, with an average age of 69 years, 49% female, 85% white, 3.2% of Hispanic origin, 73% with Medicare/Medicaid, and 47% with diagnosis and treatment at the same facility. The percent of cancers diagnosed at early-stage (stages 0-2) was 44% in the pre-COVID and 46% in the COVID period ($p<0.01$). Minor differences in the Initial treatment were observed. (Table.1). The TTI was 5.5 days higher in the COVID period (45.8 days) than during pre-COVID (40.3 days) ($p<0.01$) (Table.1) (Figure.1). Community cancer programs had a higher pre-COVID TTI (41.8 days) than other programs and experienced a greater TTI increase during COVID (7 days), while other programs experienced a 5-day increase. New England facilities experienced a higher increase in TTI (7 days) than other regions. Individuals diagnosed with early-stage disease had an increase of 8 days in TTI in the COVID period ($p<0.01$). Black and Hispanic individuals experienced higher TTI, respectively, 49.7 and 46.4 days in the COVID period, when compared to white (45.4 days).

Conclusions: Time to Treatment Initiation for NSCLC increased after COVID-19. Further studies are needed to determine the consequences of delay in lung cancer care due to the pandemic on the levels of survival and effects on health care systems, and whether this persisted in more recent years.

Keywords: non-small cell lung cancer, National Cancer Data Base (NCDB), COVID-19

P2.17A GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS - CLINICAL MANAGEMENT, SUNDAY, SEPTEMBER 8, 2024 - 18:15 - 19:45

P2.17A.07 Impact of Preoperative Anxiety on Postoperative Outcomes in Patients Undergoing Minimally Invasive Thoracoscopic Surgery

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Introduction: Preoperative anxiety is a common preoperative psychological state in patients with cancer and associated with worsening perioperative outcomes. However, high-quality prospective research studies on preoperative anxiety in patients undergoing lung surgery are scarce. We conducted this study to observe the incidence of preoperative anxiety and its effect on short-term postoperative outcomes,

including postoperative complications and non-complicated adverse events (e.g., sleep, pain, nausea, and vomiting).

Methods: We prospectively used the Hospitalization Anxiety Scale to measure preoperative anxiety in patients undergoing thoracic surgery. Patients were grouped according to the Hospitalization Anxiety Scale scores as follows: no anxiety (score < 8) and anxiety (score ≥ 8). The association of preoperative anxiety with postoperative complications and non-complicated adverse events was determined by univariate regression and polynomial regression analyses.

Results: A total of 121 patients (22.4%) presented with preoperative anxiety. The mean length of hospitalization was longer in the anxiety group than in the non-anxiety group (4.33 vs. 3.85 days, respectively). However, the rates of postoperative complications were comparable between the two groups. Regarding perioperative sleep quality, the Athens Insomnia Scale scores at baseline were comparable between the two groups. Nonetheless, the mean score was higher in the anxiety group than in the non-anxiety group; the difference was statistically significant on postoperative days 1 and 3. The anxiety group had a significantly higher rate of severe and mild pain on postoperative days 2 and 3, respectively, compared with the non-anxiety group. The incidence of postoperative nausea and vomiting on postoperative day 1 was significantly higher in the anxiety group than in the non-anxiety group.

Conclusions: Preoperative anxiety may not increase the rates of postoperative complications in patients undergoing lung surgery. However, it may be associated with postoperative sleep disturbances, pain, nausea, and vomiting, as well as prolong the length of postoperative hospitalization. Typically, even high levels of preoperative anxiety do not meet the clinical diagnosis of generalized anxiety disorder. Importantly, preoperative anxiety is modifiable. Identification of patients developing preoperative anxiety provides an opportunity to increase psychological comfort and, thus, improve postoperative outcomes. Hence, preoperative anxiety should be closely monitored and treated accordingly.

Keywords: Thoracoscopic Surgery, Postoperative Nausea and Vomiting, Postoperative Pain

P2.17A GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS - CLINICAL MANAGEMENT, SUNDAY, SEPTEMBER 8, 2024 - 18:15 - 19:45

P2.17A.08 Trends in Pulmonary Embolism Outcomes Among Lung Cancer Patients: A Nationwide Analysis Across a Decade

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Introduction: Lung cancer[LC] is the second most common cancer and leading cause of cancer mortality in the United States[US]. Pulmonary embolism[PE] contributes to nearly 10% mortality in LC. Nationally representative data on the trends of PE among LC patients are lacking. Determining these trends will assist in evaluating adequacy of current guidelines and assess for scope of any improvements.

Methods: This is a longitudinal study of all LC patients admitted with PE across the US from 2012 to 2021 using National Inpatient Sample. Incidence, mortality, health care utilization, rates of surgical intervention among LC patients admitted with PE were assessed and compared with PE patients without LC. Confounders were adjusted for using multivariate regression analysis. Conditional marginal effects were used to adjust for changing demographics over years.

Results: Total hospital admissions for PE increased from 179615 to 197115 from 2012 to 2021 in the US with a decline in the LC patient admissions with PE from 3.8% to 3.4%. There was an increase in adjusted odds of mortality from 2.7 to 3.1 from 2012 to 2021 for PE patients without LC while mortality increased from 7.2 to 7.7% during the same period for PE patients with LC. Surgical interventions rates were 2% and 3.8% for PE patients with and without LC in 2012 which increased to 4.2% and 12.9% in 2021 with similar increasing trends in mechanical thrombectomy, catheter guided thrombolysis and embolectomy rates in both groups. Use of IVC filters was greater among LC patients compared to non-LC patients with a declining trend in usage across the years[17% vs 10% in 2012 & 5.8% vs 4% in 2021]. ICU admission rates were higher in LC compared to non-LC patients with PE with an increasing trend over the years[3.5% vs 2.7% in 2012 & 4% vs 3.8% in 2021] with a similar pattern in rates of respiratory failure and intubation. Mean length of hospitalization was higher among PE patients with LC compared to those without LC across years with a declining trend in number of days overall[5.7 vs 5.1 in 2012 & 5.1 vs 4.4 in 2021]. Total hospitalization charges increased from $53588 to $61441 for PE patients with LC from 2012 to 2021 while it increased from $44670 to $61503 for PE patients without LC during the same period after adjusting for inflation.

Conclusions: Though there is a declining incidence of PE in LC, mortality rates are increasing over the decade with an associated decreased usage of surgical interventions, higher morbidity and increased health care utilization compared to non-LC patients. Surgical interventions in general are reserved for high risk PE patients. Further assessment of adequacy of these policies in catering to the unique characteristics of LC patients with PE may help in reducing their morbidity and mortality. There is also a compelling need to revisit the thromboprophylaxis guidelines in this subpopulation.

Keywords: Lung cancer, Pulmonary embolism, Mortality

P2.17A GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS - CLINICAL MANAGEMENT, SUNDAY, SEPTEMBER 8, 2024 - 18:15 - 19:45

P2.17A.09 Real-World Study of the Efficacy and Safety Analysis of Immunotherapy in Advanced Lung Cancer Under Internet-Based Full-

course Management

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Introduction: Internet-based full-course management for cancer patients is considered an effective mode for enhancing treatment outcomes. This study aims to understand and evaluate the impact of outpatient management via an internet-based physician-patient communication tool on the treatment outcomes of lung cancer patients undergoing immunotherapy.

Methods: Physicians can formulate outpatient management plans for patients on the platform(Wedoc). Patients can also engage in online communication with their attending physicians, report symptoms and corresponding test reports encountered outside the hospital, and receive timely guidance from physicians. We conducted a retrospective cohort study using data collected from this platform. Data were collected from 35 hospitals nationwide, establishing a cohort of lung cancer patients treated with PD-1/L1 inhibitors to explore the effects of this outpatient management model on the efficacy and adverse reactions of immunotherapy.

Results: A total of 1110 lung cancer patients receiving immunotherapy for at least two cycles were included. 86.3% of patients were male, with a median age of 67 years. Squamous cell carcinoma accounted for 34.1%, adenocarcinoma for 39.4%, and stage IV patients for 57.7%. Patients received a median of 8.5 cycles of immunotherapy, evaluated by physicians using RECIST 1.1 criteria. The overall response rate (ORR) was 64.7%, and disease control rate (DCR) was 93.3%. The median follow-up duration for all patients was 108 days. Patients initiated a median of 220 dialogues with physicians on the platform, with a median communication frequency of 3.8 times per week. 52.8% of patients reported adverse reactions after immunotherapy, with 35.9% experiencing grade 3 or higher adverse reactions. The most common adverse reactions were decreased appetite, rash, and fatigue. Pearson analysis showed a strong correlation between patient communication frequency and density on the platform and the occurrence of adverse reactions (correlation coefficients 0.52 and 0.46, respectively). However, these factors showed weak correlations with short-term treatment efficacy and the number of treatment cycles (correlation coefficients 0.14 and 0.1; 0.19and 0.04, respectively).

Conclusions: Internet-based outpatient management plays a positive role in promptly identifying adverse reactions following immunotherapy and providing timely interventions. In this retrospective analysis, no significant correlation was found between patient communication behavior on the platform and treatment efficacy evaluated by physicians based on RECIST criteria. Further rigorous controlled trial designs are needed for further exploration.

Keywords: Real-World Study, Lung Cancer, Internet

P2.17A GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS - CLINICAL MANAGEMENT, SUNDAY, SEPTEMBER 8, 2024 - 18:15 - 19:45

P2.17A.10 Major Cardiovascular and Cerebrovascular Events in Lung Cancer - A Nationwide Inpatient Sample Database Analysis.

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Introduction: New and advanced therapies have improved the 5-year survival of lung cancer patients. With increased lifespan of patients, major adverse cardiovascular and cerebrovascular events (MACCE) occur during treatment. The use of potentially cardiotoxic therapies further emphasizes the importance of pretreatment risk stratification and monitoring for MACCE.

Methods: Using ICD-10 codes, the National Inpatient Sample (NIS) database of the Agency of Healthcare Research and Quality (AHRQ), was queried from 2016 to 2020, for patients with lung cancer. MACCE including all-cause in hospital mortality (ACIHM), myocardial infarction (MI), atrial fibrillation (AF), cerebral events, and sudden cardiac death (SCD) were identified. Characteristics including demographics, comorbidities and MACCE were studied using chi-square for categorical or ANOVA for continuous data (statistical significance p-value < 0.05) and results were stratified based on patient's races. Multivariate regression models were applied to adjust for cofounders.

Results: Among 1,961,429 lung cancer hospitalizations, 32.8% (643,404) experienced MACCE. Predominantly, 77.39% (1,518,040) were White, 12.6% (247,310) African American, 4.6% (90,250) Hispanic, 2.88% (56,565) Asian/Pacific Islanders, 0.38 % (7640) Native Americans and 2.12% (41,624) other races. Dyslipidemia (41.9%) prevailed in Whites while hypertension (46.8%), renal failure (21.5%), congestive heart failure (19%) prevailed in African Americans. Diabetes (32.5%) was frequent in Hispanics, whereas obesity (8.8%) in Native American patients. ACIHM was higher in Asian/Pacific Islanders as compared to Whites, with adjusted odds ratio (aOR) of 1.22 (95% CI 1.14-1.3,

p<0.001). African Americans had lower mortality (aOR of 0.96, 95% CI 0.92-0.99, p 0.041) when compared to Whites. MI was higher in African Americans, aOR 1.1 (95% CI 1.06-1.15, p<0.001) and lower in Hispanics, aOR 0.88 (95% CI 0.80-0.98, p 0.021), and cerebral events were also higher in African Americans (aOR 1.1, 95% CI 1.06-1.15, p<0.001) and lower in Hispanics (aOR 0.91, 95% CI 0.85-0.97, p 0.008), when compared to Whites. As compared to Whites, SCD was higher in African Americans (aOR 1.67, 95% CI 1.55-1.81, p<0.001), Hispanics (aOR 1.41, 95% CI 1.24-1.60, p<0.001), Asian/Pacific Islanders (aOR 1.23, 95% CI 1.04-1.47, p 0.016), and other races (aOR 1.25, 95% CI 1.01-1.54, p 0.038).

Conclusions: This study underscored the high prevalence of MACCE across the lung cancer population with a disproportionately higher incidence in the non-White patients with lung cancer. This highlights the need for equitable healthcare access to all patients, to address underlying risk factors and comorbidities to mitigate these racial and ethnic disparities. Involvement of cardio-oncology in this high-risk population, may improve outcomes.

Characteristics, Comorbidities, and Adjusted Odds Ratio of Major Cardiovascular and Cerebrovascular

Characteristics

White

African American

Hispanic

Asian or Pacific

Native American

Other

P-Value

No. of patients

1518040

247310

90250

56565

7640

41624

Age at Admission (mean)

69.8

66.8

68

69

67.6

68.1

<0.001

Gender

<0.001

Male

50.60%

51.20%
55.30%
54.60%
49.90%
54.40%

Female
49.40%
48.80%
44.70%
45.40%
50.10%
45.60%

Median household income national quartile for patient ZIP Code

<0.001
0-25th percentile
26.10%
57.00%
37.40%
13.70%
45.90%
26.60%

26th to 50th percentile (median)
28.70%
20.30%
25.20%
17.90%
27.30%
22.00%

51st to 75th percentile
25.20%
14.00%
22.20%

27.40%

17.00%

24.10%

76th to 100th percentile

20.10%

8.70%

15.30%

40.90%

9.80%

27.20%

Primary expected payer (uniform)

<0.001

Medicare

68.70%

60.40%

58.20%

55.70%

63.90%

58.00%

Medicaid

7.70%

18.00%

17.40%

15.40%

16.20%

14.20%

Private insurance

19.20%

16.40%

18.10%

24.90%

14.00%

21.90%

Self-pay
1.40%
2.20%
3.50%
1.90%
1.60%
2.90%

No charge
0.10%
0.20%
0.30%
0.20%
0.00%
0.30%

Other
2.80%
2.80%
2.50%
1.80%
4.20%
2.80%

Region of hospital

Northeast
21.20%
16.80%
18.70%
21.40%
6.90%
31.80%

Midwest
26.00%
22.70%
7.10%
8.30%
26.00%
10.10%

South
39.40%
53.20%
45.50%
15.60%
40.90%
40.00%

West
13.50%
7.30%
28.70%
54.70%
26.10%
18.10%

Comorbidities
White
African American
Hispanic
Asian or Pacific
Native American
Other
P-Value
Hypertension
43.10%

46.80%
43.10%
43.90%
41.80%
43.20%
<0.001
Diabetes
22.50%
30.70%
32.50%
30.30%
29.40%
26.90%
<0.001
Smoking
20.20%
23.10%
13.50%
6.90%
25.40%
15.70%
<0.001
Dyslipidemia
41.90%
34.70%
36.50%
40.00%
33.20%
37.40%
<0.001
Obesity
8.60%
8.40%
8.50%
2.80%
8.80%
5.90%
<0.001
Renal failure
15.70%
21.50%
17.40%

15.10%

15.80%

15.70%

<0.001

Congestive heart failure

17.40%

19.00%

14.20%

10.1%

18.30%

14.30%

<0.001

Pulmonary circulatory disease

8.40%

10.90%

7.80%

7.20%

9.10%

8.40%

<0.001

Coagulopathy

0.70%

0.90%

1.00%

1.00%

1.00%

1.10%

<0.001

COPD

55.30%

47.70%

38.80%

24.90%

55.60%

41.80%

<0.001

Depression

13.60%

8.50%

9.40%

5.00%

12.40%

9.80%

<0.001

Outcomes

White

African American

Hispanic

Asian or Pacific

Native American

Other

P-Value

Died during hospitalization

128395 (8.5%)

21870 (8.8%)

8170(9.1%)

5830 (10.3%)

755 (9.9%)

4320 (10.4%)

<0.001

Myocardial infarction

49910 (3.3%)

7185 (2.9%)

2525 (2.8%)

1540 (2.7%)

255 (3.3%)

1355 (3.3%)

<0.001

Cerebral events

96990 (6.39%)

19755 (8%)

5685 (6.3%)

4000 (7%)

485 (6.35%)

2925 (7.03%)

<0.001

Sudden cardiac arrest

16180 (1.07%)

4855 (1.96%)

1390 (1.54%)

725 (1.28%)

110 (1.44%)

560 (1.35%)

<0.001

Atrial fibrillation

359470 (23.68%)

35215 (14.24%)

14425 (15.98%)

9004(15.92%)

1480 (19.37%)

7380 (17.73%)

<0.001

Adjusted Odds Ratio of MACCE

ACIHM

Race

Odds Ratio

Lower CI

Upper CI

P-Value

White (Reference)

1

African American

0.9630218

0.9289131

0.9983829

0.041

Hispanic

1.057316

1.00001

1.117905

0.05

Asian/Pacific Islander

1.223715

1.14469

1.308195

<0.001

Native American

1.19843

0.9855471

1.457297

0.07

Other

1.24328

1.14947

1.344745

<0.001

MI

Race

Odds Ratio

Lower CI

Upper CI

P-Value

White (Reference)

1

African American

0.7877885

0.7413183

0.8371717

<0.001

Hispanic

0.8876056

0.8019565

0.9824021

0.021

Asian/Pacific Islander

0.9111076

0.8053517

1.030751

0.139

Native American

1.008276

0.723306

1.405518

0.961

Other

1.028553

0.9023126

1.172454

0.673

Cerebral events

Race

Odds Ratio

Lower CI

Upper CI

P-Value

White (Reference)

1

African American

1.106333

1.06371

1.150664

<0.001

Hispanic

0.9143978

0.8560198

0.9767571

0.008

Asian/Pacific Islander

0.9532797

0.882789

1.029399

0.222

Native American

1.035106

0.8283418

1.29348

0.762

Other

1.01424

0.9244056

1.112805

0.765

Sudden cardiac arrest

Race

Odds Ratio

Lower CI

Upper CI

P-Value

White (Reference)

1

African American

1.678645

1.554745

1.812418

<0.001

Hispanic

1.412942

1.240475

1.609388

<0.001

Asian/Pacific Islander

1.236822

1.040275

1.470504

0.016

Native American

1.361506

0.8128755

2.280422

0.241

Other

1.252648

1.013006

1.548981

0.038

Atrial fibrillation

Race

Odds Ratio

Lower CI

Upper CI

P-Value

White (Reference)

1

African American

0.5492076

0.5326221

0.5663097

0.5663097

Hispanic

0.6198799

0.5923808

0.6486555

0.6486555

Asian/Pacific Islander

0.6355334

0.6012681

0.6717514

0.6717514

Native American

0.8352824

0.7162623

0.9740799

0.9740799

Other

0.7307426

0.6872016

0.7770424

0.7770424

Keywords: Lung Cancer, MACCE, Racial Disparities

P2.17B GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS - SCREENING, SUNDAY, SEPTEMBER 8, 2024 - 18:15 - 19:45

P2.17B.01 The Construction and Application of a Novel Precise Health Management Model for Lung Nodule Population

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Introduction: The early screening of lung cancer faces issues such as a high rate of false positives, overtreatment, complex patient visit processes, poor compliance, and significant psychological harm. To optimize the patient management processes, a novel precise health management model for lung nodules has been proposed.

Methods: A novel precise health management model for lung nodules was proposed. In this proposed model, a series of workflows including a new follow-up communication protocol and multidisciplinary treatment (MDT) for lung nodules has been designed. To compare

the proposed model with traditional model, consecutive participants undergoing early lung cancer screening with LDCT at our department from May 1, 2021 to December 31, 2021 were selected to be studied. Initially, patient were divided into two groups: the new model group managed by the Laoshan District and studied by using the new model, and the old model group managed by the Shinan District and traditional model will be applied to. To investigate the performance of new proposed model, different aspects, such as loss to follow-up rate, timely return visits after detection of lung nodules, the proportion of surgical patients who underwent surgery at our hospital, the proportion of benign nodules among surgical patients, the follow-up interval for low-risk lung nodule patients, the psychological health status of patients, and patient satisfaction with lung nodule management services were evaluated between the two groups.

Results: A total of 2816 individuals were included in the two groups with 1178 individuals in the new model group and 1638 individuals in the old model group. Following the detection of lung nodules, the rate of loss to follow-up was notably lower in the new model group compared to the old model group (28.5% versus 32.5%, P=0.025). Among those who completed the follow-up process, the new model group demonstrated a significantly higher rate of timely return visits (60.3% versus 53.0%, P=0.001). Additionally, a larger proportion of surgical patients in the new model group underwent surgery at our hospital (93.9% versus 82.6%, P=0.035), and among these surgical patients, the incidence of postoperative benign lesions was lowered from 13.0% to 3.0% by applying the proposed model. The follow-up interval for low-risk lung nodule patients was also much longer in the new model group (12.152±3.439 months versus 11.295±4.823 months, P=0.022). As of January 1, 2024, or the conclusion of the follow-up period, the prevalence of anxiety among patients was lower in the new model group (15.0% versus 21.1%, P<0.001), and patient satisfaction with lung nodule management services was notably higher in the new model group (83.8% versus 76.2%, P<0.001).

Conclusions: This study proposes a novel precision health management model for lung nodules and its effectiveness is demonstrated. The proposed model provides a more rational and effective management strategy for patients with lung nodules, simplifies the patient visit process, improves patient compliance, avoids overdiagnosis of lung nodules, reduces psychological harm to patients, and enhances the technical level and service quality of our medical institution.

Keywords: Lung Nodules, Precise Health Management Model, Follow-up Communication Protocol

P2.17B GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS - SCREENING, SUNDAY, SEPTEMBER 8, 2024 - 18:15 - 19:45

P2.17B.02 Healthcare Providers' Perceptions of Barriers and Enablers to Adopting New Surveillance Protocols

A. Fraser, R. McNeill, J. Robinson

University of Auckland, Auckland/NZ

Introduction: Lung cancer patients with non-curative disease currently face frequent follow-up visits to the outpatient clinic associated with anxiety, time commitment, and out of pocket costs. In New Zealand (NZ) there are significant equity issues for Indigenous Māori around access to healthcare, impacting diagnosis and outcomes. Unsustainable demand for oncology services in NZ has led to calls for the introduction of a new national framework for managing people with cancer. Evidence suggests virtual follow-up can lead to higher patient satisfaction without negatively impacting on health outcomes such as survival time, as well as reducing demand on clinical space. The aim of this study was to explore healthcare providers' perception of barriers and enablers to adopting new surveillance protocols for people with non-curative lung cancers or mesothelioma.

Methods: Semi-structured interviews were conducted with a range of healthcare providers (HCPS) across NZ, including medical oncologists, primary care providers, radiation oncologists, oncology psychologists, oncology nurses and navigators, respiratory physicians, and Māori HCPs. A generally inductive thematic analysis method was used to explore the themes around barriers and enablers to using new surveillance protocols. Themes were organised using a Micro-Meso-Macro level framework to identify day-to-day attributes, institutional factors, or influences, and regulatory or economic conditions which might impact on how services are delivered.

Results: There was a general agreement from HCPs that there is a lack of evidence around current practice, and clinicians recognised the need to provide flexibility for surveillance options. Enablers for developing novel models of care identified by clinicians were equity focused with a strong emphasis on developing connections, building on trusted relationships between HCPs and patients, improving communication within and across services, and developing options for local delivery of care. New models of care could be strengthened through use of supportive care roles and better education of oncology pathways for primary care clinicians. Micro level barriers included: Costs to attend follow-up, communication, patient experience, nihilism and stigma, quality of communication, clinician engagement, anxiety, health literacy, patient choice, paternalism. Micro level enablers included: Trusted relationships, connection, and engagement with providers. Meso level barriers included: Travel and regional variation and challenges. Meso level enablers included: support roles and local delivery of care. Macro level barriers included: Capacity in clinics and radiology, diagnostics, and IT issues for both patients and providers. There were no macro level enablers identified.

Conclusions: Alternative models of care (MOC) are acceptable to HCPs, and clinician flexibility was identified as a key enabling theme. Māori HCPs identified the importance of co design in development of MOC, emphasizing a 'one size fits all' approach did not provide the flexibility individual communities needed to enable them to access care and stay connected to their HCP. Implications for future MOC development include working in co design with patients and families to develop flexible MOC.

Keywords: models of care, pathway implementation, equity

P2.17B GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS - SCREENING, SUNDAY, SEPTEMBER 8, 2024 - 18:15 - 19:45

P2.17B.03 Improving Lung Cancer Screening Utilization and Efficiency Through a Patient-Centered Pathway with Virtual Visits

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Introduction: Lung cancer screening (LCS) via low-dose computed tomography (LDCT) remains underutilized, with fewer than 6% of those deemed eligible for LCS getting screened in the United States. One of the many barriers to screening is the requirement of a face-to-face shared decision-making (SDM) counseling visit before ordering LDCT, imposed by third-party payers. During the COVID-19 pandemic, screening rates declined dramatically due to reduced clinic and personnel resources and concerns about potential exposures. Under the COVID-19 Public Health Emergency waiver, Medicare temporarily approved telehealth services for SDM visits. Established LCS programs (LCSP) could transition their in-person visits to telehealth. Despite the extension of the waiver, utilization of telehealth services has diminished in many areas. It is unclear if the predominant use of telehealth for LCS evaluation outside of a pandemic health emergency is practical or feasible. The purpose of this research is to evaluate the effectiveness of implementing virtual visits as part of a centralized LCSP (C-LCSP) in rapidly increasing LCS in an efficient, patient-centered pathway.

Methods: This research was performed in a large academic medical center in Los Angeles. Considering the diversity of clinic practices with a mix of faculty, staff physicians, and affiliated community private practitioners, a hybrid LCSP with a centralized navigated pathway alongside a decentralized provider-managed screening was launched in April 2022. The goal of the C-LCSP was to navigate the screening process and address some common barriers to screening, such as the time-consuming SDM counseling. To further facilitate the screening process, virtual visits were offered. We use a retrospective cohort analysis to investigate the utilization and efficiency of LCS in the two years following the launch of the C-LCSP. We report the number of LDCTs performed in the navigated and provider-managed pathways.

Results: In the three years preceding the launch of the LCSP, fewer than 100 LDCTs for LCS were performed annually. 1540 LDCTs were done between April 2022 and March 2024, representing a 670% increase compared to the prior two years. 38% of the screening studies were part of the C-LCSP, 95% of which were performed via telehealth. Our efforts steadily increased the number of screenings, with 106% more screening in the C-LCSP and 85% more screening in the provider-managed pathway from April 2023 to March 2024 compared to the previous year.

Conclusions: We report the successful implementation of a patient-centered pathway for LCS featuring virtual SDM counseling visits. We show that virtual SDM visits are feasible outside of the public health emergency of a pandemic and are associated with a rapid screening uptake. Our research is limited as it does not explore the causality for this rapid uptake. Rapid growth is noted in centralized and provider-managed pathways, likely attributable to extensive efforts to educate patients and providers within the health system. Further studies are needed to explore whether the convenience of virtual visits by a dedicated provider trained to perform SDM counseling for LCS drives rapid uptake in the C-LCSP.

Keywords: Virtual Visit, Lung Cancer Screening, Patient-Centered Screening Pathway

P3.01D RISK FACTORS, RISK REDUCTION & TOBACCO CONTROL - DISPARITIES, INEQUITIES & GEOGRAPHIC DIFFERENCES
MONDAY, SEPTEMBER 9, 2024 - 12:00 - 14:00

P3.01D.01 Racial Disparities Among Patients Diagnosed with Lung Cancer at a Young Age

A. Manoharan, K. Edwards, N. El-Abbar, L. Ramos, N. Parikh, S. Kareff, G. Lopes, E. Rodriguez, C. Olazagasti, University of Miami, Miami/FL/USA

Introduction: Lung cancer is the leading cause of cancer mortality in the US. Survival trends vary by sex, age, race/ethnicity, and socioeconomic status. While lung cancer outcomes have improved among all groups, mortality is highest among Black males. Studies showed that Black patients have lower smoking rates than White patients. Despite this, Black patients have a worse overall survival. Furthermore, the rates of lung cancer among younger patients have been increasing, with little known about this unique population. We aimed to explore racial disparities among young patients with lung cancer.

Methods: We created a single institution study at the University of Miami. A total of 128 patients (111 White and 17 Black) under the age of 45, who were treated for lung cancer from 2013-2021 were included in the analysis. Data analysis was conducted using t-tests and chi square analysis.

Results: The median age at diagnoses was 38 and 39 years for White and Black patients (p=0.34), respectively. (Table 1) While 59.4 % of White patients smoked tobacco, only 41.1% of Black patients endorsed a history of smoking tobacco (p=0.009). The average days between a positive biopsy and surgical intervention was 102 days for White and 15 days for Black patients (p=0.72). The average number of days between a positive biopsy and chemotherapy initiation for White vs Black patients was 37 days vs 44 days, respectively (p=0.59). The most common histology for White patients was adenocarcinoma (62%), whereas Black patients had only 35% prevalence of adenocarcinoma (p=0.017). Most patients in both groups had stage IV disease at diagnosis, 61% white vs 64% Black (p=.35). Despite lack of statistical association, Whites had more than two-fold rates of actionable mutations than Black patients, 56% in White patients vs 25% in Black patients (p=0.177).

Conclusions: Our single institution analysis revealed notable trends in the clinicopathologic characteristics of young patients with lung cancer. We found that Black patients had lower rates of adenocarcinoma despite lower rates of tobacco use, which is paradoxical to prior studies which have shown that adenocarcinoma is more common in non-smokers. Notably, Black patients were found to have lower rates of actionable mutations and were more frequently diagnosed with metastatic disease than their white counterparts. Thus likely resulting in less targetable and precise treatment plans for Black patients. Ongoing large prospective studies would be of paramount important to assess and understand potential racial disparities in young patients with lung cancer.

Keywords: Racial, disparities, young patients

Characteristic	White (N=111)	Black (N=17)	p-value
Age, Median	38.86 yrs	39.94 yrs	0.34
Smoking Status			0.009
No Smoking History (%)	45 (40.5%)	10 (58.8%)	
Current or Former Smoker (%)	66 (59.5%)	7 (42.2%)	
Days between positive biopsy and surgery	102 days	15 days	0.72
Days between positive biopsy and chemotherapy	37 days	44 days	0.59
Stage at Diagnosis			.35
Stage 1-3	43 (38.7%)	6 (36%)	
Stage 4	68 (61.2%)	11 (64%)	
Presence of Actionable Mutation	36 (56%)	1 (20%)	0.177

P3.01D RISK FACTORS, RISK REDUCTION & TOBACCO CONTROL - DISPARITIES, INEQUITIES & GEOGRAPHIC DIFFERENCES
MONDAY, SEPTEMBER 9, 2024 - 12:00 - 14:00

P3.01D.02 Lung Cancer Incidence Trends by Histology and Sociodemographic Characteristics in the US from 2000-2019

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Introduction: Lung cancer incidence has been decreasing in the US overall, largely due to declining smoking trends. However, adenocarcinoma incidence has been relatively stable compared to the other histological types until recently, causing its proportion among lung cancer cases to increase. Trends of histology-specific lung cancer incidence vary by sociodemographic characteristics, but the extent of this variation is unknown.

Methods: SEER 17 registry data was used to calculate annual age-adjusted lung cancer incidence over 2000-2020 by histology stratified by sex, race/ethnicity (non-Hispanic White, non-Hispanic Black, non-Hispanic American Indian/Alaska Native [NH-AI/AN], non-Hispanic Asian/Pacific Islander [NH-API], Hispanic), education (US counties grouped in quartiles of the percentage of people who are 25 or older and have at least bachelor's degree based on the American Community Survey (ACS)), poverty (US counties grouped in quartiles of the percentage of persons at above the federal poverty line based on the ACS), and region (Rural-Urban Continuum Codes were used to stratify US counties into metro counties (Urban) and non-metro counties (Rural)). Histology was categorized into four groups: adenocarcinoma, small cell carcinoma, squamous cell carcinoma, and other cell carcinoma. Age-adjusted incidence rates were computed using the 2000 US Standard Population. Incidence trends were assessed using Joinpoint regression analyses.

Results: Incidence of small cell, squamous cell, and other cell carcinoma have been decreasing since 2000 in both sexes and all racial/ethnic groups, although the decrease is either slower or statistically not different from 0 among the NH-AI/AN population. On the other hand, adenocarcinoma incidence was roughly stable for both sexes, with increases among female NH-API and Hispanic populations until 2019. Similar temporal patterns in lung cancer incidence by histology were observed in the analyses by education, poverty, and region. In general, counties with higher education levels or lower poverty rates experienced faster declines in small cell and squamous cell carcinoma in recent years. For example, the average annual percent change [AAPC] of small cell carcinoma in females from 2015 to 2019 was -0.7 (95% CI: -1.2, -0.1), -1.6 (95% CI, -2.0, -1.1), -3.2 (95% CI, -6.6, -2.2), and -3.9 (95% CI, -4.6, -3.5) for the first, second, third, and fourth education quartiles, respectively. Incidence of small cell and squamous cell carcinoma has been decreasing more rapidly in urban than rural areas in recent years. The analysis also found a clear gradient by educational attainment, poverty level, and region—with the lowest lung cancer incidence in the most educated and wealthy counties and urban areas in both sexes and all histological types, except for the adenocarcinoma among females, which showed the highest incidence rates in these subpopulations.

Conclusions: Disadvantaged groups have higher lung cancer rates and slower decreases in incidence over time, resulting in widening disparities. This highlights the need for targeted prevention strategies to accelerate lung cancer decreases in vulnerable populations. It will be important to continue monitoring lung cancer trends by histology to evaluate potential differential impacts of screening and the changing tobacco and nicotine landscape across different sociodemographic groups.

Keywords: Lung cancer incidence trends, Lung cancer disparity, Histology

P3.01D.03 Evaluating Lung Cancer Disparities Among Transgender Populations: A Retrospective Cohort Analysis

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Introduction: Lung cancer remains the leading cause of cancer-related mortality in the United States, imposing a significant burden on healthcare systems and communities across all demographic groups. The epidemiology of lung cancer among transgender and gender diverse (TGD) individuals remains incompletely understood. TGD individuals face unique risk factors including a high rate of cigarette smoking and decreased access to healthcare and screening. The impact of gender-affirming hormone therapy (GAHT) on lung cancer risk also remains unclear, with conflicting results from previous studies. In this large retrospective cohort study we used a large nationwide database to investigate lung cancer incidence in transgender individuals compared to cisgender counterparts.

Methods: Utilizing the TriNetX platform, we accessed de-identified electronic health records from 105.9 million patients, identifying 93,836 transgender individuals, including 39,573 trans men and 54,263 trans women. These cohorts were subdivided based on GAHT status, and the age-stratified lung cancer incidence was compared to the age-adjusted incidence of lung cancer among cisgender cohorts constructed from the same database.

Results: We observed significantly elevated lung cancer incidence among transgender men not undergoing testosterone therapy (TMNI) compared to cisgender females in specific age groups: 15-39 (SIR 4.96, 95% CI 2.42-9.10), 65-74 (SIR 2.43, 95% CI 1.13-4.62), and 75+ (SIR 3.96, 95% CI 1.01-10.78). No significant differences were observed for transgender men receiving testosterone therapy (TMHT) or transgender women, regardless of hormone treatment status (TWHT, TWNI).

Conclusions: These results highlight the importance of targeted interventions and supportive health practices to address cancer disparities among transgender populations. Further research is needed to understand the mechanisms underlying these observations and inform effective prevention strategies. This study contributes to advancing inclusive, gender-affirming healthcare practices and addressing health disparities within the transgender community.

Keywords: Hormone Therapy, Epidemiology, Lung Cancer

Table 1. Standardized Incidence Ratios for Lung Cancer in Transgender Men

	Follow up time (years)	Observed Cases	Cis Female Cohort Incidence Rate (per 100,000 person-years)	Expected Cases Female	Standardized Incidence Ratio (95% CI[a])
TMNI					
15-39	24,099	9	7.53	1.82	**4.96 (2.42-9.10)**
40-64	7,508	12	107.83	8.10	1.48 (0.80-2.52)
65-74	1,010	8	325.80	3.29	**2.43(1.13-4.62)**
75+	241	3	314.35	0.76[b]	**3.96(1.01-10.78)**
TMHT					
15-39	29,317	4	7.53	2.21	1.81 (0.58-4.37)
40-64	6,750	7	107.83	7.28	0.96(0.42-1.90)
65-74	574	3	325.80	1.87	1.60 (0.41-4.37)
75+	86	1	314.35	0.27[b]	3.70 (0.19-18.24)

Note: TM = Transgender Men, HT = Received gender-affirming testosterone therapy, NI=No intervention Bold indicates statistically significant standardized incidence ratio (SIR). [a] 95% CI calculated by mid-exact p test with p<0.05. [b] SIRs based on expected case counts less than 1 are inherently variable and may not reliably indicate risk due to disproportionate sensitivity to small changes in observed cases.

Table 2. Standardized Incidence Ratios for Lung Cancer in Transgender Women

	Follow up time (years)	Observed Cases	Cis Male Cohort Incidence Rate (per 100,000 person-years)	Expected Cases	Standardized Incidence Ratio (95% CI[a])
TWNI					
15-39	40,686	0	14.50	5.90	-
40-64	6,623	7	139.71	9.25	0.76 (0.42-1.92)
65-74	898	3	438.24	3.94	0.76 (0.36-3.82)
75+	350	1	452.28	1.58	0.63 (0.03-3.12)
TWHT					
15-39	20,626	1	14.50	2.99	0.33 (0.02-1.65)
40-64	6,309	7	139.71	8.81	0.79 (0.35-1.57)
65-74	788	4	438.24	3.45	1.16 (0.37-2.79)
75+	84	0	452.28	0.38[b]	-

Note: TW = Transgender Women, HT = Received gender-affirming testosterone therapy, NI=No interventionBold indicates statistically significant standardized incidence ratio (SIR). [a] 95% CI calculated by mid-exact p test with p<0.05. [b] SIRs based on expected case counts less than 1 are inherently variable and may not reliably indicate risk due to disproportionate sensitivity to small changes in observed cases.

P3.01D RISK FACTORS, RISK REDUCTION & TOBACCO CONTROL - DISPARITIES, INEQUITIES & GEOGRAPHIC DIFFERENCES
MONDAY, SEPTEMBER 9, 2024 - 12:00 - 14:00

P3.01D.04 Disparities in Lung Cancer Risk Assessment for People Living with HIV

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Introduction: People living with HIV (PLWHIV) are experiencing an increased incidence in non-AIDS-defining malignancies. Lung cancer is one of the most common cancers diagnosed in this population and the number one cause of cancer mortality. Lung screening reduces mortality from lung cancer. Screening may be even more beneficial in PLWHIV, as this population has been shown to have a higher incidence of lung cancer with shortened survival following diagnosis. To evaluate these disparities, we compared personalized PLCOm2012 lung cancer risk scores and incidence of lung cancer diagnosis in screening participants with and without HIV.

Methods: Retrospective chart review was performed on 4,233 patients enrolled in a lung cancer screening program at a single academic institution from November 2017 to November 2023. All enrolled patients met the current United States Preventive Services Task Force lung screening guidelines. PLCOm2012 risk prediction model was used to assign personalized 6-year lung cancer risk scores to patients based on demographic data from baseline lung screening. PLWHIV were identified through ICD-10 diagnostic codes and chart-review. Statistical difference in median PLCO score by HIV status was estimated by Wilcoxon rank-sum test. Logistic regression was performed to estimate lung cancer risk among HIV-positive patients after controlling for baseline risk as determined by PLCO score. All analyses were performed with Stata v18.

Results: PLWHIV (n = 269, Table 1) had a higher prevalence of lung cancer (3.35%) compared to those without HIV (2.57%, n = 3,964). However, the median PLCO score in PLWHIV was 2.2 compared to 2.7 in those without HIV (p-value 0.0001). The likelihood for receiving a lung cancer diagnosis was about 50% greater (OR=1.5; 95% CI 0.77-3.12; p=0.22) among the HIV-positive population compared to the HIV-negative cohort after controlling for baseline PLCO score in the lung screening program.

Conclusions: A statistically significant difference in baseline lung cancer risk as determined by PLCO was observed with the HIV-negative group having higher baseline score but lower prevalence of lung cancer compared to PLWHIV. This suggests that HIV status may be an independent risk factor for lung cancer in this population. This finding, while not statistically significant, should be investigated in larger cohorts of PLWHIV, given our strong, single-site observations. These data suggest that lung cancer screening guidelines may not be adequately including higher risk individuals living with HIV.

Keywords: Lung Cancer, Risk Score, HIV

Table 1: Demographic Data and HIV Status for Lung Screening Participants

Lung Screening Participants	Without HIV N= 3964	Living with HIV N= 269
Lung cancer detected by LCS	102 (2.57%)	9 (3.35%)
Median PLCO Risk Probability	2.70%	2.20%
Average PLCO Risk Probability	4.13%	3.24%
Average Age	64	59
Average pack-years	44.12	39.9
Personal history of Cancer	9.00%	8.18%
Personal history of COPD	25.70%	27.14%
Family history of Lung Cancer	18.60%	10.41%
Education level		
0 = unknown/declined	0.78%	1.12%
1 = <HS	7.42%	15.99%
2 = HS/GED	26.61%	29.74%
3 = Post-HS training	3.63%	1.49%
4 = Some college/Assoc degree	30.78%	28.25%
5 = College graduate	19.93%	14.87%
6 = Postgraduate degree	10.85%	8.55%
Race		
0 = unknown/declined/other	1.74%	0.00%
1 = American Indian/indigenous	0.15%	1.86%
2 = Asian	0.48%	0.37%
3 = Black/AA	12.89%	31.97%
6 = White	83.88%	64.68%

P3.01D RISK FACTORS, RISK REDUCTION & TOBACCO CONTROL - DISPARITIES, INEQUITIES & GEOGRAPHIC DIFFERENCES
MONDAY, SEPTEMBER 9, 2024 - 12:00 - 14:00

P3.01D.05 Gender Differences in Lung Cancer Incidence Among Patients Who Never Smoked Cigarettes: A Systematic Literature Review

D. Molena[1], C. Aggarwal[2], N. Florez[3], S. Peters[4], J. Brahmer[5], E. Shum[6], R. Salomonsen[7], J. Chaieb[7], M. Chau[7], R. Shenolikar[7], L. Luciani-Silverman[7], D. Guy[8], L. Woldmann[8], A-A. Ciritel[8], H. Wakelee[9], [1]Memorial Sloan Kettering Cancer Center, New York/NY/USA ,[2]University of Pennsylvania Medical Center - Abramson Cancer Center at Perelman Center for Advanced Medicine, Philadelphia/PA/USA ,[3]Dana-Farber Cancer Institute, Boston/MA/USA ,[4]CHUV, Lausanne University, Lausanne/CH ,[5]Johns Hopkins Medicine, Baltimore/MD/USA ,[6]NYU Langone, New York/NY/USA ,[7]AstraZeneca, Gaithersburg/MD/USA ,[8]Amaris Consulting, Barcelona/ES ,[9]Stanford University School of Medicine, Stanford/CA/USA

Introduction: Lung cancer is a leading cause of mortality worldwide. While cigarette smoking is a main driver of lung cancer, a subset of cases also occurs in patients that have never smoked, particularly in women. Understanding the gender-based nuances of lung cancer incidence among patients who do not smoke, alongside other demographic characteristics, is essential for refining screening strategies and improving outcomes for all individuals at risk, irrespective of smoking history.

Methods: A systematic literature review was conducted to synthesize published literature on the gender-based differences in lung cancer incidence rates among patients who do not smoke cigarettes, considering additional factors such as race, ethnicity, age, and histology subtypes. Embase, MEDLINE, MEDLINE In-Process, and Cochrane databases were searched. Relevant conference proceedings and additional literature from experts were also considered. English language studies published between January 2004 and February 2024 that reported global, regional, or national lung cancer incidence rates for men and women were included.

Results: We found 879 studies, 609 remained after de-duplication. Of these, 550 were ineligible based on titles/abstracts. From the 59 remaining articles, eight studies will be evaluated.

Conclusions: We plan to present the incidence rates among women who never smoked compared to men, particularly in younger age groups, and indicate potential areas of differences.

Keywords: gender differences, lung cancer incidence, never-smokers

P3.01E RISK FACTORS, RISK REDUCTION & TOBACCO CONTROL - LUNG CANCER PREVENTION STRATEGIES
MONDAY, SEPTEMBER 9, 2024 - 12:00 - 14:00

P3.01E.01 Real-World Analysis of GLP-1 Receptor Agonists and Lung Cancer Risk in Treatment-Naïve Type 2 Diabetes: Potential Impact of Obesity and Gender

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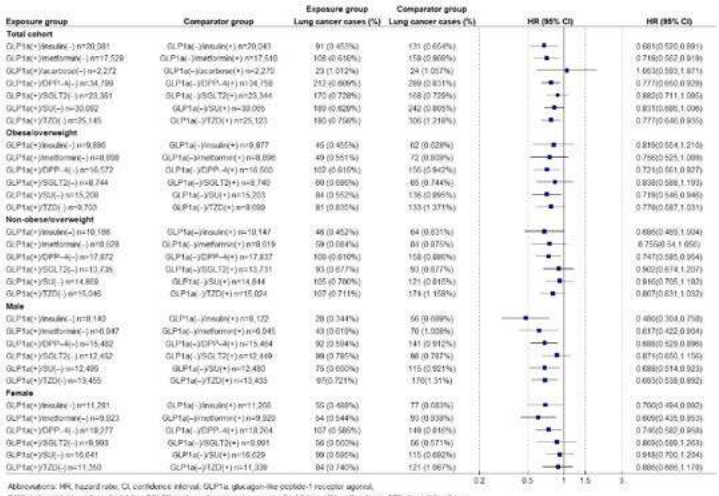
Introduction: Type 2 diabetes (T2DM) affects over 30 million people in the United States, with approximately 15% of lung cancer patients also affected by this condition. Glucagon-like peptide-1 receptor agonists (GLP1a) have become popular in T2DM treatment and are proposed to have anti-inflammatory and immunomodulatory functions in addition to weight loss and glucose control. Initial studies of GLP1a raised concerns for increased risk of malignancies, especially pancreatic cancer. However, recent studies have proposed the contrary for colorectal cancer based on real-world data, hypothesizing that the weight-reducing effect of GLP1a may be the mechanism behind this observation. In this study, we aim to explore the association of GLP1a and the risk of developing lung cancer - which has been suggested to be inversely related to obesity.

Methods: We utilized TriNetX Global Collaborative Network, a deidentified real-world electronic health record database containing 122.6 million patient records. We included patients over the age of 18 diagnosed with T2DM who started their first diabetic medication (drug-naïve) between 2010 and 2019. Patients previously diagnosed with pulmonary nodules or lung cancer prior to initiating their initial diabetic medication were excluded. We conducted 1:1 propensity score matching to control for potential risk factors and confounders. Subsequently, survival analyses were performed among GLP1a users and comparison cohorts within the total and subgroups, calculating the incidence and hazard ratio (HR) of newly developed lung cancer.

Results: During a 15-year follow-up of 734,835 drug-naïve T2DM patients, GLP1a was associated with a decreased risk of lung cancer when compared to insulin (HR:0.681, 95% CI:0.520-0.891), metformin (HR:0.719, 95% CI:0.562-0.919), DPP4 inhibitor (HR:0.777, 95% CI:0.650-0.928), and thiazolidinediones (HR:0.777, 95% CI:0.646-0.935), and the trend was similar among the obese and non-obese population. GLP1a's protective association appeared to be more pronounced in males, especially compared to insulin (HR:0.480, 95% CI:0.304-0.758) and metformin (HR:0.617, 95% CI:0.422-0.904).

Conclusions: GLP1a use was associated with decreased lung cancer risk among drug-naïve T2DM patients. This effect was primarily driven by the male cohort, where patients on GLP1a had a 52% decrease in the risk of lung cancer development compared to insulin. In contrast to the previous study of colorectal cancer, lung cancer risk reduction was similar among the obese/overweight and non-obese/overweight populations. These findings are significant, especially considering initial concerns about increased cancer risk associated with these commonly used antidiabetic agents. Further investigations into GLP1a's preventive role in lung cancer development and underlying mechanisms are warranted.

Keywords: Lung cancer risk, GLP-1 receptor agonist, Obesity



P3.01E RISK FACTORS, RISK REDUCTION & TOBACCO CONTROL - LUNG CANCER PREVENTION STRATEGIES
MONDAY, SEPTEMBER 9, 2024 - 12:00 - 14:00

P3.01E.02 Association Between Composite Dietary Antioxidant Index and Lung Cancer Risk in Former Smokers: A Large Prospective Cohort Study in UK Biobank

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Introduction: Lung cancer is the leading cause of cancer death worldwide. There is limited epidemiological evidence regarding the association between Composite Dietary Antioxidant Index (CDAI) and lung cancer risk. Therefore, this study was to investigate the relationship between CDAI and lung cancer.

Methods: This prospective cohort study used data from the UK Biobank cohort study on adults aged 40 to 69 years who were recruited at 22 assessment centers throughout the UK Biobank between March 13, 2006, and October 1, 2010, with follow-up through June 1, 2022. The CDAI was calculated based on the standardized intake levels of six dietary antioxidants, including manganese, selenium, zinc, and vitamins A, C, and E. The lung cancer cases were confirmed via the International Classification of Diseases-10th (ICD-10) code “C34”. Cox proportional hazards regression models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for the association of CDAI with lung cancer risk. Subgroup analyses were conducted to investigate the association stratified by age, sex, ethnicity, Townsend Deprivation Index, education level, Body Mass Index (BMI), weekly physical activity, smoking status, alcohol intake frequency, and family history of lung cancer. Furthermore, additive interaction was used to assess whether CDAI modifies the risk of lung cancer among smokers. Besides, the robustness of the results was assessed by multiple sensitivity analyses.

Results: A total of 201,316 participants from the UK Biobank were included in the study. During a median follow-up of 11.8 years, 1229 incident lung cancer cases were documented. The analysis showed a trend for a higher quartile of CDAI associated with a lower lung cancer risk after adjusting for covariates (HRQ4vs.Q1, 0.69; 95% CI, 0.56-0.85; Ptrend < 0.001). Similar findings were also observed in non-small cell lung cancer (HRQ4vs.Q1, 0.72; 95% CI, 0.58-0.89; Ptrend= 0.003) and small cell lung cancer (HRQ4vs.Q1, 0.38; 95% CI, 0.17-0.85; Ptrend= 0.019). In subgroup analyses, the association between CDAI and the risk of lung cancer was more significant in participants with higher education (HR, 0.94; 95% CI, 0.9-0.98; P= 0.004), BMI <25 kg/m2 (HR, 0.95; 95% CI, 0.91-0.99; P= 0.007), former smoking (HR, 0.95; 95% CI, 0.92-0.98; P= 0.002), and without a family history of lung cancer (HR, 0.97; 95% CI, 0.94-0.99; P= 0.006). Additionally, a negative interaction was observed between CDAI and smoking status, indicating that HRs (95% CIs) of lung cancer for former smokers in the lowest and highest quartile of CDAI were 4.28 (3.16-5.79) and 0.66 (0.43-1), respectively, compared to non-smokers with the lowest CDAI quartile. In the sensitivity analysis, there was no significant difference in the HR for lung cancer after excluding participants with incomplete covariate data (HRQ4vs.Q1, 0.74; 95% CI, 0.59-0.93; Ptrend = 0.005), and the association remained consistent within the subset after removing outliers of CDAI (HRQ4vs.Q1, 0.68; 95% CI, 0.56-0.84; Ptrend < 0.001).

Conclusions: Dietary antioxidants may reduce the risk of lung cancer, especially among former smokers.

Keywords: composite dietary antioxidant index, lung cancer, UK Biobank

P3.01F RISK FACTORS, RISK REDUCTION & TOBACCO CONTROL - RISK FACTORS BEYOND SMOKING
MONDAY, SEPTEMBER 9, 2024 - 12:00 - 14:00

P3.01F.01 Evaluating the Relationship Between Veteran Toxic Exposure Status and Lung Cancer Prevalence

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Introduction: Veterans face a greater risk for lung cancer. Military service-related exposures may increase the likelihood for developing lung cancer. Screening guidelines rely on tobacco use history and age, but inadequately capture the breadth of risk factors prevalent among veterans. We linked the Veterans Affairs (VINCI) and the Department of Defense service (DaVINCI) electronic health records to obtain tobacco use and military exposures. This study assesses the association between lung cancer and veteran-specific toxic exposures.

Methods: We combined individual tobacco use strata ("Ever," "Never," or "Unknown") with self-reported toxic exposure survey data among all veterans receiving care between 1/1/2022 and 12/31/2023. Toxic exposures surveyed were Agent Orange, Airborne Hazard/Burn Pit, Camp Lejune, Radiation, Gulf War, and Other. We excluded veterans who declined toxic exposure screening. Patients were stratified by toxic exposure status, tobacco use status, and age. We investigated the association between service branch and exposure. Finally, we performed logistic regression modeling to adjust for age, tobacco use status, and exposure status.

Results: 7,031,577 veterans completed toxic exposure screening. 2,132,015 (29.8%) screened positive for toxic exposure. Unadjusted prevalence of lung cancer was 1.6% in the overall cohort, 1.7% among veterans with any toxic exposure, and 1.5% with no exposure. The unadjusted lung cancer prevalence ranged from 3.6% (Agent Orange) to 0.9% (Gulf War) with marked differences in median age (Table 1). Among all services and exposures, Marine Veterans had the highest prevalence (3.8%) from Agent Orange and Coast Guard with Gulf War exposures had the lowest (0.3%, Table 2).

Conclusions: Lung cancer among veterans with any tobacco use and age greater than 50 varied widely by service branch and toxic exposure status. Many were more than PLCO 1.6% cutoff. Our investigation highlights the critical role of toxic exposure consideration in risk assessment and the critical need for veteran specific guidelines.

Keywords: Lung Cancer, Veterans, Toxic Exposure

Table 1. Unadjusted Lung Cancer Rates Among Veterans With Age Greater than 50 Years and Any Tobacco Use History by Military Exposure

	No Toxic Exposure	Agent Orange	Airborne Hazard/Burn Pit	Camp Lejune	Gulf War	Radiation	Other
N	2,664,829	601,360	447,682	139,184	118,755	95,240	248,267
Median Age	73	77	62	72	59	67	67
Median Age at Lung Cancer Diagnosis	71	72	67	69	60	68	68
Lung Cancer Prevalence	2.6	3.6	1.4	2.9	0.9	2.1	2.4

Table 2. Unadjusted Lung Cancer Rates Among Veterans With Age Greater than 50 Years and Any Tobacco Use History by Military Exposure Type and Service Branch

	Any Toxic Exposure	Agent Orange	Airborne Hazard/Burn Pit	Camp Lejune	Gulf War	Radiation	Other
Air Force (N = 183,333)	0.6	3.1	1.1	2.2	0.8	1.9	2.0
Army (N = 676,405)	2.5	3.7	1.4	2.4	0.9	2.2	2.3
Coast Guard (N = 9,690)	2.0	3.4	1.5	1.0	0.3	1.6	1.9
Marine Corps (N = 203,148)	2.8	3.8	1.6	3.0	0.8	2.6	2.2
Navy (N = 256,634)	2.6	3.4	1.7	2.5	0.9	1.9	2.7

N represents total number with a toxic exposure, positive tobacco use history, and age 50 years or greater.

P3.01F RISK FACTORS, RISK REDUCTION & TOBACCO CONTROL - RISK FACTORS BEYOND SMOKING
MONDAY, SEPTEMBER 9, 2024 - 12:00 - 14:00

P3.01F.02 Retrospective Characterization of Patients with Primary Lung Cancer Related to World Trade Center Disaster Exposure

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Introduction: Over twenty years after the World Trade Center (WTC) disaster, exposed responders and citizens continue to be diagnosed with cancers due to the toxicity of the dust, fires, and clean-up. The two decades since then have revealed common "9/11 Cancers", with lung cancer being the third most common. Here, we analyze a cohort of 250 patients treated at NYU Langone Health between 2011 and 2023 with a diagnosis of primary lung cancer who had exposure to the WTC disaster. We aim to assess how this exposure incident impacts features of patients' pulmonary tumors and resultant disease course, in order to expand providers' knowledge as these cancers continue to be diagnosed.

Methods: This is a retrospective chart review of primary lung cancer patients treated at NYULH Perlmutter Cancer Center (PCC), diagnosed between January 1, 2006 and December 31, 2023, with documented WTC exposure. Data points include age, sex, race, diagnosis date, smoking status, stage at diagnosis, disease course, next generation sequencing, and date of death (if applicable). Study dataset was curated by PCC Data Hub then manually annotated when data were inaccessible.Summary statistics were computed for demographics and clinical characteristics. Statistical tests, including the Kruskal-Wallis Rank Sum, Fisher's Exact, and Chi-Squared tests, and clustering analyses were performed as appropriate. All time-to-event outcome variables ('time to response to first-line therapy,' 'progression-free survival,' and 'overall survival') were analyzed using the Kaplan-Meier (KM) product limit method and Cox proportional hazard (CPH) regression models.

Results: Initial data curation identified 250 lung cancer patients with documented WTC toxicity exposure. Our analysis found that more than half of the study population were diagnosed with Stage I (50%) or Stage II (7.2%) disease, followed by Stage III (14%) and IV (21%), and 8.4% unknown. 160 patients were former smokers and 14 were current smokers. Of the 174 patients with smoking history, 52 had under 20 pack year histories. 67 patients in the cohort (27%) had no smoking history at all. Interestingly, the non-smoking patients as a group had the highest proportion of Stage IV disease at diagnosis, when compared to groups with smoking history.

Conclusions: In this population, there was a higher rate of diagnosis at lower stage (I-II) compared to lung cancer patients in the United States, which are commonly diagnosed at Stages III-IV. The national recommendation for annual lung cancer screening is for patients with 20 pack year histories, and a majority of the patients included here would not have qualified for screening. Thus, their earlier diagnosis could be linked to known exposure and screening through the September 11th Victims Compensation Fund (VCF). Current WTC-related lung cancer research is limited to incidence and demographics without description of detailed clinical factors. Our work highlights that screening these patients can increase the rate of earlier lung cancer diagnosis, and hopefully improve prognosis. Future studies with this population can allow us to better understand whether lung cancer in this group differs from that of patients with other exposure histories.

Keywords: 9/11, WTC, Toxic dust exposure

P3.02F TUMOR BIOLOGY - PRECLINICAL BIOLOGY - METASTASIS
MONDAY, SEPTEMBER 9, 2024 - 12:00 - 14:00

P3.02F.01 CD47 Promotes Migration and Metastasis in Non-Small Cell Lung Cancer

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Introduction: CD47 is a cell surface protein frequently overexpressed in non-small cell lung cancer (NSCLC). Although it has multiple biological functions, most CD47 studies in cancer have focused on its role in promoting tumor immune evasion. This inspired the development of CD47-targeted immunotherapy which is currently being evaluated in clinical trials. High CD47 expression is associated with poor survival, advanced tumor stage, and metastasis in NSCLC patients, and inhibition of CD47 impairs lung tumor growth and progression, highlighting its therapeutic potential. Yet, little is known about the involvement of CD47 in regulating NSCLC metastasis. We hypothesize that CD47 promotes metastasis by positively regulating signal transduction pathways required for cell migration and invasion. In this study, we examined the effect of CD47 loss-of-function (LOF) on lung cancer migration and metastasis and relevant signaling pathways in NSCLC models.

Methods: CRISPR/Cas9 was used to induce CD47 LOF by deleting its transmembrane and extracellular domains (ΔCD47) in the mouse NSCLC models, Lewis Lung Carcinoma (LLC) and CMT167 (CMT), as well as the human NSCLC line, H1299. ΔCD47 was confirmed in these lines using Sanger sequencing of genomic DNA, and immunofluorescence and flow cytometry to assess expression of CD47 on the cell surface. The functional effects of ΔCD47 on cell proliferation and migration were assessed using growth competition and scratch assays, respectively. Metastasis to the lungs in syngeneic mice was quantified using bioluminescence imaging (BLI) after tail-vein injections of wildtype (WT) or ΔCD47 LLC cells expressing Luciferase. Proteins related to migration and metastasis were measured in isogenic cells using immunoblotting.

Results: We observed no difference in the proliferation of LLC, CMT or H1299 cells with WT or ΔCD47 in competitive growth assays performed in vitro. However, we found that ΔCD47 significantly impaired migration of CMT and H1299 cells in vitro. We could not measure migration with scratch assays in the LLC model due to its loose adherence, but ΔCD47 significantly impaired metastasis of LLC cells to the lungs of mice after tail-vein injection. Concordantly, mice injected with ΔCD47 LLC cells exhibited significantly longer metastasis-free survival than mice injected with WT control cells. Our initial assessment of signaling proteins involved in migration/metastasis pathways suggests that E-cadherin expression is increased and phospho-AKT, phospho-FAK, and vimentin expression are reduced in ΔCD47 cells, consistent with the migration defect we observed in cells with CD47 LOF.

Conclusions: Our findings indicate that CD47 promotes migration and metastasis of NSCLC cells both in vitro and in vivo. This suggests that CD47-targeted therapy could effectively inhibit NSCLC tumors by antagonizing metastatic spread in addition to tumor immune evasion. At the molecular level, our results suggest that migration and metastasis are regulated, at least in part, by a CD47-FAK-AKT signaling axis. Future experiments will continue to unravel the metastasis signaling cascade governed by CD47 in NSCLC.

Keywords: CD47, metastasis, signaling

P3.02F TUMOR BIOLOGY - PRECLINICAL BIOLOGY - METASTASIS
MONDAY, SEPTEMBER 9, 2024 - 12:00 - 14:00

P3.02F.02 Long Non-Coding RNA STEAP2-AS1 Promotes Non-Small-Cell Lung Cancer Cells Progression by Interacting with ARNTL2 To Upregulate DARS2

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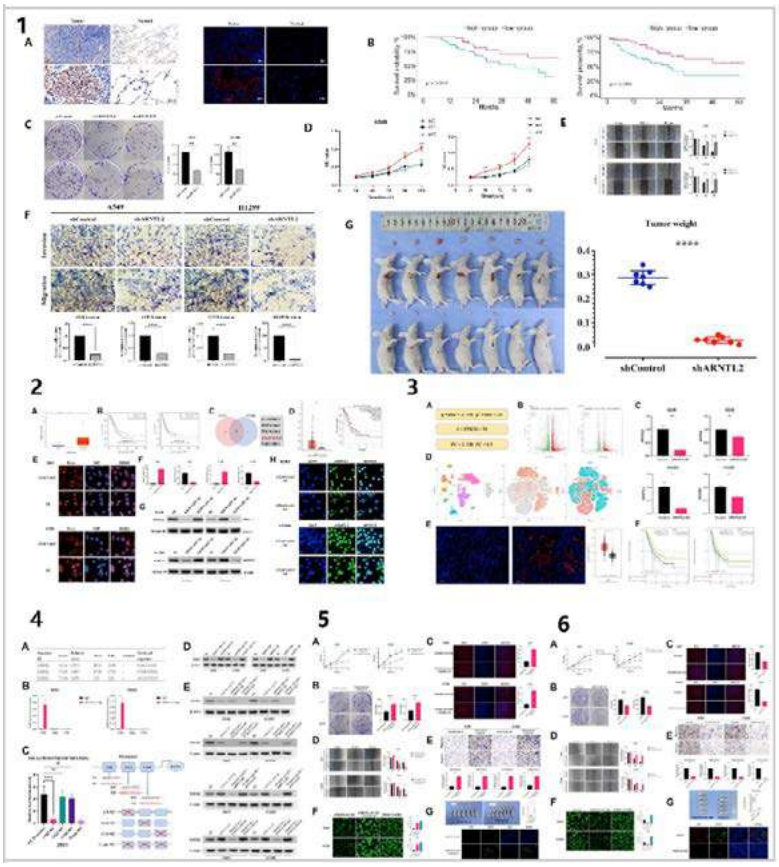
Introduction: Circadian rhythm plays an important role in tumors. Though ARNTL2 serves as one of the core genes of circadian rhythm, there are few studies on its regulation and mechanism of lung cancer. We sought in this study to firstly define the expression, prognostic effects, and potential regulatory roles of ARNTL2 in non-small-cell lung cancer (NSCLC). We subsequently clarified the key regulatory role of the "non-coding RNA-ARNTL2-target gene" regulatory axis in the tumorigenesis and development of NSCLC through a series of cytological and animal assays.

Methods: First, the expression and prognostic significance of ARNTL2 in NSCLC were identified by data from The Cancer Genome Atlas (TCGA) and the single-cell RNA sequencing of our department. Subsequently, long non-coding RNA (lncRNA) regulatory mechanisms and target genes of ARNTL2 were fully explored by Immunoprecipitation sequencing of RNA (RIP-Seq) and transcriptome sequencing of RNA (RNA-Seq) in A549 and H1299 cells, respectively. Further, we take full advantage of molecular techniques such as bioinformatics analysis, Chromatin Immunoprecipitation (ChIP), Western blot, Immunofluorescence and Fluorescence in situ hybridization; cytological and animal experimental to fully explore the regulatory effects and mechanisms of "LncRNA-ARNTL2-target gene" regulatory axis in the proliferation, migration, and invasion of NSCLC.

Results: We found that the expression of ARNTL2 was upregulated in NSCLC and significantly associated with worse prognosis. Through bioinformatics analysis, cytology, and animal experiments, we discovered the effect of ARNTL2 in cell proliferation, migration, and invasion of NSCLC. In addition, we found that LncRNA STEAP2-AS1 was an important non-encoding RNA interacting with ARNTL2 in A549 and H1299 cells by RIP-Seq. And STEAP2-AS1 had the role of transferring the transcription factor ARNTL2 through the cytoplasm to the nucleus. We also identified DARS2 as a direct transcriptional target of ARNTL2 and verified its binding site through Luciferase reporter and ChIP assays. In addition, we found LncRNA STEAP2-AS1/ARNTL2/DARS2 axis promotes proliferation, migration and invasion, and was significantly associated with a poor prognosis in NSCLC patients.

Conclusions: The present study elucidates for the first time in NSCLC cells that ARNTL2 undergoes "Cytoplasmic-Nuclear translocation" through the LncRNA STEAP2-AS1-dependent guidance effect and binds to the promoter region of the target gene DARS2 to promote the expression. LncRNA STEAP2-AS1/ARNTL2/DARS2 axis plays an important role in promoting cell proliferation, migration, and invasion of NSCLC. Our findings will shed light, to some extent, on the key roles and regulatory mechanisms of the circadian element ARNTL2 in the development and progression of NSCLC.

Keywords: ARNTL2, LncRNA, Non-small-cell lung cancer



P3.02F TUMOR BIOLOGY - PRECLINICAL BIOLOGY - METASTASIS
MONDAY, SEPTEMBER 9, 2024 - 12:00 - 14:00

P3.02F.04 Investigating the Role of Lactate Import and Metabolism in Non-Small Cell Lung Cancer

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Introduction: Metabolic reprogramming is a hallmark of cancer, but our knowledge of nutrient preferences in cancer cells has been limited to non-physiological cell culture systems. In preclinical animal models and patients with patients with non-small cell lung cancer (NSCLC), we demonstrated that lactate, commonly thought of a waste product of cancer cells, is instead an important nutrient. Furthermore, increased lactate uptake via monocarboxylate transporter 1 (MCT1) is associated with worse disease-free and overall survival. How lactate import reprograms metabolism and how this supports aggressive lung cancers remains unclear.

Methods: In vitro studies utilized H1299 cells cultured in standard (RPMI) or physiological (HPLM) nutrient conditions. Cells were treated with the MCT1 inhibitor AZD3965 (100 uM) for 24h prior to the addition of physiological concentrations of glucose or lactate. Either glucose or lactate was uniformly labeled with the stable isotope 13C to investigate the metabolism of each nutrient. Metabolites were extracted after 24 h and were measured using GC-MS. Mouse xenografts were generated using NSCLC cell lines injected subcutaneously and were infused with 13C labeled metabolites prior to euthanasia.

Results: Adding lactate to RPMI results in decreased glucose incorporation into the TCA as demonstrated by increased m+0 citrate labeling. Lactate was taken up and incorporated into the TCA cycle, as demonstrated by m+2 citrate labeling. This incorporation was decreased by treatment with the MCT1 inhibitor AZD3965. While lactate was the preferred carbon source to generate alanine, the inhibition of MCT1 induced metabolic rewiring, as cancer cells compensated by re-directing glucose to generate alanine. Importantly, culturing cells with the physiological HPLM condition displayed greater alterations in metabolism, including diminished glucose utilization for generating lactate and citrate when compared to RPMI conditions. In cell culture, physiological media conditions (including adding lactate as a nutrient source) better recapitulated the metabolic reprogramming of lung tumors in vivo.

Conclusions: Lactate is an important nutrient in NSCLC. Addition of lactate to cell culture media allows for the import and metabolism of lactate, and results in the metabolic rewiring of other nutrients such as glucose. By further mimicking physiological nutrient conditions, such as the use of HPLM, we are better able to model the metabolism of tumors in vivo. Further optimization of culture conditions can provide a foundation to understand the role of MCT1 inhibition as a therapeutic target for NSCLC.

Keywords: NSCLC, metabolism, stable isotope tracing

P3.02F TUMOR BIOLOGY - PRECLINICAL BIOLOGY - METASTASIS
MONDAY, SEPTEMBER 9, 2024 - 12:00 - 14:00

P3.02F.05 A Genetic Engineering Approach to Interrogate Myosin 10 As a Driver of Non-Small Cell Lung Cancer Metastasis

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Introduction: A major contributor of lung cancer mortality is associated with late cancer stage at diagnosis, with 5-year survival rates for persons with regional and distant metastasis at 29.7 and 4.7% compared to localized (non-metastatic) lung cancer at 56.3%. While minimizing lung cancer metastasis can improve overall survival, few models exist where subpopulations with stable high and low metastatic potential can be easily and reliably isolated. Previous work characterized two stable subpopulations, termed Leaders and Followers, from the H1299 Non-Small Cell Lung Cancer model. H1299 Leaders and Followers have different transcriptional profiles, biomarkers, genomic methylation patterns, metabolic states, and morphologies. Of note, H1299 Leaders express high levels of Myosin 10 (MYO10) and drive collective invasion and metastasis.

Methods: To determine how MYO10 contributes to Leader cell biology and lung cancer metastasis, we utilized CRISPR-Cas9 to generate edited pools of H1299 cells targeting MYO10. Fluorescence-activated cell sorting using a Leader-Follower biomarker, IL13R–2, was used to generate single cell derived candidate clones. Candidate clones were screened using western blot for Leader and Follower cell biomarkers (JAG1, MYO10, HTATIP2 and IL13R2) followed by Sanger sequencing of candidate clones was also conducted to confirm target gene status (Figure 1A-B).

Results: Three (3) MYO10-/- and two (2) wildtype MYO10+/+ single-cell derived clones were generated (Figure 1C). Data show that loss of MYO10 in Leader cells significantly reduces proliferation and alters the transcriptional profile of Leader cells but is not essential for survival.

Conclusions: While loss of MYO10 abrogates proliferation there is much left to be interrogated regarding how MYO10 contribute to metastasis. Clones generated in this model will be used to assess how loss of MYO10 in Leader cells influences the survival and patterns of metastasis in our in vivo model. This work is the foundation of future studies which aim to enhance our understanding not only of MYO10-dependent mechanisms that drive the Leader metastatic phenotype but also how MYO10 influences Leader cell interactions with endothelial cells as a part of the metastatic cascade.

Keywords: metastasis, lung cancer, myosin 10

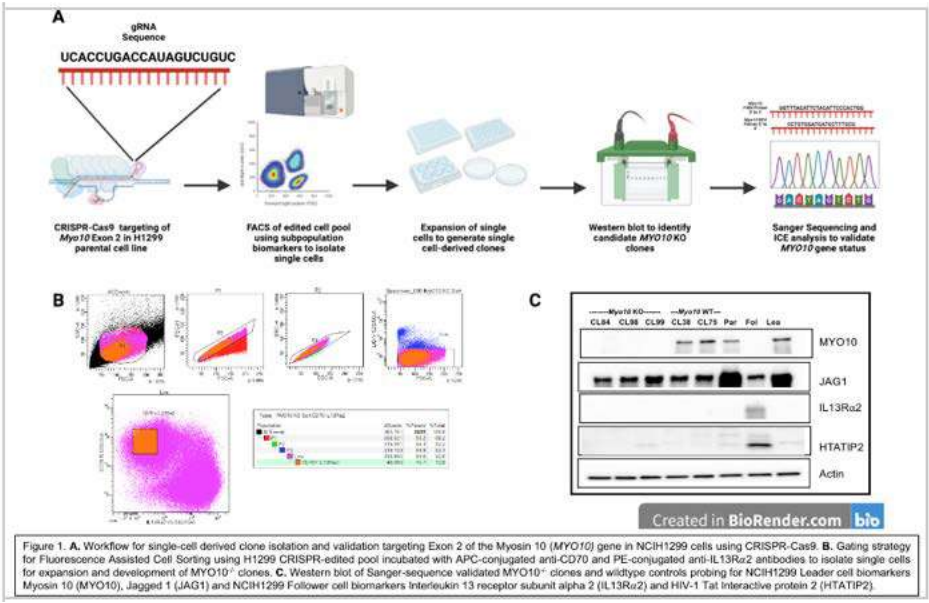

Figure 1. **A.** Workflow for single-cell derived clone isolation and validation targeting Exon 2 of the Myosin 10 (*MYO10*) gene in NCIH1299 cells using CRISPR-Cas9. **B.** Gating strategy for Fluorescence Assisted Cell Sorting using H1299 CRISPR-edited pool incubated with APC-conjugated anti-CD70 and PE-conjugated anti-IL13Rα2 antibodies to isolate single cells for expansion and development of MYO10$^{-/-}$ clones. **C.** Western blot of Sanger-sequence validated MYO10$^{-/-}$ clones and wildtype controls probing for NCIH1299 Leader cell biomarkers Myosin 10 (MYO10), Jagged 1 (JAG1) and NCIH1299 Follower cell biomarkers Interleukin 13 receptor subunit alpha 2 (IL13Rα2) and HIV-1 Tat Interactive protein 2 (HTATIP2).

P3.02F TUMOR BIOLOGY - PRECLINICAL BIOLOGY - METASTASIS
MONDAY, SEPTEMBER 9, 2024 - 12:00 - 14:00

P3.02F.06 Multi-Omics Reveals Effects of Gut Microbiome on Tumor Immune and Metabolism in Mouse Lewis Lung Carcinoma Model

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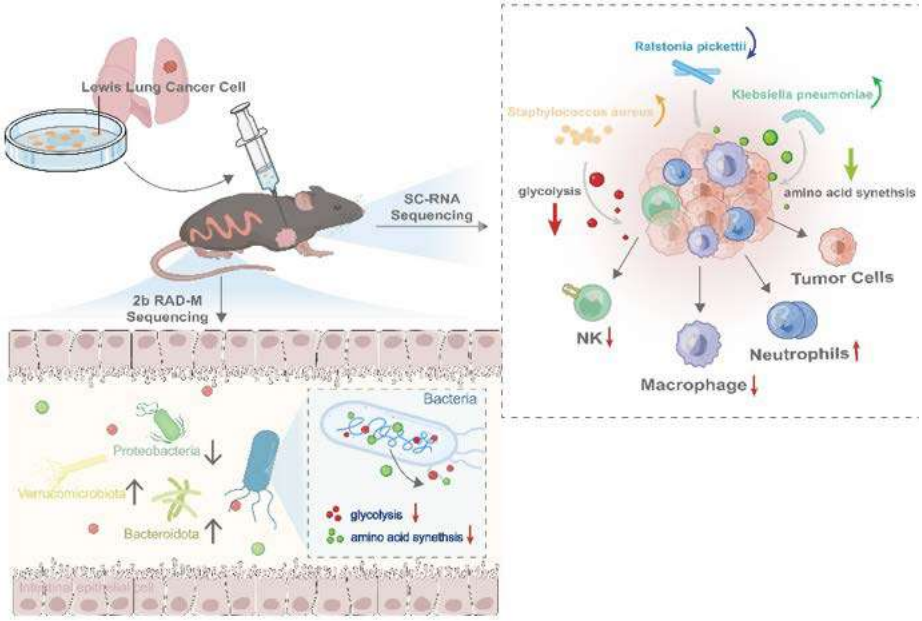
Introduction: The gut microbiota represents the predominant symbiotic microbial community in mammalian organisms, lung cancer has long been a challenging human disease. Investigating the role of the gut microbiota in the occurrence and progression of lung cancer holds value. Our objective was to investigate the impact of gut microbiota on lung cancer progression and the effects on tumor metabolism and immune through multi-omics methods between germ-free(GF) and specific pathogen-free(SPF) mouse models.

Methods: Subcutaneous tumor was established using Lewis lung carcinoma cells(LLC) in 10 GF mice and 12 SPF mice. The distribution of intestinal and tumor microbiota as well as tumor metabolites was examined using simplified metagenomics(2bRAD-M) and metabolomics(GC/LC-MS) in random selected 6 GF and 6 SPF mice. Single-cell-RNA sequencing was performed in random selected 2 GF and 2 SPF mice.

Results: Tumor growth in SPF mice was significantly faster than in GF mice. Metagenomic analysis showed a significant difference of beta-diversity in gut microbiota between SPF and GF mice while no significant difference in tumor microbiota. Chao1 was used to quantify the alpha-diversity of microbiotas. The alpha-diversity of gut microbiota in SPF mice was significantly higher than that in GF mice while no significant difference in tumor microbiota. Pearson analysis showed a positive correlation between gut flora Chao1 value and tumor volume. Single-cell-RNA sequencing indicated the functions of vasculogenesis and morphogenesis in tumor cells of SPF mice were upregulated, as well as the number and function of neutrophils and fibroblasts related to tumor progression were increased. In GF mice, the number of CD8 cells for anti-tumor immunity was upregulated and the tumor killing function was upregulated while the number of macrophages was increased and the tendency of differentiation towards M1 macrophages was increased. Metabolomics showed glycolysis and amino acids metabolism was downregulated in SPF tumors. Combining the gut microbiota KO(KEGG Orthology) enrichment and single-cell subclustering analysis, the function of glycolysis and amino acids metabolism in gut microbiota of SPF mice was lower while no significant difference in that of tumor microbiota.

Conclusions: Gut microbiota promotes tumor development and the malignancy, upregulates the number and function of cancer-related Neutrophils and Fibroblasts while downregulates that of tumor-killing CD8 T cells and M1-type Macrophages. The relative abundance and diversity of gut flora is positively correlated with tumor progression, but not the tumor flora. The gut flora correlates with the regulation of glycolysis and amino acids metabolism in tumor, but not the tumor flora.

Keywords: Gut-Lung axis, Tumor immune, Tumor metabolism



P3.02G TUMOR BIOLOGY - PRECLINICAL BIOLOGY - TARGETED THERAPY/NOVEL THERAPY
MONDAY, SEPTEMBER 9, 2024 - 12:00 - 14:00

P3.02G.01 Therapeutic Targeting of Lung Cancer-Associated Fibroblasts Mitigates Mediastinal Lymphatic Dissemination in Non-Small Cell Lung Cancer

J.C. HO, C. Chen, The University of Hong Kong, Hong Kong SAR/HK

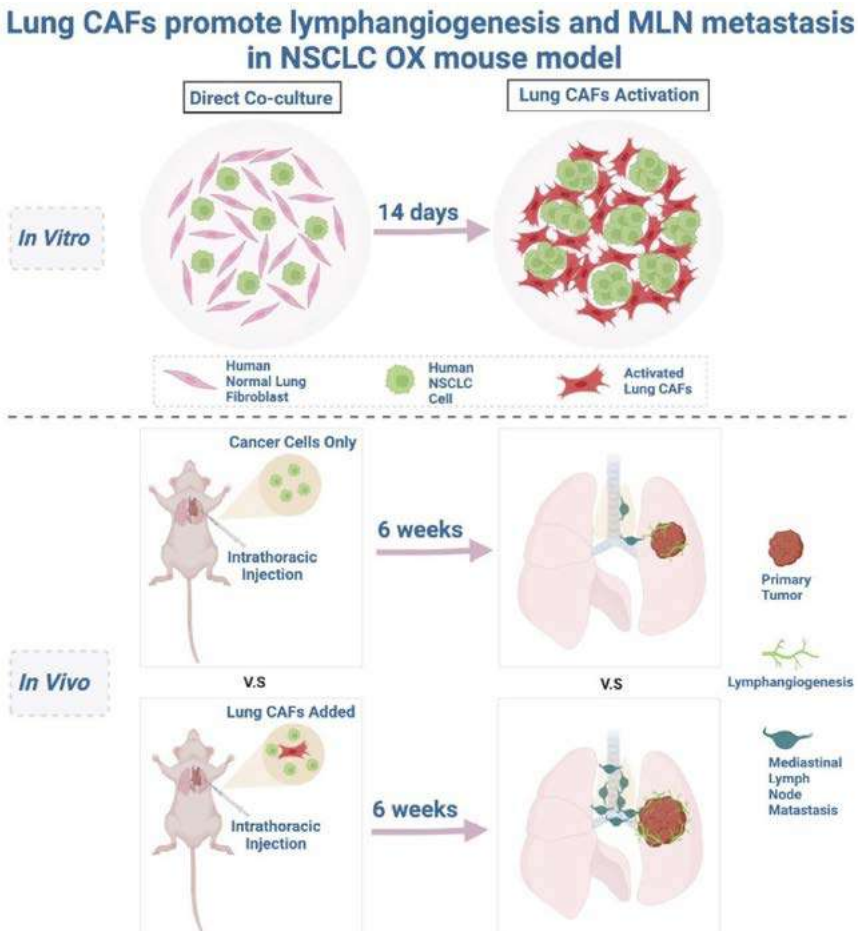
Introduction: Cancer-associated fibroblasts (CAFs) represent a pivotal component in tumor microenvironment. Yet, the biological function of lung CAFs in the context of mediastinal lymph node metastasis in non-small cell lung cancer (NSCLC) remains unknown. Our study endeavors to address this critical knowledge gap and explore potential therapeutics employing a novel CAFs-rich orthotopic xenograft model.

Methods: Lung CAFs were generated through the co-culturing of normal human lung fibroblasts (MRC-5) with non-small cell lung cancer (NSCLC) cell lines (H358 and HCC827). To establish orthotopic xenograft models, NSCLC cells were percutaneously injected into the left lung of mice, with or without the presence of lung CAFs. The efficacy of CAF inhibitors, namely ABT-199 and NNMTi (Nicotinamide N-Methyltransferase inhibitor), was assessed to determine their ability to inhibit lymphangiogenesis and prevent mediastinal lymph node metastasis. Tumor growth was monitored sequentially using micro-computed tomography (CT), and the response was evaluated according to RECIST v1.1 criteria. Confirmation of mediastinal lymph node metastasis was achieved through H&E staining and immunohistochemistry.

Results: The activation of lung CAFs was successfully achieved through direct co-culture. The co-inoculation of cancer cells alongside lung CAFs resulted in tumors characterized by heightened peritumoral lymphangiogenesis and a higher frequency of mediastinal lymph node metastasis compared to tumors derived from cancer cells only. In contrast, the administration of ABT-199 led to a significant reduction in lung CAFs, effectively suppressing tumor growth (mean ± SEM: 7.17 ± 0.33 vs 5.89 ± 0.28, $p<0.01$), lymphangiogenesis (mean ± SEM: 1.40 ± 0.24 vs 0.31 ±0.07, $p<0.01$), collagen deposition (mean ± SEM: 16.75 ± 0.74 vs 5.05 ± 0.78, $p<0.0001$), and mediastinal lymph node metastasis (mean ±SEM: 6.82 ± 0.55 vs 2.83 ± 0.21, $p<0.001$) in the H358-CAFs-rich NSCLC orthotopic xenograft model. Our findings unequivocally demonstrate that NNMTi administration significantly curtails tumor burden (mean ± SEM: 62.51 ± 5.68 vs 48.46 ± 1.36, $p<0.05$), proliferation (mean ± SEM: 20.86 ± 1.24 vs 15.35 ± 1.32, $p<0.05$), lymphangiogenesis (mean ± SEM: 2.00 ± 0.27 vs 0.34 ± 0.06, $p<0.0001$), and collagen deposition (mean ± SEM: 19.46 ± 1.31 vs 2.23 ± 0.49, $p<0.0001$) in the HCC827-CAFs-rich NSCLC orthotopic xenograft model.

Conclusions: Lung CAFs promote tumor-associated lymphangiogenesis and mediastinal lymph node metastases in NSCLC orthotopic xenograft model. The strategy of targeting lung CAFs holds promise in limiting cancer cells spread via lymphatics, particularly in CAFs-rich NSCLC scenarios.

Keywords: cancer associated fibroblasts, non-small cell lung cancer, lymphangiogenesis



P3.02G TUMOR BIOLOGY - PRECLINICAL BIOLOGY - TARGETED THERAPY/NOVEL THERAPY
MONDAY, SEPTEMBER 9, 2024 - 12:00 - 14:00

P3.02G.02 Integrin-Linked Kinase Facilitates Drug Tolerant Persister Cell Survival and EMT in Response to EGFR Targeted Therapy

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Introduction: Lung cancer is the leading cause of cancer-related deaths worldwide. The 3rd-generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI), osimertinib (Osi), has extensively improved patients outcomes. However, patients inevitably develop resistance against. Epithelial-mesenchymal transition (EMT) is an established non-genetic resistance mechanism that also associated with increased metastatic potential of tumours. In the progression towards EMT-mediated resistance exists a key transitory cell state of drug-tolerant-persistence (DTP), in which increased phenotypic plasticity permits cell survival during drug treatment. Integrin-linked kinase (ILK), an important regulator of integrin signaling, has been implicated in the pathogenesis of other cancers through the promotion of EMT. Additionally, a recent study in lung adenocarcinoma (LUAD) patients treated with EGFR-TKIs found that high ILK expression was correlated with worse prognosis. Therefore, we hypothesized that ILK may be important for DTP cell survival and EMT-mediated Osi resistance in EGFR mutant LUAD.

Methods: ILK expression and gene set enrichment analysis (GSEA) was performed on both internal and external LUAD patient databases. Conditional genetic and pharmacological manipulation of ILK were used to regulate ILK function both in vitro and in vivo. Cell viability and clonogenic assays were used to evaluate Osi sensitivity and DTP cell survival. Osi-resistant (OsiR) cells were made by dose-escalation. RNAseq and western blots were performed to assess expression levels and MSK-IMPACT to define genetic alterations. Confocal microscopy was used to evaluate YAP activity.

Results: High ILK expression was found to be significantly correlated with an EMT expression signature in patients. Genetic suppression of ILK in HCC4006 cells, an EGFR mutant LUAD line with high basal ILK expression, limited EMT progression and reduced the viability of DTP cells by impairing SRC mediated YAP activation both in vitro and in mouse models, ultimately improving Osi response. Conversely, EGFR mutant lung cancer cells with low ILK levels that were engineered to overexpress ILK lead to increased DTP cell survival after EGFR TKI treatment. Importantly, these ILK high DTP cells were able to persist long enough to acquire additional mutations that maintained their mesenchymal features and their insensitivity to Osi independent of ILK. Lastly, we show that pharmacological inhibition of ILK suppressed EMT and improved Osi response in LUAD cells, providing evidence that combination therapy of targeting ILK and EGFR is a feasible strategy in combating tumour persistence and resistance driven by EMT.

Conclusions: Our results show that ILK is important in promoting EMT and DTP survival in EGFR-driven LUAD. Targeting ILK may be a viable strategy to manage minimal residual disease and EGFR TKI resistance in lung cancer.

Keywords: Drug tolerance, Persister cells, EGFR TKI

P3.02G TUMOR BIOLOGY - PRECLINICAL BIOLOGY - TARGETED THERAPY/NOVEL THERAPY
MONDAY, SEPTEMBER 9, 2024 - 12:00 - 14:00

P3.02G.03 High-Dose Ascorbic Acid Sensitizes Immunotherapy in LKB1-Deficient Lung Cancer by Promoting Tumor Cell Pyroptosis

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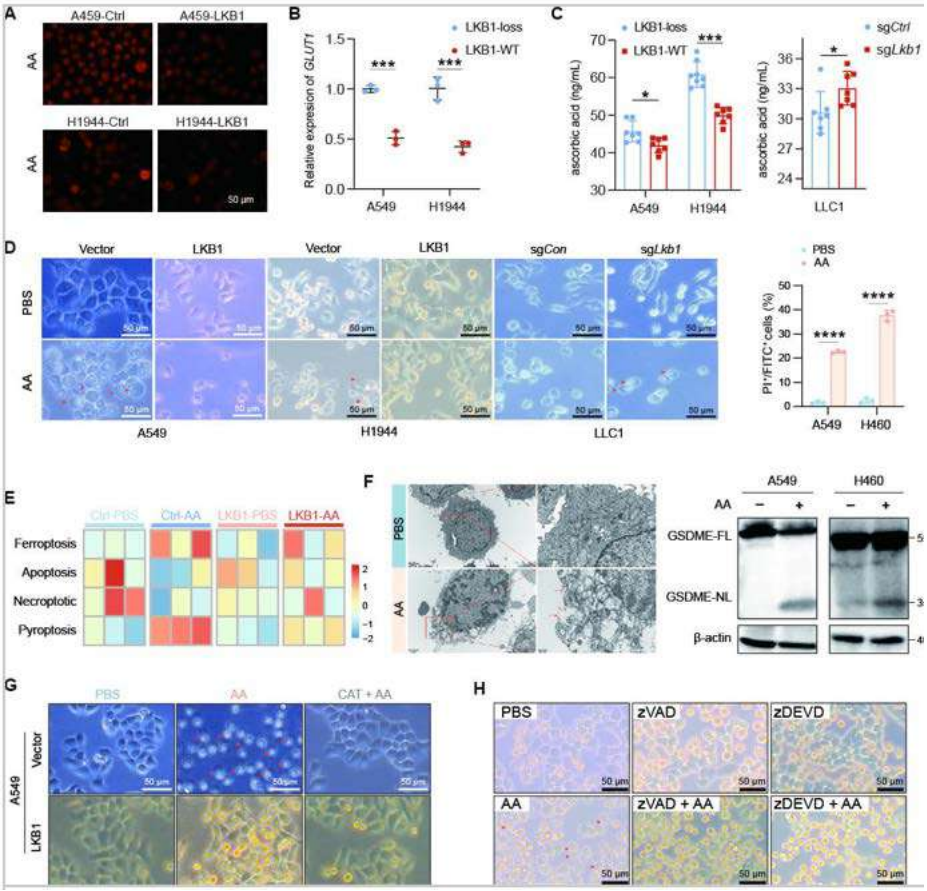
Introduction: Loss-of-function mutation of STK11/LKB1 leads to the primary resistance to immune checkpoint blockade (ICB). High-dose ascorbic acid (AA) could induce cell redox imbalance and selectively kill tumor cells with specific mutation. Whether high-dose AA could selectively kill redox-imbalanced LKB1-deficient lung cancer cell and synergize ICB remain unknown.

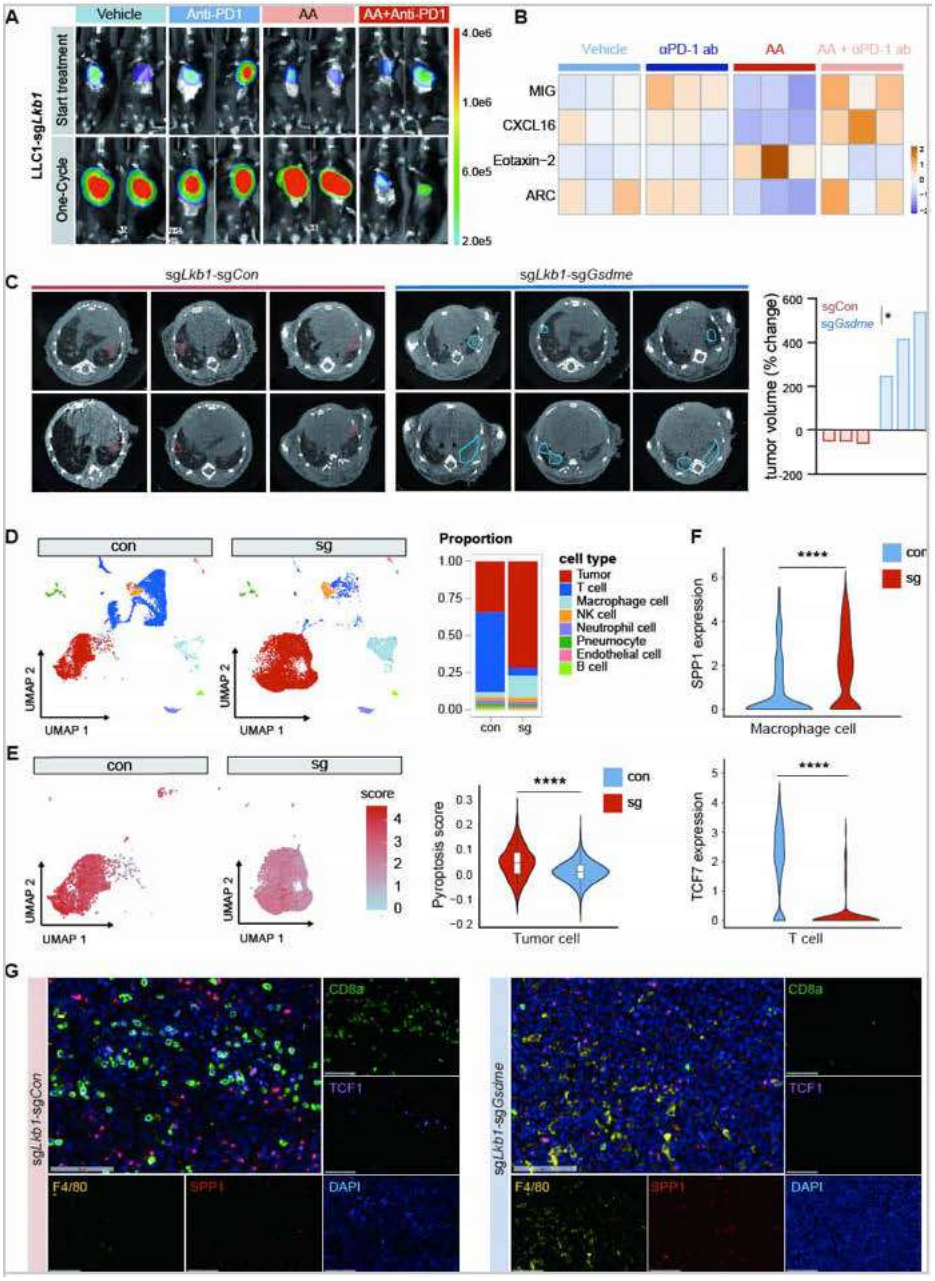
Methods: LKB1-deficient human lung cancer cell lines and LLC1-sgLkb1 murine lung cancer models were established and utilized to explore the effect of high-dose AA on LKB1-deficient lung cancer. Transcriptomic and transmission electron microscope were performed to distinguish the precise mechanism, validated by the inhibitors of the candidate targets and inner blockade of the key molecule. Single-cell transcriptomic atlas and multiplex immunohistochemical were mapped to decipher the immune microenvironment fueled by high-dose AA and ICB.

Results: Treating with high-dose AA, intracellular ROS level of LKB1-deficient cell were significantly accumulated and LKB1-deficient lung cancer took up significantly more AA by upregulating GLUT1. Performing integrative analysis of cellular morphology and transcriptomic data, we identified high-dose AA selectively induced LKB1-deficient lung cancer cells pyroptosis via activating the cleavage of GSMDE depending on H2O2/ROS-Caspase-3-GSDME signaling pathway. Furthermore, high-dose AA potentiated ICB efficacy in LKB1-deficient orthotopically tumor models and cytokine array analysis elucidated that high-dose AA mediated pyroptosis provoked the release of immune active chemokines and substances to ignite tumor immune microenvironment (TIME). Leveraging single cell RNA sequencing data and multiplex immunohistochemical, high-dose AA enhanced the infiltration of TCF1+ CD8+ T cells and reduced the infiltration of SPP1+ macrophages in TIME. Inner blockade of GSDME reversed the inflamed TIME and the synergistic effect of high-dose AA.

Conclusions: LKB1-deficient lung cancer is susceptible to pyroptosis induced by high-dose AA. High-dose AA might be a promising translational therapeutic strategy to potentiate ICB efficacy in LKB1-deficient lung cancer pending further clinical validation.

Keywords: LKB1-deficient NSCLC, High-dose ascorbic acid, immunotherapy

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CD8a
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DAPI

P3.02G TUMOR BIOLOGY - PRECLINICAL BIOLOGY - TARGETED THERAPY/NOVEL THERAPY
MONDAY, SEPTEMBER 9, 2024 - 12:00 - 14:00

P3.02G.04 JP11646-mediated PIM2 Inhibition Has Potent Antitumor Effects in Small Cell Lung Cancer and Large Cell Neuroendocrine Carcinoma of the Lung

K. Minton, P.D. Pham, M. Opyrchal, K.P. Lee, M.D. Shields, Indiana University School of Medicine, Indianapolis/IN/USA

Introduction: Small cell lung cancer (SCLC) is an aggressive neuroendocrine (NE) lung carcinoma characterized by acquired chemoresistance at relapse. SCLC tumor plasticity and chemoresistance is driven, at least in part, by the downstream effects of MYC amplification or overexpression, namely the activation of Notch and subsequent induction of NE dedifferentiation. Despite increased molecular characterization of SCLC, few effective options at relapse are available, highlighting the urgency for novel therapeutic approaches, namely those that target MYC-dependent pathways. C-MYC is stabilized by the proviral integration site for Moloney murine leukemia virus 2 (PIM2) kinase through phosphorylation. Recently, a novel pan-PIM non-ATP competitive inhibitor JP11646 has shown promising antitumor activity in various cancers; however, JP11646 has not yet been studied in SCLC. Here, we report the antitumor efficacy of JP11646 in MYC-amplified SCLC and large cell neuroendocrine carcinomas of the lung (LCNEC).

Methods: Cell culture/reagents: Human SCLC lines (H209, SHP-77, H1417, H187, H2171, H69, H524) and LCNEC line H1155 were obtained from ATCC, cultured in RPMI-1640 with 10% fetal bovine serum, and incubated at 37°C in 5% CO2. JP11646 (10 mM stock, Jasco Pharmaceuticals) was gifted by Dr. Kelvin Lee. Drug sensitivity assay in vitro: A total of 1,000 cells/well were seeded in a 384-well plate and incubated overnight at 37°C. Serial dilutions of JP11646 (1 nM - 10 μM) were added in triplicate with 2-3 biological replicates and incubated for 72 h at 37°C. Viability was measured with Promega CellTiter-Glo™ Luminescent Assay Kit. Effects of JP11646: Cells were plated at 2 x 106 per 100 cm2 dish on Day 0. JP11646 (or H2O) was added at a concentration of 500 nM for 24 hours. Cells were harvested for WB analysis. Western blot analysis: Cell lysates were generated utilizing RIPA lysis buffer with protease and phosphatase cocktail inhibitors, quantified utilizing Bradford reagent, and stabilized with SDS at 95°C. Samples were loaded on a 10% precast gel, transferred with Transblot Turbo, blocked with EveryBlot Blocking Buffer (EBB) for 5 minutes, primary 1:1000 in EBB for 30 minutes, followed by serial washes, secondary 1:5000 in EBB for 30 minutes, followed by serial washes, and exposed with ECL reagent. Films were analyzed by BioRad Image Lab and BioRender.com. Antibodies utilized: PIM2 (D1D2, CST), C-MYC (D84C12, CST), N-MYC (D4B2Y, CST), and vinculin (E1E9V, CST).

Results: PIM2 protein is expressed in SCLC and LCNEC. Across the panel of SCLC and LCNEC, the mean IC50 for JP11646 was 87 nM. MYC paralog-amplified cell lines' IC50 ranged from 7 nM to 117 nM, with C-MYC amplified H524 harboring exquisite sensitivity. With JP11646 treatment, we find that PIM2 protein expression decreases. Furthermore, MYC paralog (C-MYC, N-MYC) protein expression decreases within 24 hours of JP11646 treatment across the panel.

Conclusions: PIM2 is expressed in neuroendocrine carcinomas and serves as a potential therapeutic target for relapsed disease. Treatment with a PIM2 inhibitor effectively inhibits cell viability in SCLC and LCNEC. JP11646 leads to reductions in MYC paralogs. Validation with xenograft models and exploration of the downstream effectors of MYC with JP11646 are planned.

Keywords: Small Cell Lung Cancer, PIM2, MYC

P3.03H TUMOR BIOLOGY - TRANSLATIONAL BIOLOGY - METASTASIS/TUMOR PROGRESSION
MONDAY, SEPTEMBER 9, 2024 - 12:00 - 14:00

P3.03H.01 Tumour Educated Platelets Display a Distinct RNA Content Profile Across Metastatic Patterns in NSCLC.

J. Flynn[1,2], M.G. Best[3], S.G.J.G. In 't Veld[3], S. Finn[1,4], O. Sheils[1,4], A-M. Baird[1,2], [1]Trinity Translational Medicine Institute, Trinity College Dublin, Dublin/IE ,[2]Trinity St. James's Cancer Institute (TSJCI), St. James's Hospital, D[08] RX[0]X, Dublin/IE ,[3]Department of Neurosurgery, Brain Tumor Centre Amsterdam, Cancer Center Amsterdam, Amsterdam UMC, VU University Medical Center, Amsterdam/NL ,[4]Department of Histopathology and Morbid Anatomy, Trinity Translational Medicine Institute, Trinity College Dublin, D[08] W[9]RT, Dublin/IE

Introduction: The pro-metastatic nature of non-small cell lung cancer (NSCLC) is a significant contributing factor to poor overall survival. Platelets are known to play a role in the metastatic cascade through their interaction with tumour cells. During these interactions, platelets can sample tumour macromolecules, thus changing their functionality and gene signature, resulting in tumour educated platelets (TEPs). This study examined the expression signature of TEPs in stage IV disease in the context of metastatic site patterns.

Methods: The GSE183635 dataset, which contains stage IV NSCLC TEP (n=399) and asymptomatic controls platelet (n=390) expression data, was downloaded from the Gene Expression Omnibus. Differentially expressed genes (DEGs) were identified using EdgeR from TEPs and platelets from stage IV NSCLC samples and asymptomatic controls. Further expression analysis was performed by comparing TEPs from samples with different metastatic profiles. These DEGs were used to perform gene set enrichment analysis (GSEA) to further elucidate the potential functional impact of these TEPs within the metastatic cascade.

Results: The initial analysis of stage IV NSCLC highlighted 28 significantly upregulated genes compared to asymptomatic controls. Enrichment of pathways including hydrogen peroxide metabolic processes suggests that tumours may prime platelets for aggregation upon stimulation with other tumour agonists. Other enriched processes included metabolism, gas transport and immune processes. In the cohort of brain metastases (n=56), 15 upregulated genes were identified and included CD163 (logFC = 2.13, FDR<0.05), IGHA1 (logFC = 1.85, FDR<0.01), and KSR1 (logFC = 1.9, FDR<0.001), the latter of which has been linked to epithelial-mesenchymal transition (EMT). Conversely, two genes were downregulated, CST7 (logFC = -1.83, FDR<0.001) and GLYATL2 (logFC = -1.76, FDR<0.05). TEPs from those with bone metastases (n=55) demonstrated upregulation of 34 genes including CA1 (logFC = 1.63), SNX24 (logFC = 1.04) and IFITM3 (logFC = 0.97), of which both SNX24 and IFITM3 have been implicated in tumour progression and cancer metastasis. 370 genes were downregulated in the bone metastases group. Interestingly, these downregulated genes are involved in cytoplasmic translation, ribosomal biogenesis, and immune response pathways. The gene CST7 (logFC = 1.9, FDR<0.001) was the only differentially expressed gene and was upregulated in the liver metastasis group (n=26). CST7 is a known immune regulator and prognosis marker in pancreatic ductal adenocarcinoma. ECE1 (logFC = 1.33, FDR<0.05) was upregulated in the adrenal metastases group (n=12). ECE1 is an unfavourable prognostic marker in NSCLC. Of note, the upregulated genes are unique to each group, thus highlighting distinct TEP signatures across metastatic profiles.

Conclusions: TEPs from people with NSCLC can be used to investigate potential contributing mechanisms to the metastatic process, including platelet metabolism pathways. This study highlights distinct TEP signatures across different metastatic patterns. Further investigation may elucidate how these metastatic site-specific alterations impact and guide the spread of NSCLC and identify potential anti-metastatic targets.

Keywords: Non-small cell lung cancer, Tumour educated platelets, metastasis

P3.03H TUMOR BIOLOGY - TRANSLATIONAL BIOLOGY - METASTASIS/TUMOR PROGRESSION
MONDAY, SEPTEMBER 9, 2024 - 12:00 - 14:00

P3.03H.02 PMS2 Amplification Contributes Brain Metastasis from Lung Cancer

J. Chen, C. Su, Shanghai Pulmonary Hospital, Shanghai/CN

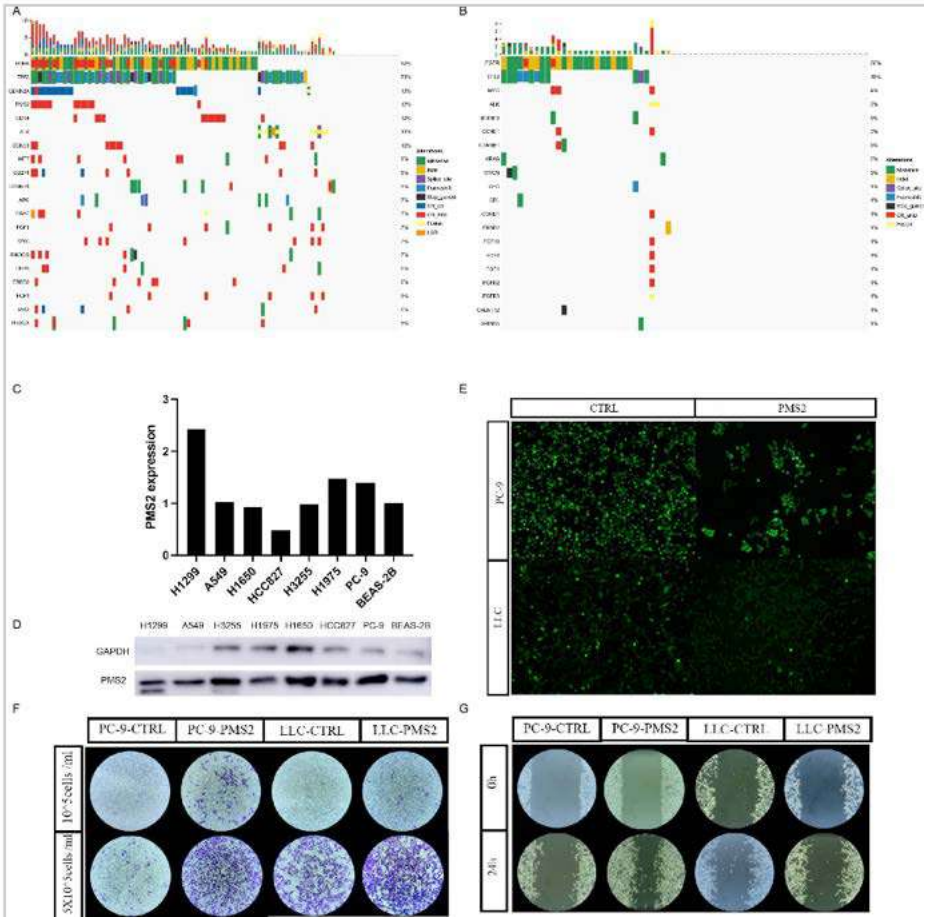
Introduction: Lung adenocarcinoma metastasizing to the brain results in a notable increase in patient mortality. The high incidence and its impact on survival presents a critical unmet need to develop an improved understanding of its mechanisms.

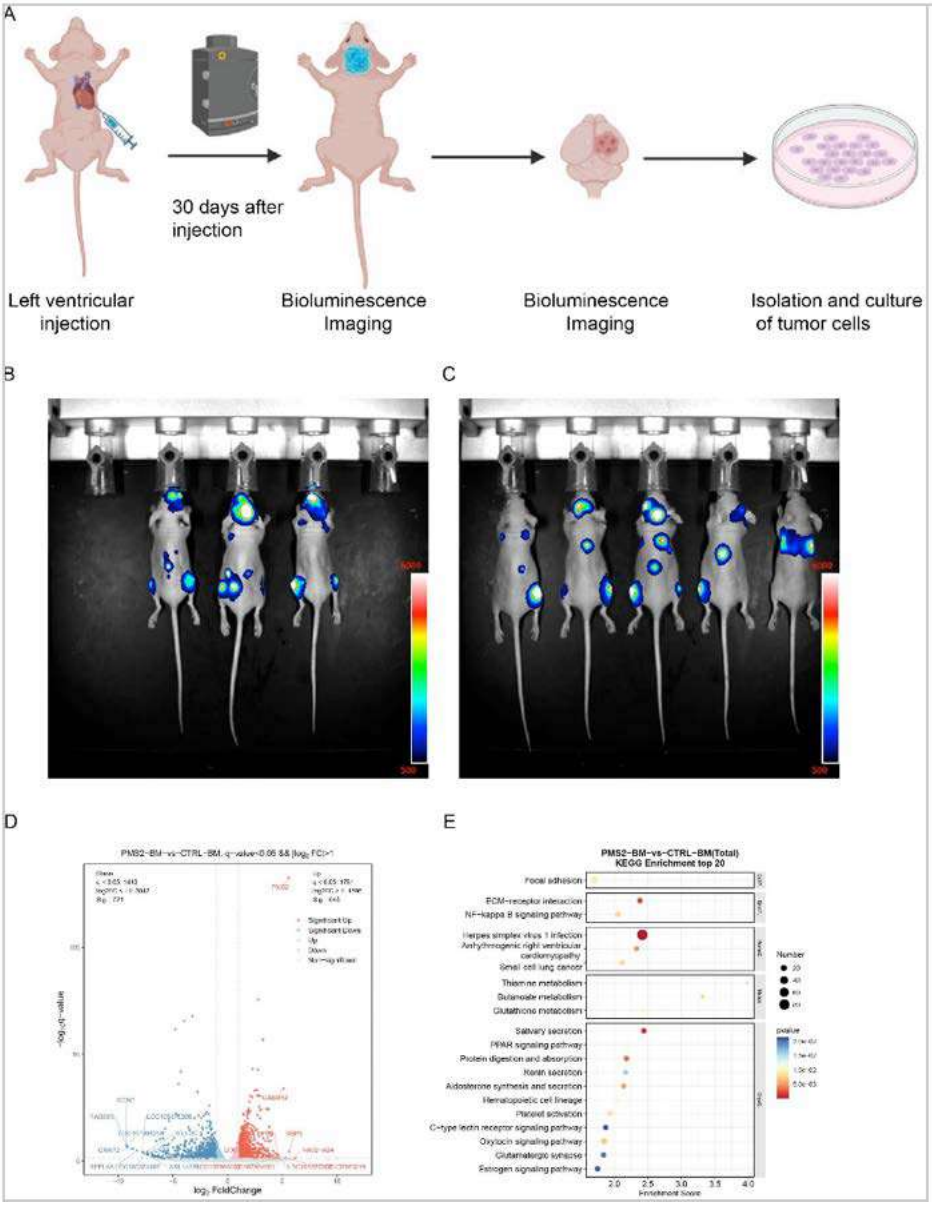
Methods: To identify genes that drive brain metastasis of tumor cells, we collected cerebrospinal fluid samples and paired plasma samples from 114 lung adenocarcinoma patients with brain metastasis and performed 168 panel-targeted gene sequencing. We examined the biological behavior of PMS2-amplified lung cancer cell lines through wound healing assays and migration assays. In vivo imaging techniques are used to detect fluorescent signals that colonize the mouse brain. RNA sequencing was used to compare differentially expressed genes between PMS2 amplification and wild-type lung cancer cell lines.

Results: We discovered that PMS2 amplification was a plausible candidate driver of brain metastasis. Via in vivo and in vitro assays, we validated that PMS2 amplificated PC-9 and LLC lung cancer cells had strong migration and invasion capacity. The functional pathway of PMS2 amplification of lung cancer cells is mainly enriched in thiamine, butanoate, glutathione metabolism.

Conclusions: Tumor cells elevated expression of PMS2 possess the capacity to augment the metastatic potential of lung cancer and establish colonies within the brain through metabolism pathways.

Keywords: Lung cancer, Brain metastasis, PMS2

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Bioluminescence Imaging
Bioluminescence Imaging
Isolation and culture of tumor cells
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C
D
E
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ECM-receptor interaction
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Small cell lung cancer
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Glutathione metabolism
Salivary secretion
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Protein digestion and absorption
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P3.03H TUMOR BIOLOGY - TRANSLATIONAL BIOLOGY - METASTASIS/TUMOR PROGRESSION
MONDAY, SEPTEMBER 9, 2024 - 12:00 - 14:00

P3.03H.03 Feasibility of Metastatic Lymph Node-informed ctDNA Analysis in Surgically Resected NSCLC Patients

S. Ohara[1], K. Suda[1], E. Kalashnikova[2], A. Hamada[1], M. Chiba[1], M. Shimoji[1], T. Takemoto[1], S. Sudhaman[2], S. K. Cheung[2], M. Krainock[2], J. Feeney[2], H. Sethi[2], M.C. Liu[2], J. Soh[3], Y. Tsutani[1], T. Mitsudomi[4], [1]Kindai University, Osaka-Sayama/JP ,[2]Natera, Inc., Austin/TX/USA ,[3]Osaka Metropolitan University, Osaka/JP ,[4]Izumi City General Hospital, Izumi/JP

Introduction: Circulating tumor DNA (ctDNA) analysis is useful to detect molecular residual disease (MRD) after pulmonary resection in patients with early-stage non-small cell lung cancer (NSCLC). A tumor-informed approach for ctDNA testing typically tracks single nucleotide variants (SNVs) identified from DNA sequencing of the primary tumor. In this study, we explored the mutational landscapes of primary tumor tissue and metastatic lymph nodes (mLN) and explored the feasibility of mLN-informed ctDNA testing in patients with locally advanced NSCLC undergoing resection.

Methods: Plasma samples from 46 with clinical stage IIA-IIIA NSCLC (TNM 8th edition) were collected between January 2018 and June 2020, at Kindai University Hospital before surgery, after surgery (landmark), and then every 6 months until 2 years thereafter. Of these 46 patients, 18 patients with both primary tissue and resected mLN available were included in this study. SNVs were selected from whole exome sequencing of the primary tumor and mLN along with matched normal DNA obtained from blood. Parallel ctDNA analyses were performed using the personalized, tumor-informed 16-plex mPCR-NGS assays (SignateraTM, Natera, Inc.) developed from the primary tumor and mLN.

Results: Among the total of 64 longitudinal plasma samples analyzed, 61 (95%) had concordant sample call results between the primary tumor-informed vs. mLN-informed assays. The remaining three plasma samples had low level positive results by one of the assays only. Moreover, on comparing the total shared variants identified in the WES data from both primary and LN tissue, an average of ~30% overlap, ranging up to 93%, was observed.

Conclusions: We observed a high concordance rate between primary tumor-informed vs. mLN-informed ctDNA analysis in early-stage NSCLC patients before and/or after surgery. These data support the use of alternative tissue sources for designing personalized tumor tissue-informed ctDNA assays.

Keywords: ctDNA, Signatera, surgery

P3.03H TUMOR BIOLOGY - TRANSLATIONAL BIOLOGY - METASTASIS/TUMOR PROGRESSION
MONDAY, SEPTEMBER 9, 2024 - 12:00 - 14:00

P3.03H.04 Molecular and Clonal Evolution of Primary Lesions vs Brain Metastasis and Progressive Disease of EGFR Mutated Patients

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Introduction: Clonality is an intrinsic phenomenon of disease evolution, with certain clones conferring increased aggressiveness and apparent tropism toward certain metastatic sites. In this analysis, we sought to evaluate the different divergent and unique mutational patterns present in brain metastases

Methods: A retrospective cohort study encompassing patients diagnosed with EGFR-mutated lung adenocarcinoma either presenting with brain metastases upon diagnosis or experiencing progression to this site. All patients underwent three NGS-based genomic profiling assessments. The initial two analyses involved tissue samples from the primary and predominant brain lesions, while the third utilized either liquid biopsy or tissue from an extracranial lesion at disease progression. Treatment for all patients consisted of Osimertinib and stereotactic radiosurgery following RANO-BM evaluation of brain lesions.

Results: The analysis comprised a total of 30 Hispanic patients. Of these, 22 patients (73%) were female, with a median age of 55 years. Nearly all patients, except one (97%), had a history of smoking, while the remaining individual was a lifelong non-smoker. Central nervous system (CNS) involvement was noted in 27 patients (90%) at diagnosis, with three experiencing subsequent compromise during disease progression. The median number of brain lesions was 2 (range: 1-3).Regarding molecular characteristics, 14 patients (46%) exhibited exon 19 deletions, while the remainder had an L858R mutation. The most frequently mutated gene in the primary lesions was TP53, accounting for 15 cases (50%), followed by RBM10 in 7 patients (23%), with three instances of co-occurrence with TP53, as well as STK11 (n=2, 6%), GNAS (n=4, 13%), and RB1 (n=1, 3%). The mean tumor mutational burden (TMB) in the primary lesion was 3.2 mut/Mb, compared to 8.5 mut/Mb in the brain metastasis. Notably, all patients exhibited increased TMB between the primary and CNS lesions. Additionally, EGFR mutations were lost in 9 patients (30%), with an almost equal distribution among Exon 19 and L858R mutations. Regarding co-mutations in brain metastases, alterations in PIK3CA/PTEN/AKT were present in 11 cases (36%). Other observed mutations included BRAF V600E (n=1, 3%), non-V600 BRAF mutations (n=3, 10%), and RB1 (n=4, 13%). Interestingly, amplifications across various genes were observed in 19 patients (63%). Upon systemic disease progression, MET amplification was detected in 5 cases (15%), while small cell transformation occurred in 2 (7%). PIK3CA mutations, initially identified solely in brain metastases, re-emerged in systemic disease in 4 cases (13%), along with a V600E mutation in one patient (3%).

Conclusions: The molecular features observed in brain metastases exhibit distinctions from both primary tumors. Results indicate that specific brain metastasis clones can also result in systemic progressions.

Keywords: Clonal evolution, Brain metastasis, EGFR Non Small Cell Lung Cancer

P3.03H TUMOR BIOLOGY - TRANSLATIONAL BIOLOGY - METASTASIS/TUMOR PROGRESSION
MONDAY, SEPTEMBER 9, 2024 - 12:00 - 14:00

P3.03H.05 AKAP12 Deficiency Leads to Blood-Brain Barrier Disruption and Serves as a Crucial Diagnostic Marker for Brain Metastasis in Lung Adenocarcinoma

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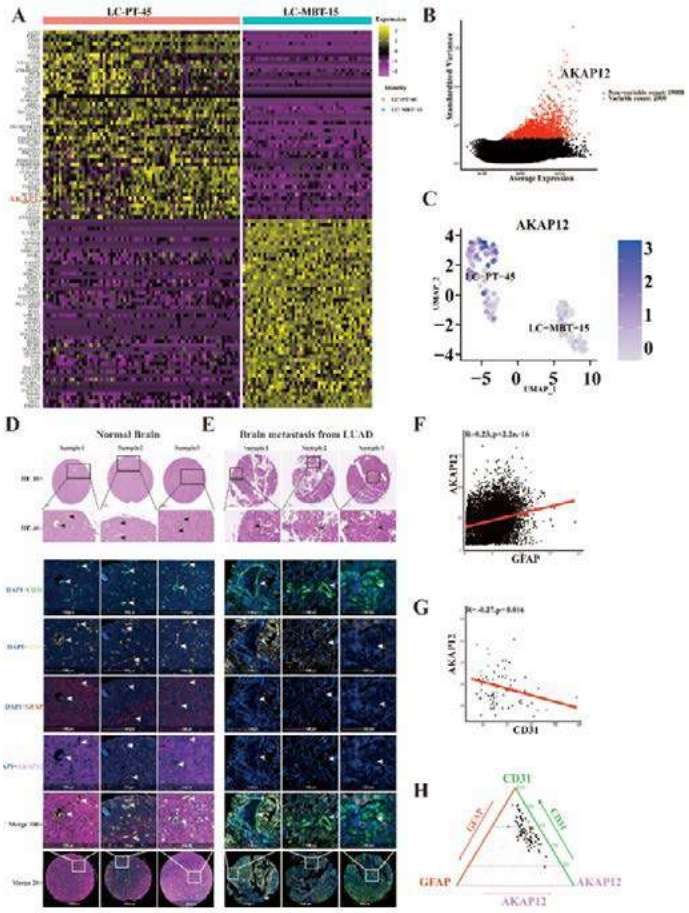
Introduction: The occurrence of brain metastasis in patients with lung adenocarcinoma is linked to poor prognoses, with approximately 50% of patients experiencing this form of metastasis. Despite this, there is a lack of well-established biomarkers for predicting the likelihood of brain metastasis in lung adenocarcinoma.

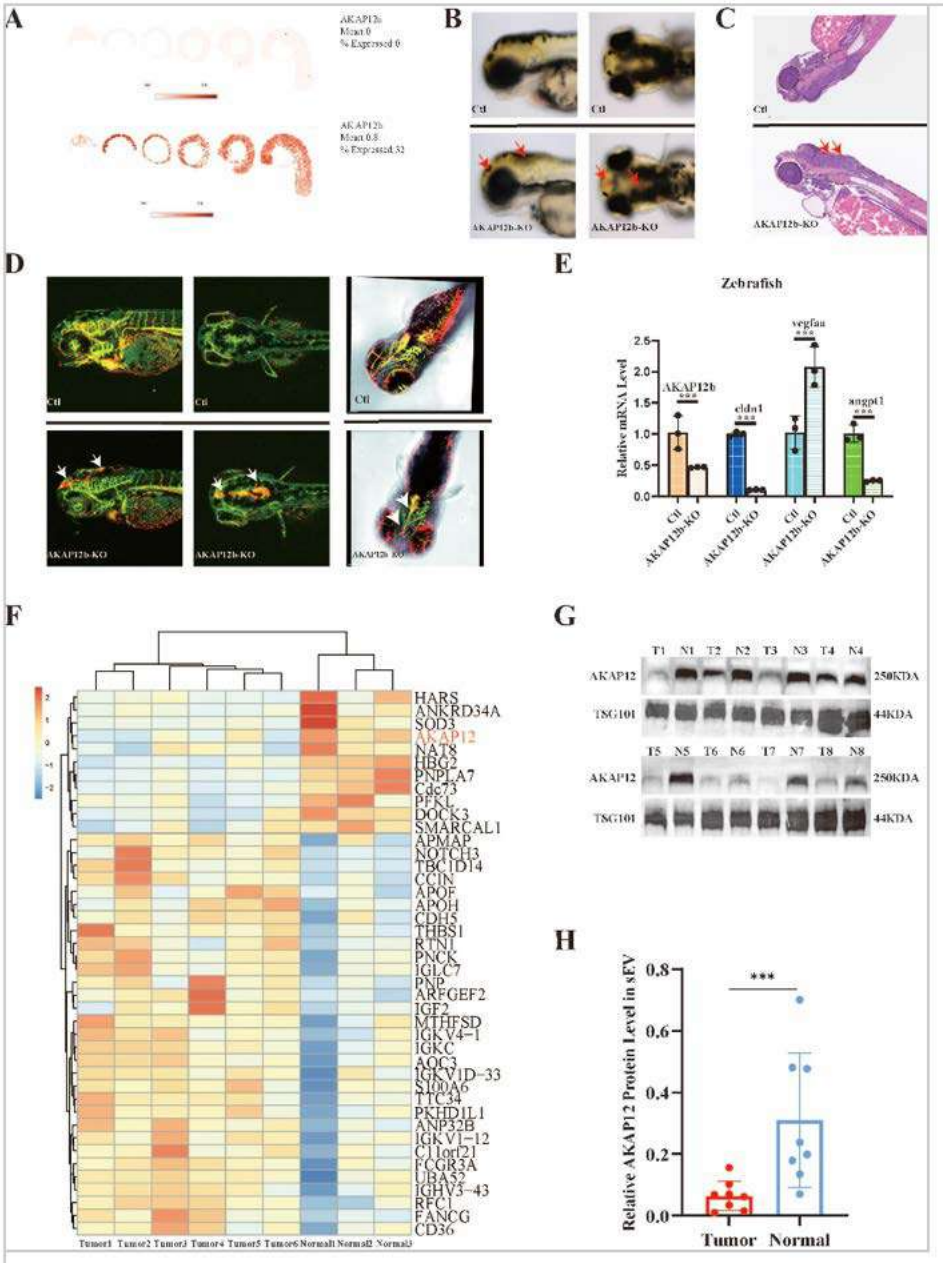
Methods: We started by analyzing single-cell RNA sequencing data from GSE69405 to identify DEGs and highly variable genes in primary lung cancer cells compared to metastatic cells. We then used mIHC and HALO software to analyze TMAs of lung adenocarcinoma brain metastases. Spatial transcriptomics of zebrafish at different developmental stages were examined using Crispant technology to suppress the AKAP12b gene. PCR analysis was used to study genes related to the blood-brain barrier. Proteomics identified protein expression differences in extracellular vesicles from lung adenocarcinoma patients and healthy individuals.

Results: The study determined AKAP12 to be a critical gene in differentiating primary tumor cells from metastatic cells in lung adenocarcinoma. Utilizing multiplex immunohistochemistry (mIHC) analyses, a connection was established between the lack of AKAP12 and the impairment of the blood-brain barrier (BBB) in individuals with brain metastases originating from lung adenocarcinoma. Spatial transcriptomic analysis revealed increased expression of the AKAP12b gene in specific brain regions of a zebrafish model, leading to significant brain hemorrhage upon knockdown of AKAP12b. Furthermore, our results indicated a notable reduction in AKAP12 expression in extracellular vesicles (EVs) isolated from the plasma of patients with lung adenocarcinoma compared to those from healthy individuals, suggesting its potential as a diagnostic biomarker.

Conclusions: Our findings elucidate that the deficiency of AKAP12 is intricately linked to the destruction of the blood-brain barrier (BBB) during the brain metastasis of lung adenocarcinoma. Moreover, the presence of AKAP12 within extracellular vesicles (EVs) in plasma emerges as a critical diagnostic biomarker for patients afflicted with this condition.

Keywords: AKAP12, BBB, EVs

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AKAP12b
Mean 0
% Expressed 0
AKAP12b
Mean 0.8
% Expressed 52
B
Ctl
Ctl
AKAP12b-KO
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C
Ctl
AKAP12b-KO
D
Ctl
Ctl
Ctl
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E
Zebrafish
Relative mRNA Level
AKAP12b
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vegfaa
angpt1
Ctl
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F
HARS
ANKRD34A
SOD3
AKAP12
NAT8
HBG2
PNPLA7
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PFKL
DOCK3
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NOTCH3
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AOC3
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CD36
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G
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AKAP12
250KDA
TSG101
44KDA
T5 N5 T6 N6 T7 N7 T8 N8
AKAP12
250KDA
TSG101
44KDA
H
Relative AKAP12 Protein Level in sEV
***
Tumor
Normal

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P3.03I.01 Targeting RLIP76 with a Novel Small Molecule for Lung Cancer Therapy

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Introduction: KRAS and TP53 (p53), the most common mutations in non-small-cell lung cancer (NSCLC), are associated with poor prognosis and poor treatment responses. The tumor suppressor functions of p53 are evident by the near universal predisposition to cancer in mice and humans with hereditary alterations of p53 function. RLIP76 (RALBP1 or RAL-Binding Protein 1) is an ATP-dependent transporter in the mercapturic acid pathway that catalyzes the efflux of cellular toxins and serves as a regulator of p53, Ras, PI3K/AKT, and TGF-ß signaling through direct interaction of RLIP76 to p53 instead. We discovered from crosses of RLIP76 knockout mice with p53 knockout mice that hereditary RLIP76 deficiency exerts a strong dominant negative effect on the cancer susceptibility of p53-/- mice. There are currently no RLIP76-targeted therapeutics.The newly discovered small molecule TTU-1 provides a unique opportunity and starting point from which to generate first-in-class therapeutics with an entirely novel mechanism of action.

Methods: Based on a partial crystal structure of RLIP76 and contact residue maps generated from 3-dimensional NMR, a in-silico search using the Vina docking algorithm, and an induced fit docking (IFD) method that allows side-chain flexibility for model refinement (MCule Inc.), we identified novel small molecule TTU-1. We performed growth inhibition of lung cancer cell lines by TTU-1 in vitro and in vivo mouse models. We examined TTU-1's effect on HDAC, DMNT, and caspase-3 activity, and performed qRT-PCR analyses of signaling protein transcripts in A549-luc xenograft tumor tissues from control and TTU-1 treated mice.

Results: Using virtual high throughput screening, we discovered a non-toxic lead compound, TTU-1, with broad-spectrum sub-micromolar potency against multiple lung cancer (LC) cell lines. A plot of docking scores vs. LD50 revealed a reasonably good linear fit. These compounds could serve to develop a structure-activity relationship (SAR). TTU-1 competitively binds RLIP76 as demonstrated in binding studies, and inhibits RLIP76 transport activity. TTU-1 also exhibits activation of caspase-3 and inhibition of DNMT and HDAC activity; these mechanisms of anticancer activity are different from how doxorubicin kills cancer cells. Transcript analysis indicated that several cancer hallmark pathways were suppressed following TTU-1 treatment.

Conclusions: RLIP76 knockdown modulates gene expression between p53 wild-type vs. null NSCLC (non-isogenic) cell lines, potentially through CpG island methylation changes, and the novel compound TTU-1 shows good activity and specificity as a RLIP76 inhibitor. TTU-1 itself will serve as an excellent tool for the mechanistic studies proposed and as a first proof-of-principle that targeting RLIP76. TTU-1 can exert the antineoplastic and cancer preventative effects.

Keywords: Lung cancer, RLIP76, TTU-1

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P3.03I.02 Co-Inhibition of MEK/RTK Pathways Induces High Therapeutic Efficacy in Pan-KRAS-Mutant Non-Small Cell Lung Cancer

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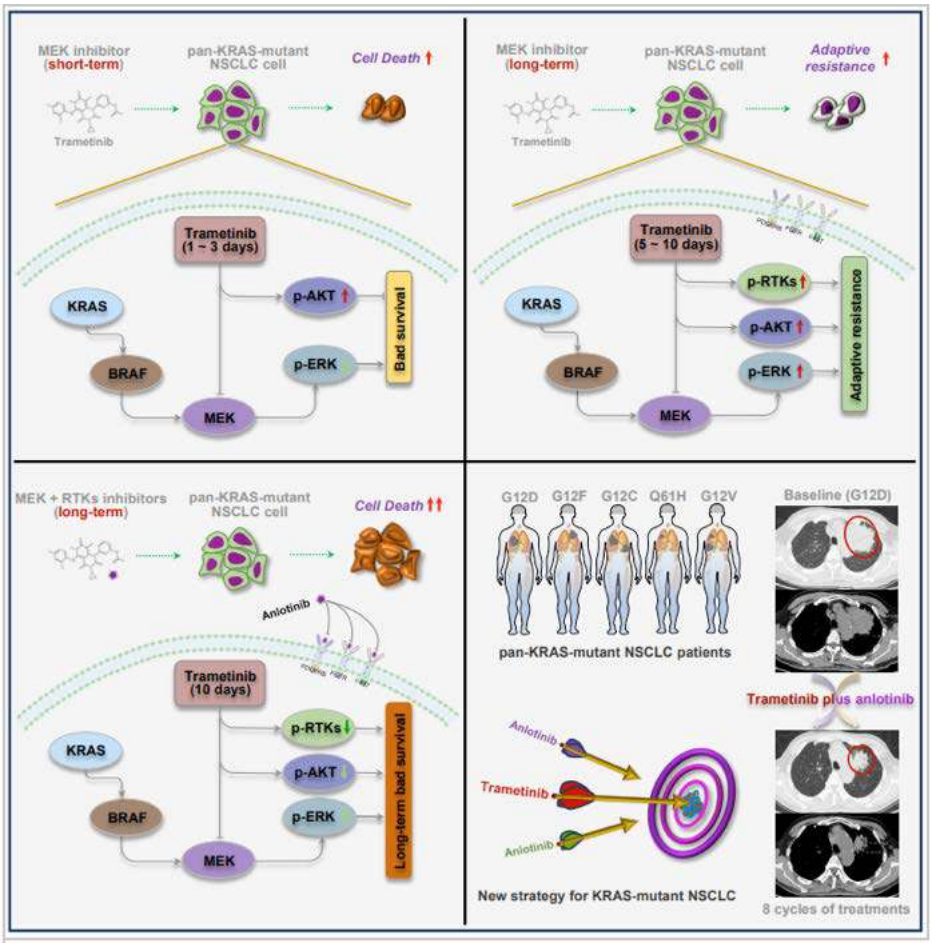
Introduction: Oncogenic KRAS mutations frequently detected in non-small cell lung cancer (NSCLC). It still remains as a big challenge to target all the KRAS mutants. MEK inhibitors have been considered as candidates to address the KRAS-mutant NSCLC; however, the easily adaptive resistance to MEK inhibitor precluded the further application.

Methods: To assess the effectiveness of anlotinib in combination with trametinib for KRAS-mutant NSCLC, a panel of KRAS-mutant NSCLC cell lines was employed for functional analysis. These cell lines included H23 (G12C), H358 (G12C), SW1573 (G12C), Calu1 (G12C), SK-LU-1 (G12D), SW900 (G12V), A549 (G12S), and H460 (Q61H). Molecular mechanism analyses were conducted not only on these cell lines but also on the cell-derived xenografts. Transcriptome and proteome analyses were conducted to elucidate the underlying targets. Western blotting, RT-qPCR, H&E staining, immunofluorescent staining, and other techniques were employed to validate alterations in signaling pathways. Five advanced NSCLC patients, each harboring distinct KRAS mutations (KRASG12D, KRASG12F, KRASG12C, KRASQ61H, and KRASG12V), were enrolled to evaluate therapeutic efficacy. Companion plasma ctDNA mutation profiling and protein profiling were utilized to analyze potential associations with drug response.

Results: Here, we found that MEK inhibitor-trametinib treatment results in the feedback activation of multiple receptor tyrosine kinases (RTKs) in NSCLC, and combined with a pan-RTK inhibitor-anlotinib treatments effectively inhibited KRAS-mutant lung cancer progression. Furthermore, our data suggested that the co-inhibition of MEK/RTKs pathways resulted in synergistic anti-tumor efficacy in pan-KRAS-mutant NSCLC, potentially mediated through the MEK/RTKs-IGFBP2-RTKs signal loop. Importantly, we observed the effective demonstration of the combination strategy involving MEK inhibitor-trametinib and RTK inhibitor-anlotinib in 5 advanced NSCLC patients harboring different KRAS mutations including KRASG12D, KRASG12F, KRASG12C, KRASQ61H, and KRASG12V, respectively. Companion plasma ctDNA mutation profiling suggested that the combination strategy is effective for pan-KRAS mutations, regardless of whether KRAS co-mutates with other driver genes. Additionally, plasma protein profiling analysis indicated upregulation of multiple protein levels in blood, such as PLP2 and GINS1, potentially associated with drug response.

Conclusions: Collectively, this study provides a potential combinational therapeutic strategy for pan-KRAS-mutant NSCLC through co-targeting MEK and RTKs.

Keywords: KRAS-mutant NSCLC, Targeted therapy, Trametinib plus anlotinib



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P3.03I.03 AptBCis1 - A Novel DNA Therapeutics for Lung Cancer Leptomeningeal Carcinomatosis

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Introduction: Therapy for lung cancer leptomeningeal carcinomatosis (LM) remains challenging partly due to the biological nature of blood-brain-barrier (BBB). Cisplatin serves as the backbone for systemic chemotherapy in lung cancer, but it has limited effects on LM diseases and it is notorious for neurotoxicity. Aptamers are small synthetic oligonucleotides considered as antibody surrogates for targeted delivery. Here we report an aptamer-cisplatin conjugate, AptBCis1. The AptBCis1 is a BBB-penetrating and cancer-targeting novel DNA aptamer therapeutics.

Methods: The aptamer was identified via in vivo SELEX using a lung cancer LM orthotopic mouse model. The aptamer was then conjugated with cisplatin to form AptBCis1. The tumor suppressive effects were investigated using mouse models. The AptBCis1 was administered through the tail vein and the tumor burden was monitored via In Vivo Imaging System. The plasma and the CSF cisplatin concentrations were measured via Inductively Coupled Plasma Mass Spectrometry.

Results: AptBCis1 1 mg/kg (equivalent to cisplatin 0.35 mg/kg) showed superior tumor suppressive effects than cisplatin 2 mg/kg in lung cancer LM orthotopic mouse models. The aptamer sequence was identified both in the plasma and cerebrospinal fluid (CSF). The CSF platinum concentration in the AptBCis1 1 mg/kg treatment group was 5% of that in the cisplatin 2 mg/kg treatment group. The AptBCis1 at an equivalent cisplatin dose of 0.7 mg/kg showed identical tumor suppressive effects to cisplatin 2 mg/kg in lung cancer subcutaneous xenograft mouse models. Aptoprecipitation and Mass Spectrometry studies revealed three interacting proteins that might contribute to the promising tumor suppressive effects of the AptBCis1.

Conclusions: The AptBCis1 showed promising anti-tumor effects at lower cisplatin concentrations both in lung cancer LM orthotopic and subcutaneous xenograft mouse models. The data suggested the translational potential of AptBCis1 as novel therapeutics in cancer.

Keywords: Leptomeningeal carcinomatosis, Blood-Brain-Barrier, Aptamer drug conjugate

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P3.03I.04 Annamycin: Opening New Doors for Organotropic Targeting of Primary and Metastatic Lung Cancer

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Introduction: Lung cancer and distant metastasis to lung is a major cause for cancer related deaths- worldwide. Targeting topoisomerase II-alpha (Top2a) is an effective therapy for a wide range of human malignancies. However, primary lung cancer or lung metastatic cancers are less responsive to Top2a targeting agents, including doxorubicin (DOX). Even sarcomas that are usually highly sensitive to DOX are not responsive after metastasis to lungs. Annamycin (ANN) is a novel potent Top2a poison that displays activity against multidrug resistant cancers and lack of cardiotoxicity. It is currently clinically evaluated (NCT03388749; NCT05319587; NCT04887298) as a liposome formulated drug (L-ANN). ANN and L-ANN display unique organotropism and dramatically increased lung uptake compared to DOX. We hypothesize that suboptimal tissue-organ distribution is a significant factor limiting DOX efficacy in lung localized cancers. The objective of this study was to correlate PK and tissue-organ distribution of ANN and DOX with preclinical efficacy in orthotopic models of lung cancer and lung-metastasis of breast, sarcoma, and colon cancer.

Methods: Pharmacokinetics and tissue-organ distribution of ANN, L-ANN, and DOX was performed in rats and mice using LC/MS. In vivo preclinical efficacy was assessed in orthotopic NSCLC models (H1299 and LLC) and lung metastasis models 4T1-Luc (triple negative breast cancer), MCA205 (fibrosarcoma), K7M3 (fibrosarcoma), and CT26-luc (colorectal cancer). Survival was a primary output of the studies. Tumor burden was also confirmed by ex vivo analysis.

Results: Pharmacokinetics and tissue organ-distribution demonstrated superior penetration and accumulation of ANN administered as free drug or L-ANN when compared to DOX. In mice, calculated AUC levels were 6.7 to 7.5-fold higher for L-ANN and ANN than for DOX. In a lung metastasis MCA205 model (Fig. 1), no survival benefits were observed in DOX treated mice but ANN elicited a significant increase in survival and inhibition of metastatic nodule growth. Similar activity was observed in orthotopic NSCLC (H1299 and LLC) and experimental metastatic models (K7M3, 4T1, CT26).

Conclusions: Our data clearly support the notion that low concentrations of DOX in lung correlates with low efficacy, while a significantly higher uptake of ANN in lung tissue positively correlates with robust in vivo activity in lung localized cancers. These results are opening doors for clinical testing of a new class of Top2a targeting drugs with high lung uptake for treatment of cancer patients with primary lung and lung metastatic cancers

Keywords: Annamycin, lung metastatsis, cardiotoxicity

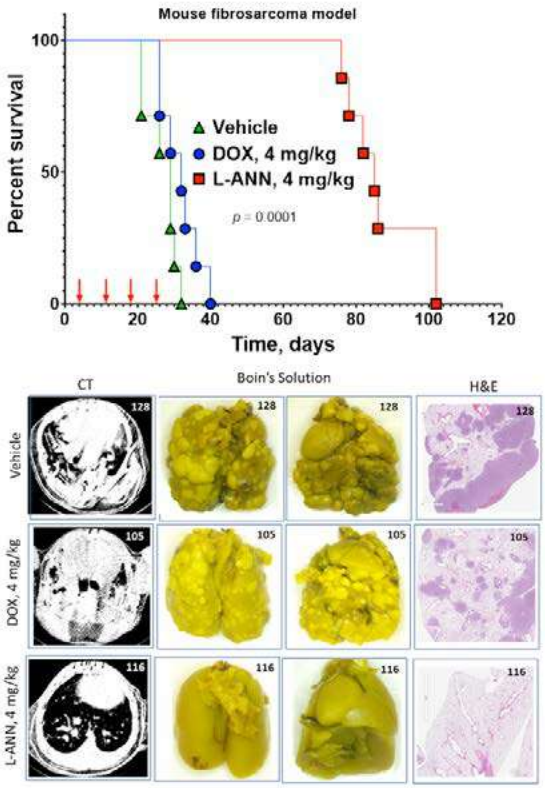

Figure 1. *In vivo* activity of L-ANN and DOX in mice MCA205 lung metastasis model.

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P3.03I.05 DSTYK Inhibition as a Novel Strategy for Taxane-Based Chemotherapy Sensitation in Early and Advanced Lung Cancer

M. Echepare[1], B. Picabea[1], A. Arricibita[1], A. Teijeira[1], A. Pasquier[1], C. Zandueta[1], E. Santamaría[2], J. Fernández-Irigoyen[2], O. Romero[3], M. Sánchez-Céspedes[3], F. Lecanda[1], J. Hernández[4], E. Felip[4], A. Cruz[5], M. Provencio[5], L.M. Montuenga[1], K. Valencia[1], [1]Center of Applied Medical Research. University of Navarra, Pamplona/ES ,[2]Navarrabiomed, Pamplona/ES ,[3]Josep Carreras Leukaemia Research Institute, Barcelona/ES ,[4]Hospital Universitari Vall d'Hebron & Vall d'Hebron Institute of Oncology (VHIO), Barcelona/ES ,[5]Hospital Universitario Puerta de Hierro, Madrid/ES

Introduction: One of the main problems of lung cancer treatments is resistance, which is acquired to every therapy over time, including chemotherapy. Chemotherapy continues to be the standard treatment for patients non-eligible for targeted or immune-based therapies. We previously found that DSTYK, a poorly explored dual serine/threonine and tyrosine kinase frequently amplified in cancer, identifies lung cancer patients with bad response to immune checkpoint inhibitors and whose inhibition experimentally sensitizes to immunotherapy. At the molecular level, DSTYK has been observed to be a central regulator of autophagy and oxidative stress response, being these molecular pathways also described to be involved in chemotherapy resistance. Besides, DSTYK KO cells are severely damaged under stressful conditions, being more prone to apoptosis.

Methods: In silico analysis to study the differential sensitivity to Paclitaxel, Carboplatin, Pemetrexed and Cisplatin drugs were performed using pan-cancer human cancer cell line DSTYK CN data downloaded from Depmap portal (https://depmap.org/portal/depmap/). Two cohorts of lung cancer patients were used. An adjuvant cohort composed of Advanced IV stage lung adenocarcinoma patients treated with Carboplatin+Paclitaxel or Carboplatin+Pemetrexed in first line from VHIO; A neoadjuvant cohort including resectable stage IIIA or IIIB NSCLC tumor samples of patients from NADIM I and NADIM II clinical trials perioperative treated with nivolumab plus chemotherapy (Carboplatin+Paclitaxel). DSTYK CN was assessed by FISH and qRT-PCR. Proteomics and bioinformatic analyses were performed to study differentially expressed protein signatures. Functional in vitro experiments (adhesion, migration, invasion) in both murine and human systems, and in vivo lung orthotopic, intracardiac and intratibial xenograft and syngeneic models complete the study.

Results: Here we report that DSTYK depletion overcomes resistance to chemotherapy. We show that DSTYK inhibition specifically sensitizes lung cancer cells to taxane-based chemotherapy, particularly in combination with Carboplatin. Consistently, clinical data of early (neoadjuvant) and advanced (adjuvant) treated lung cancer patients shows a correlation between DSTYK amplification and taxane resistance. Mechanistically, DSTYK inhibition remodels the cytoskeleton, reducing cellular tumorigenic hallmarks and impairing homing and metastasis establishment in vivo. DSTYK downregulation sensitizes both primary and metastatic lung tumors to Carboplatin+ Paclitaxel+ anti-PD1 treatment in mouse models leading to the cure of 100% of the mice.

Conclusions: Our data indicates that DSTYK amplification may be a predictor of resistance to taxane-based treatments and could be an actionable target for lung cancer patients in early or/and advanced stages.

Keywords: DSTYK, taxane resistance, metastasis

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P3.03I.06 Neoadjuvant Gefitinib in EGFR Mutated NSCLC (a Phase 2 Window-Of-Opportunity Study): Deep Genomic and Transcriptomic Analysis

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Introduction: EGFR TKI therapy is well established as first-line therapy in advanced EGFR mutated NSCLC. Despite high response rates, the determinants of therapeutic response remain poorly understood. We conducted a phase 2 window-of-opportunity study to uncover the dynamics and mechanisms of anti-tumour response through comprehensive in-depth tissue sequencing of resected tumours. The clinical outcomes from this study have been presented previously (JTO 2019, 14;10:S609-610; NCT02804776). Here, we present the deep multi-region genomic and transcriptomic translational analyses from the study.

Methods: Patients (pts; n=13) with stage IA-IIIA EGFR mutated NSCLC received minimum 4-weeks of gefitinib 250 mg orally prior to surgery. Translational studies included multi-region whole exome sequencing (WES; n=44 sectors) and both bulk and spatial RNA sequencing (RNA-seq; n=39 sectors) in resected tumours, and compared with a matched treatment naive cohort (n=21 pts; n=66 sectors).

Results: The objective response rate (ORR) was 62% and disease control rate (DCR) was 100% to neoadjuvant gefitinib. All pts underwent surgical resection, with pathological downstaging in 6 (46%) pts, and major pathological response (MPR) in 1 (8%) pt. Deep genomic (including multi-region) and transcriptomic (including spatial) sequencing revealed early indicators of response and adaptation in both the tumour and microenvironment. On multi-region WES, neoadjuvant gefitinib tumours had no appreciable development of EGFR T790M gatekeeper or other genomic features of reported EGFR TKI resistance; apart from an increase in ERBB2 gene amplification (although this was of low magnitude and ERBB2 was not over-expressed). TMB was also not significantly different between neoadjuvant gefitinib versus treatment naive tumours, suggesting known resistance mechanisms may not commonly be present de novo or during the early phases of EGFR TKI therapy. However, early tumour genomic adaptation were observed, with neoadjuvant gefitinib treated tumours having lower tumour purities, lower clonal diversity and lower levels of EGFR amplification. On RNA-seq in neoadjuvant gefitinib tumours, upregulation of immune regulatory/inflammatory response genes (such as the T-cell inflamed gene expression profile [GEP] score), upregulation of immune tolerance checkpoint genes and metabolic switching from glycolysis to oxidative phosphorylation was observed. Using both immunofluorescence and whole transcriptome digital spatial profiling, this metabolic switch was seen to be occurring predominantly in cancer cells rather than immune or stromal cells. This suggests a dynamic metabolic state within the tumour microenvironment, with diverse metabolic reactions serving as key potential drivers of the initial tumour response to neoadjuvant gefitinib. This observed shift also underscores the adaptability of tumour cells, and a potential role for additional metabolic interventions.

Conclusions: After neoadjuvant gefitinib, deep genomic and transcriptomic sequencing, including multi-region and spatial analysis, provided unique insight into early adaptive response in both the tumour and local microenvironment. This phase 2 window-of-opportunity study uncovered the potential for rational combination approaches to improve therapeutic efficacy in EGFR mutated NSCLC.

Keywords: Neoadjuvant, Gefitinib, EGFR

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P3.03I.07 Comprehensive Pan-Cancer Analysis of Oncogenic MET Rearrangements with a Focus on Targetability in NSCLC

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Introduction: Rearrangements of receptor tyrosine kinases play a pivotal role in driving oncogenesis in NSCLC. While activating rearrangements involving ALK, ROS1, RET, and NTRK1/2/3 are FDA-recognized biomarkers of response to tyrosine kinase inhibitors (TKI), the lack of FDA-approved therapies for MET rearrangements remains a challenge. Here, we provide a pan-cancer analysis of oncogenic MET rearrangements, focusing on its targetability in NSCLC.

Methods: We conducted an in-depth manual curation of structural genomic variants involving MET from a large institutional NGS cohort. Demographic variables, histopathology, genomic alterations, and treatments were annotated. Cases were classified according to the presence of co-occurring MET/RTK/RAS/RAF drivers into: 1) Group A: MET amplification-negative and RTK/RAS/RAF-negative, representing putative de novo drivers, 2) Group B: MET amplification-positive, representing amplified rearrangements or rearrangements arising as a result of amplification of wild-type MET, and 3) Group C: MET amplification-negative and RTK/RAS/RAF-positive, representing rearrangements putatively acquired during or after completion of targeted therapies. Oncogenicity and response to type I/II MET-TKIs were profiled in vitro and in patients.

Results: Fifty-six MET rearrangements from 91,119 patients (0.06%), involving MET exon 15 (52%) and 30 different partners, were recurrently detected in lung (30%), brain (20%), and other tumor types. A comparison of 45 cases where NGS was performed using both DNA and RNA sequencing revealed that 38% (17/45) of cases were DNA-negative but RNA-positive for MET fusion. Thirty partners were recurrent while others were present in single cases only. Fusion partner distribution was heterogeneous, with exclusive detection of HLADRB1 and CD47 in LUAD. We identified 17 cases (0.17%) of NSCLC harboring a MET rearrangement. Group A events were more frequent in lung cancer (n=13/38, 34%) than in other locations. MET-rearranged NSCLC patients were more frequently female never-smokers (8/13, 62%) and slightly younger (median age: 63). Nearly all cases (12/13, 92%) were LUAD or harbored an adenocarcinoma component, mostly TTF1-positive (11/12, 92%), non-mucinous (8/12, 67%), and lacking STK11/KEAP1 mutations. Acquired MET rearrangements (Group C) were also recurrently found in NSCLC coincidental with resistance to osimertinib (n=1), capmatinib (n=1), and crizotinib (n=1). Growth of Ba/F3 cells transformed with ZKSCAN1::MET was inhibited upon treatment with type 1 (crizotinib, capmatinib, savolitinb) and type 2 (cabozantinb) MET-TKI. We examined the clinical activity of MET-TKIs in a cohort of 11 cases from Group A, including 6 NSCLC (5 LUAD and 1 LUPC). Exceptional clinical responses were observed in patients with LUAD driven by HLADRB1::MET or CD47::MET.

Conclusions: MET rearrangements are widely distributed pan-cancer drivers with prevalence in NSCLC. We observed distinct paradigms of fusion pathogenesis defined by partner homodimerization and genomic contexts with substantial differences in in vitro sensitivity to, and clinical responses to, MET-TKIs. We also describe a cohort of patients with acquired MET fusions as a resistance mechanism to different targeted therapies. Our findings provide further support for clinical trial evaluation of MET inhibitors in MET fusion driven cancers, particularly NSCLC.

Keywords: MET fusion, NSCLC, Oncogene driver

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P3.03I.08 Efficacy of Novel Third-Generation Tyrosine Kinase Inhibitors for Uncommon EGFR Mutations- Anin Vitrostudy

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Introduction: Clinical guidelines recommend afatinib or osimertinib for patients with non-small cell lung cancer (NSCLC) harboring uncommon EGFR mutations, albeit with limited efficacy. Here, we evaluated novel third-generation tyrosine kinase inhibitors (3G-TKIs) including almonertinib(=aumolertinib, lazertinib, alfultinib(=furmonertinib), rezivertinib, and befotertinib) in addition to osimertinib using Ba/F3 models transduced with five uncommon EGFR mutation (Del18, E709K, G719A, S768I, L861Q). Additionally, we explored secondary resistant mutations to afatinib or osimertinib.

Methods: Ba/F3 cells transduced with uncommon EGFR mutation were previously established. The efficacy of each drug was evaluated using an in vitro growth inhibitory assay after 72 h of drug exposure. Efficacy of each drug was assessed using the sensitivity index (SI), defined as the IC50 value multiplied by 100 and divided by the clinically achievable drug concentration (Ctrough) reported in the literature. We employed the N-ethyl-N-nitrosourea (ENU) mutagenesis technique to obtain resistant cells against afatinib or osimertinib. The presence of secondary mutations of the EGFR (exons 18-21) were analyzed using direct sequencing.

Results: SIs of afatinib were ≤ 5 for all uncommon EGFR mutations tested. Although 3G-TKIs were all active for L861Q with SI≤5, they were generally ineffective, especially for S768I and E709K. However, befotertinib was active for all mutations except S768I (Table 1). In the analysis of secondary resistant mutations against osimertinib, we identified a novel secondary T725M mutation in Ba/F3 cells with G719A mutation, which remained sensitive to afatinib and lazertinib. Conversely, the T790M secondary mutation emerged after afatinib treatment in Ba/F3 cells with G719A or S768I mutations, and these resistant cells were sensitive to lazertinib. Resistant cells with secondary V769L/M mutations were refractory to all EGFR-TKIs tested.

Conclusions: Afatinib exhibits broad activity against all uncommon EGFR mutations tested, while 3G-TKIs did not display generation-specific activity but rather drug-specific activity, despite befotertinib, alfultinib, and almonertinib sharing very similar structures with osimertinib. The T790M secondary mutation that emerged after afatinib treatment remain sensitive to lazertinib.We conclude that afatinib is the best drug for uncommon EGFR mutations among currently available EGFR-TKIs.

Keywords: Uncommon EGFR, EGFR mutation, novel third-generation tyrosine kinase inhibitors

Summary of sensitivity index

SI ≦ 5 | 5 < SI < 10 | SI ≧ 10

SI	Gefitinib	Erlotinib	Afatinib	Osimertinib	Alfutinib	Lazertinib	Almonertinib	Rezibertinib	Befotertinib
L858R	0.20	0.71	0.58	0.05	0.19	0.34	0.05	0.01	0.02
Del 19	0.07	0.19	0.45	0.08	0.11	0.07	0.06	0.20	0.02
Del18	54.19	14.27	0.87	5.98	3.23	19.28	8.53	5.61	2.35
E709K	75.33	15.36	2.46	13.23	8.47	18.83	10.22	13.34	1.37
G719A	19.45	3.96	2.03	10.10	4.49	3.00	16.02	6.97	0.12
S768I	36.85	9.29	2.17	16.89	34.64	18.84	13.18	32.84	17.90
L861Q	12.21	2.41	0.29	1.13	0.13	0.18	0.09	1.58	1.25
G719A/T725M	63.87	10.73	0.96	41.40	28.92	0.11	14.48	27.73	12.98
G719A T790M	n.d.	n.d.	4.41	2.85	n.d.	0.50	2.66	n.d.	n.d.
S768I V769L			22.10	84.78		134.05	21.43		
S768I V769M			16.84	80.55		113.71	98.30		
S768I T790M			318.55	22.15		4.59	12.50		
L861Q L718Q			5.63	263.25		201.35	337.00		
L861Q V769L			2.00	3.65		1.54	4.04		
EGFR Wt	86.55	7.69	14.70	109.38	500.74	36.41	14.21	180.07	36.03

n.d. : No Data

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P3.03I.09 Augmenting Post-Surgical Tumor Immune Response and Recurrence Prevention via Nanoparticle-Assisted Targeted Drug Delivery

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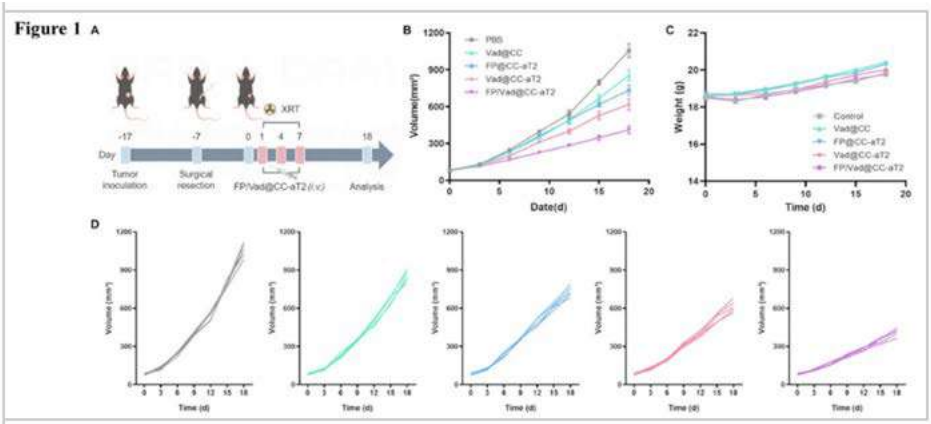
Introduction: Lung cancer patients often face post-surgery recurrence due to changes in the tumor immune microenvironment. The development of Nanoparticle-aided Targeted Drug Delivery Systems (NDDS) offers a refined approach for delivering small molecule inhibitors, enhancing therapeutic outcomes and minimizing side effects. The mechanism of ferroptosis and its associated immunogenic cell death (ICD) effect can potentially amplify the efficacy of immunotherapy through the synergistic activation of the stimulator of interferon genes (STING) pathway. This signifies a significant step towards personalized and precise treatment.

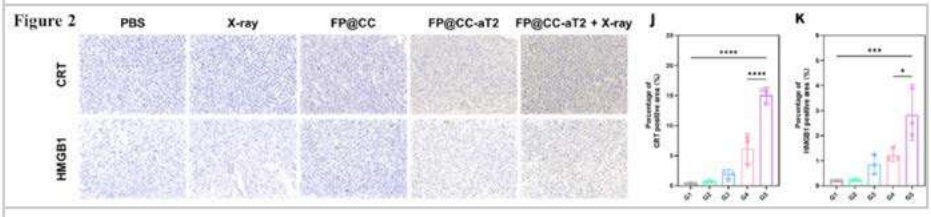
Methods: FP/Vad@CC-aT2, a biomimetic nanoparticle system containing FePt and Vadimezan, was prepared via extrusion and conjugated with anti-Trem2 antibodies. In a mouse model, subcutaneous tumors were grown and partially resected to simulate a positive margin and establish a recurrence model. Post-treatment analyses of tumor tissues, including flow cytometry and immunohistochemistry, provided insights into immune cell composition, molecular expression, and treatment efficacy.

Results: We established a mouse model for postoperative tumor recurrence. Our treatment protocol, which was evaluated by monitoring tumor volume and body weight, showed no significant weight changes, indicating its relative safety. Notably, the FP/Vad@CC-aT2 group exhibited significant tumor inhibition compared to other groups (Fig. 1B, D). Immunohistochemical analysis showed increased expression of CRT and HMGB1, proteins associated with immunogenic cell death (ICD), in tumor cells treated with FP@CC-aT2 (Fig. 2), suggesting ICD induction. Analysis of the tumor microenvironment using flow cytometry and immunostaining revealed that the treatment resulted in increased infiltration of M1-type macrophages and CD8+ T cells. Conversely, the presence of Treg was significantly reduced.

Conclusions: The study developed FP/Vad@CC-aT2, a targeted delivery system with good biocompatibility and significant antitumor effects. It was found to promote immune remodeling, induce immunogenic cell death, and alter immune cell composition in post-surgical relapse mouse models, suggesting its potential in preventing postoperative relapse and providing a basis for clinical applications.

Keywords: Immunogenic cell death, Post-surgical, Tumor Immune Microenvironment





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P3.03I.10 RRAS and RRAS2 Mutations Are Oncogenic Drivers in Lung Cancer and are Sensitive to the Pan-RAS Inhibitor RMC-6236

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Introduction: RRAS and RRAS2 encode a subfamily of Ras-like small GTPases that share considerable structural similarity with the well-known family of RAS oncogenes, including KRAS, HRAS, and NRAS. RRAS/RRAS2 are thought to play a role in signal transduction pathways that control cellular proliferation and survival. Whether RAS-like homologous mutations in RRAS/RRAS2 are oncogenic and actionable drivers in lung cancer remains unexplored.

Methods: An institutional cohort of 6,470 lung adenocarcinoma (LUAD) cases profiled by comprehensive targeted DNA sequencing (MSK-IMPACT) between 2016-2024 was evaluated for RRAS/RRAS2 mutations. Missense mutations in RRAS/RRAS2 homologous to RAS family hotspot mutations were modeled by viral transduction of cDNA constructs into murine IL3-dependent Ba/F3 cells, NIH-3T3 fibroblasts, and immortalized human bronchiolar epithelial cells (HBEC). The oncogenic potential of RRAS/RRAS2 mutations was evaluated via an IL3-withdrawal assay and tumor growth in immunocompromised mice (NSG strain). Cell viability was assessed following 96-hour treatment with targeted PI3K/AKT or MAPK signaling inhibitors, including the novel pan-RAS inhibitor RMC-6236, which is currently being evaluated in clinical trials (NCT05379985). Western blotting was used to analyze protein expression and activation state.

Results: RRASQ87L or RRAS2Q72L mutations, homologous to codon 61 substitutions in KRAS/NRAS/HRAS, were found in ~0.5% of LUAD cases (35/6,470), with all but two lacking other RTK-MAPK oncogenic drivers. Notably, RRASG38X and RRAS2G23X mutations, which are homologous to KRAS/NRAS codon 12 substitutions, were extremely rare (n=1 and n=2, respectively). Ba/F3 cells expressing either RRASQ87L or RRAS2Q72L became IL3-independent and formed xenograft tumors in mice in contrast to their wild-type counterparts, suggesting oncogenic transformation by these two mutant proteins. Expression of RRASQ87L or RRAS2Q72L in HBEC cells resulted in strong PI3K-mTOR pathway activation. Enhanced ERK phosphorylation was only observed in HBEC-RRASQ87L cells. Both cell lines exhibited strong induction of negative regulators of the MAPK pathway (SPRY2, SPRY4, SPRED1), suggesting that RRASQ87L/RRAS2Q72L oncogenicity required attenuation of ERK signaling output in the setting of upregulated PI3K-mTOR signaling. ERK1/2 (ulixertinib and SCH772984), MEK1/2 (binimetinib), and PI3K (pictilisib) inhibitors inhibited growth of RRASQ87L or RRAS2Q72L cells more potently than cells expressing wildtype proteins. Importantly, the novel pan-RAS inhibitor RMC-6236 blocked phosphorylation of ERK and S6, inhibited growth of RRASQ87L and RRAS2Q72L cell lines, and induced apoptosis. ERK, MEK and PI3K inhibitors did not stimulate apoptosis at equimolar concentrations. Ongoing studies are evaluating RMC-6236 efficacy in vivo.

Conclusions: RRASQ87L and RRAS2Q72L are actionable oncogenic drivers that display mutual exclusivity with other RTK-MAPK alterations. Oncogenic RRAS/RRAS2 mutations were detected in LUAD at a rate similar to some other well-characterized lung cancer drivers, such as HRAS/NRAS hotspot mutations or NRG1 fusions. Our study supports the inclusion of RRAS/RRAS2 into routine molecular diagnostic protocols for precision oncology and clinical development of pan-RAS inhibitors, such as RMC-6236, for patients with these driver mutations in order to fully realize the potential benefit of RAS-targeted therapies.

Keywords: Targeted Therapy, Lung Adenocarcinoma

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P3.03I.11 The ATXN3-USP25-TRMT1 Axis Regulates tRNAm2,2G Modification and Promotes Osimertinib Resistance in Lung Cancer

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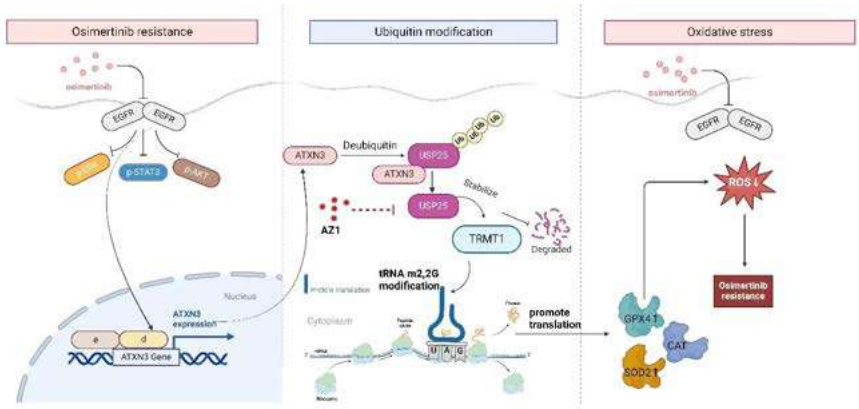
Introduction: Osimertinib is an oral third-generation EGFR-TKI, which is recommended as the first-line treatment for patients with advanced non-small cell lung cancer with EGFR activation mutation. However, patients receiving osimertinib inevitably experience acquired drug resistance. Deubiquitinases (DUBs) play a crucial role in the occurrence and development of tumors. But, there is limited research on the relationship between drug resistance and DUBs of osimertinib.

Methods: In this study, we constructed cell lines resistant to osimertinib, screened the high expression of DUBs in drug-resistant cells, and found that ATXN3 was highly expressed in drug-resistant cells and promoted osimertinib resistance. CO-IP and IP-MS screening revealed the interaction of ATXN3 with USP25, and USP25 with TRMT1. Ubiquitination assay and the CHX assay demonstrated that ATXN3 stabilizes USP25 by deubiquitination, and that USP25 in turn can regulate TRMT1 at the protein level. The tRNA mass spectrometry results revealed that TRMT1 can regulate tRNAm2,2G modification levels. Detection of ROS and osimertinib-resistant phenotypes revealed that TRMT1 promotes osimertinib resistance by downregulating intracellular ROS levels.

Results: It was found that ATXN3 promoted tumor cells resistance to osimertinib by stabilizing USP25. Further research found that USP25 interacts with TRMT1 and can regulate the expression of TRMT1 at the protein level. Mechanism studies have shown that TRMT1 regulating tRNAm2,2G modification can selectively enhance the translation efficiency of oxidoreductase and promote osimertinib resistance by reducing the level of intracellular ROS. In vitro and in vivo experiments showed that targeted USP25/TRMT1 could overcome the drug resistance of osimertinib. Clinical specimens confirmed that the expression of TRMT1 and USP25 in tumor tissues was up-regulated after osimertinib resistance, and the expression level of TRMT1 and USP25 was negatively correlated with PFS before treatment.

Conclusions: In summary, we found that: 1) ATXN3-USP25-TRMT1 axis regulates tRNAm2,2G modification by affecting the translation efficiency and activity of oxidoreductase, regulating ROS levels in tumor cells and promoting osimertinib resistance; 2) Targeting USP25 / TRMT1 can increase the sensitivity of drug-resistant cells to osimertinib and inhibit tumor growth. This study discovered a new mechanism of osimertinib resistance and provided a new treatment direction to overcome osimertinib resistance.

Keywords: Non-small cell lung cancer, osimertinib resistance, tRNA methyltransferase



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P3.03I.12 Modulation of EMT Increases the Activity of Lurbinectedin in Small Cell Lung Cancer

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Introduction: Small cell lung cancer (SCLC) comprises 15% of lung cancer cases with a poor prognosis despite recent advancements. While standard chemotherapy initially yields high response rates, chemorefractory relapse limits patient survival partly due to epithelial-mesenchymal transition (EMT) mediated by the hepatocyte growth factor (HGF)/MET pathway. Inhibiting MET receptor has potential in reversing EMT and restoring chemotherapy sensitivity. Lurbinectedin, an alkylating agent that binds to GC-rich gene promoter regions, has shown promising results in SCLC treatment and is currently used in the second-line setting. However, it only benefits a subset of patients. We hypothesize that EMT modulation through MET inhibition can revert resistance and improve lurbinectedin efficacy in SCLC.

Methods: Eleven human SCLC cell lines were characterised for SCLC subtypes, EMT state (E-cadherin, vimentin and fibronectin expression), MET and phospho-MET expression (by RT-qPCR and WB). Their sensitivity to cisplatin and etoposide (chemotherapeutic drugs), as well as lurbinectedin alone and combination with capmatinib (MET inhibitor), was tested using the Cell Titer-Glo® Luminiscent Cell Viability Assay (Promega).

Results: The cell lines H196 and H841 were classified as SCLC-I subtype, due to the lack of expression of ASCL1, NEUROD1 and POU2F3. They were the top MET expressors in basal conditions among the cell line panel and displayed a mesenchymal phenotype. Upon HGF exposure, p-MET was induced in both these cells and the rest of the MET expressor cells within the panel, suggesting functional pathway activity. Conversely, HGF exposure failed to induce MET or p-MET expression in cells lacking basal MET expression. Treatment with lurbinectedin revealed that H69M, a mesenchymal cell line derived from the parental epithelial H69 by our group, exhibited significantly greater resistance than its counterpart (74±10 % vs 50±5 % of cell viability, n=3 replicates, p<0.0001). H196 and H841 cells also exhibited resistance to lurbinectedin. In H841 cells, combined lurbinectedin and capmatinib treatment significantly reduced cell viability compared to lurbinectedin alone (70±5 % vs 49±8 % of cell viability, n=2, p=0.0003). However, this effect was not observed in H196 cells.HGF exposure affected cell viability in H69 and H196 but not in H841, making them less sensitive to lurbinectedin treatment (12±6 % vs 23±12 % n=3, p=0.04 for H69, 44±16 % vs 61±16 % n=3, p=0.04 for H196). HGF had no impact on the sensitivity of lurbinectedin in the non-expressor MET H82 model. Treatment with capmatinib reversed HGF-induced lurbinectedin in H69 and H196, resulting in a slight, albeit not significant, enhancement of cell death (72±12 % vs 63±7 % n=2, p>0.05 for H69, 58±9 % vs 46±6 % n=2, p>0.05 for H196).

Conclusions: The MET/HGF pathway is functional in MET-expressing cells, as evidenced by MET phosphorylation upon HGF exposure. Cells with a mesenchymal phenotype displayed increased resistance to lurbinectedin. HGF exposure reduced lurbinectedin sensitivity in certain cell lines, but capmatinib treatment reversed this, enhancing the effect of lurbinectedin. This highlights the potential synergy of combining lurbinectedin with MET/HGF pathway targeting. However, heterogeneous responses to HGF suggests the need for further studies to identify response biomarkers for this combination therapy.

Keywords: Small Cell Lung Cancer, lurbinectedin, epithelial-mesenchymal transition

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P3.03I.13 High EGFR Expression Confers Acquired Resistance to Adagrasib - In Vitro Study Using KRASg12C Mutated Lung Cancer Cells

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Introduction: KRASG12C inhibitors such as adagrasib can produce substantial regression of tumors in patients with non-small cell lung cancer (NSCLC) harboring KRASG12C mutation. However, the acquisition of resistance is almost inevitable, and the underlying molecular mechanisms are not fully understood. In this study, we established adagrasib-resistant cells via chronic exposure to the drug and explored the underlying molecular mechanism.

Methods: First, we confirmed that the H2122 lung cancer cell line with KRASG12C was sensitive to adagrasib (IC50 = 123 nM). Adagrasib-resistant H2122 (H2122AR) was then established by chronic exposure to increasing concentrations of adagrasib. The mechanism for the resistance was explored using direct sequencing of the KRAS gene, phospho-RTK (receptor tyrosine kinase) array, quantitative real-time PCR, and RNA sequencing.

Results: We successfully established H2122AR by the exposure to increasing concentrations of adagrasib to a final concentration of 10 μM for up to 6 months. H2122AR was > 25 times resistant compared with its parent with IC50of 3.2μM. We did not detect any KRAS secondary mutation. However, the phospho-RTK array experiment revealed high phosphorylation of EGFR in H2122AR but not in H2122, in the presence of 10 μM of adagrasib. Although there was no copy number gain of the EGFR in H2122AR cells (1.2-fold), EGFR mRNA expression was increased by 2.1-fold compared with parental H2122 cells. This was also confirmed by the Western blot. Furthermore, this resistance was overcome by a combination treatment of 50 nM afatinib with adagrasib in H2122AR cells (IC50 = 60 nM).

Conclusions: High EGFR expression, without evidence of EGFR gene amplification, led to the development of acquired resistance to adagrasib. Dual blockade of EGFR and KRASG12C could be a potential treatment option for KRASG12C - inhibitor resistant cells if the resistant cells have high EGFR protein expression.

Keywords: KRAS, Adagrasib, Acquired Resistance

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P3.03I.14 Osalmid Inhibits the Progression of Lung Adenocarcinoma and Sensitizes It to EGFR-TKIs: A Preclinical and Translational Study

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Introduction: Therapeutic resistance to current treatment strategies indicates the need for more effective agents to treat lung adenocarcinoma. Despite evidence indicating the potential efficacy of the novel RRM2 inhibitor osalmid as an anticancer agent, its exact mechanism remains unknown. We sought to explore the antitumor effects and possible underlying mechanisms of osalmid and investigated potential combinatorial approaches with third-generation EGFR tyrosine kinase inhibitors (EGFR-TKIs) for the treatment of lung adenocarcinoma patients with EGFR mutations.

Methods: Patient data were used to analyze survival based on RRM2 expression. Cell viability assays, half-maximal inhibitory concentration (IC50) determination, colony formation assays, and cell-derived xenograft (CDX) models were used to explore the antitumor effects of osalmid, AST2818, and AZD9291as single-agents and in combination. Ferroptosis-related data obtained via CRISPR screens and western blotting were used to explore the relationships between RRM2 and ferroptosis suppressor genes (GPX4 and SLC7A11). Immunohistochemical analysis of 4-hydroxynonenal (4-HNE) was conducted to evaluate lipid peroxidation in tumor tissues after treatment with osalmid.

Results: Lung adenocarcinoma patients with high RRM2 expression had poorer survival than patients with low RRM2 expression ($p<0.001$). RRM2 knockdown or osalmid treatment decreased the proliferation and colony formation of lung adenocarcinoma cell lines. When AST2818 and osalmid were combined, the IC50 value of AST2818 was decreased. The expression of RRM2 gradually increased with the increase of AST2818 treatment time, implying that RRM2 is regulated by EGFR and could be a drug-resistant target of AST2818. In addition, the tumor suppression rate in the drug combination group was larger than that in the single-drug group (89% vs. 70%, $p<0.001$). Western blotting revealed that the expression of GPX4 and SLC7A11 was lower in the shRRM2 cell line than in the shNC cell line. In addition, the abundance of 4-HNE increased as the concentration of osalmid increased.

Conclusions: Osalmid may inhibit the progression of lung adenocarcinoma and sensitize it to EGFR-TKIs by inhibiting RRM2 activity to increase ferroptosis. Besides, RRM2 could be a drug-resistant target of AST2818. Our study has translational value supporting the clinical use of osalmid as an anti-lung adenocarcinoma agent either alone or in combination with third-generation TKIs, for lung adenocarcinoma patients with EGFR mutations.

Keywords: EGFR mutation, osalmid, AST2818

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P3.03I.15 The Mechanisms and Impact of EGFR TKIs in Modulating Blood Immune Cells in Patients with Oncogene-Driven NSCLC

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Introduction: In a previous study, we demonstrated that EGFR tyrosine kinase inhibitors (TKIs) influence blood immune cell counts in patients with oncogene-driven, metastatic non-small cell lung cancer (mNSCLC). This study aims to elucidate the underlying mechanisms and validate these blood biomarkers for assessing and monitoring clinical responses at different treatment timepoints in mNSCLC patients.

Methods: To uncover the mechanisms of TKIs on immune cells, we conducted in vitro simulations using peripheral mononuclear blood cells (PMBCs) with and without osimertinib for 72 hours, followed by RNA sequencing. Bulk RNA sequencing was also performed on PBMCs isolated from patients with EGFR-mutant lung adenocarcinoma (LUAD) before and after osimertinib treatment. Additionally, we identified 139 mNSCLC patients treated with TKIs from pharmacy databases at our institute, with 114 patients having complete blood counts at four timepoints: before treatment (T0), 2-6 weeks post-treatment (T1), approximately 3 months with the first radiographic evaluation (T2), and at censor or progression (T3). Data for each blood biomarker were summarized, and progression-free survival (PFS) and overall survival (OS) were determined using Kaplan-Meier estimates. Univariable and multivariable survival analyses were performed using Cox proportional hazards models, and post-treatment changes in blood cell counts were estimated using linear mixed-effects models.

Results: In PBMCs from patients with EGFR mutant LUAD, we observed a decrease in both CD4+ and CD8+ T subsets. RNAseq differential analysis showed that osimertinib significantly inhibited lymphocyte and T cell proliferation pathways, reduced cytokine production and receptor tyrosine kinase activity, and increased apoptotic signaling, protein ubiquination, and chromosomal organization pathways. Among the 114 TKI-treated patients, there were transient but statistically significant declines in absolute lymphocyte counts (ALCs) at T1, followed by significant increases at T2 and T3 in patients with good clinical responses, and decreases at T2 and T3 in patients with poor clinical responses (P <0.001). High leukocyte counts at T0 and T3, as measured by absolute neutrophil counts (ANCs) ≥4.6 x103 cells/μL, derived neutrophil-to-lymphocyte ratio (dNLR) ≥2.4, or NLR ≥4, were associated with poor prognosis. ALCs ≥1400 cells/μL at T2 and ≥800 cells/μL at T3 were associated with good PFS in univariable and multivariable analyses, respectively. Among 29 patients who received immune checkpoint inhibitors (ICIs) after TKIs, only 3 (10.3%) were good responders. Median PFS was 8.1 ±3.4 months with TKIs and 5.3 ±1.9 months with ICIs. Despite similar patterns of dynamic ALC changes, ALCs were lower in ICI-treated patients than in TKI-treated patients (P=0.025).

Conclusions: TKIs modulate blood immune cells in a manner similar to ICIs. Our in vitro analysis suggests that osimertinib may have a direct anti-proliferative and pro-apoptotic effect on lymphocytes. ALCs and neutrophils serve as independent blood biomarkers for monitoring responses to TKI and ICI treatments in patients with oncogene-driven mNSCLC, warranting prospective validation.

Keywords: EGFR TKI, immune cells, RNA sequencing

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P3.03I.16 Treatment Outcomes in Patients who Received Bevacizumab Therapy for Radiation Induced Brain Necrosis

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Introduction: Brain metastases is the most frequently diagnosed type of brain tumor and has a higher propensity in breast and lung cancer. The use of radiation therapy for brain tumors and metastatic brain lesions is associated with radiation induced brain necrosis (RBN). There is currently no standard of care for managing RBN. Patients with RBN present with an array of neurological symptoms in addition to clinical findings. Coupled with capillary leakage and hypoxia, an increase in vascular endothelial growth factor (VEGF) is a notable characteristic of endothelial damage propagated by radiation. Bevacizumab, an anti-VEGF antibody that works by blocking VEGF from reaching its target on the endothelium, represents an attractive therapeutic modality for treating patients with RBN. This study aims to assess the safety and efficacy of bevacizumab in the treatment of RBN. The objective of the study is to evaluate the clinical benefit and safety of bevacizumab for the treatment of RBN

Methods: A retrospective chart review was performed at Memorial Cancer Institute of patients ≥ 18 years who had RBN and received treatment with bevacizumab between January 1, 2015 and January 31, 2024. Data points included: age, sex, ethnicity, race, bevacizumab dose and dosing frequency, number of treatment cycles, number of treatment events, treatment related adverse events (TRAE), and clinical benefit. The primary endpoint was to determine if patients who received bevacizumab for RBN had a clinical benefit. Clinical benefit was defined as improvements or resolution of RBN associated neurological symptoms and supporting MRI findings. The secondary outcomes were to assess the safety of bevacizumab for the treatment of RBN in adults, evaluate whether clinical benefit varied based on bevacizumab dosing strategy, and determine if there are differences in outcomes with bevacizumab and biosimilar product, bevacizumab-awwb.

Results: The study included 26 patients (37 independent treatment events [treatment incidents ranging from months to years after prior clinical benefit]) who received bevacizumab for RBN. Non-small cell lung cancer (NSCLC) and breast cancer were the most common primary pathologies, documented in 19 (73%) and 4 (15%) of the patients respectively. Most patients,15 (58%) of the 26 patients were women and the median age was 66 years. The most common dosing strategy was 10 mg/kg administered biweekly, which was utilized in 25 (68%) of the 37 treatment events. The median number of treatment cycles was 4. Clinical benefit was attained in 34 (91.89%) of the 37 treatment events. Treatment outcomes were similar for bevacizumab and its biosimilar. Bevacizumab treatment was generally well-tolerated, with hypertension (43%), mild fatigue (19%), mild occasional nosebleeds (16%) and serum creatinine elevations (11%) being the most frequent TRAE of the 37 treatment events. There was no bevacizumab-related adverse event reported in 8 (22%) of the 37 treatment events. One patient had grade 4 hypertension leading to treatment discontinuation.

Conclusions: Patients with RBN treated with bevacizumab derive meaningful clinical benefits. Bevacizumab possessed a manageable safety profile and was well-tolerated. Additionally, our study demonstrated that clinical benefits were similar across dosing strategies including dosage, frequency, and biological product.

Keywords: brain necrosis, brain metastasis, radiation therapy

P3.03I TUMOR BIOLOGY - TRANSLATIONAL BIOLOGY - TARGETED THERAPY/NOVEL THERAPY
MONDAY, SEPTEMBER 9, 2024 - 12:00 - 14:00

P3.03I.17 Exploring Autophagy Flux-Related Molecules to Overcome in Acquired Resistance to EGFR TKIs in NSCLC Patients Harboring EGFR Mutations

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Introduction: To date, mechanisms of EGFR TKI resistance in EGFR mutant non-small cell lung cancer (mEGFR NSCLC) include the EGFR T790M mutation, activation of the bypass pathway, and cellular phenotypic changes etc. Recently, it has been recognized that latent intracellular autophagy is another cause of the acquired drug resistance to targeted therapies in a variety of cancers, including melanoma, pancreatic cancer, and breast cancer. We aimed to identify autophagy flux-related signaling molecules that may be closely associated with acquired resistance in mEGFR NSCLC. .

Methods: We established H1975OR (166-fold) and PC9ER (3,650-fold) resistant cell lines by long-term exposure of H1975 (L858R/T790M), PC9 (Del19), and H838 (L858) cells to osimertinib and erlotinib, respectively. We also explored genes that drive autophagy flux activity using transmission electron microscopy (TEM), cytotoxicity, mRNA seq and qRT-PCR, western blot, and siRNA knockdown assays. Using immunohistochemical staining, we investigated protein expression of autophagy flux molecules (p-AMPK, p-Beclin1, ULK1, GABARAPL1) in the paired FFPE tissues before and after EGFR TKI treatment in the patients with advanced/metastatic mEGFR NSCLC.

Results: We found that autophagosomes were widely distributed in H1975OR with TEM. No significant changes were observed in the protein expression of c-Met and IGF1R. p-Beclin1, LC3, P62, and ATG5 were all increased in the resistant cell lines, while p-AMPK was decreased. In H1975OR cells, mRNA expressions of BECLIN1, PINK1, GABARAPL1, NBR1, and ULK1 were much higher compared to those of parental H1975 cells (11.5, 11.0, 46.4, 18.4, and 54.2 times, respectively). The differences of GABARAPL1 and ULK1 mRNA expression were significantly higher among them. Knockdown of GABARAPL1 and ULK1 genes by siRNA treatment showed a decrease in cell proliferation as well as their protein expressions. ULK1 siRNA treatment significantly decreased IGF1R, p-AMPK, and p-Beclin1, while no changes of c-Met, LC3B, and ATG5 were observed. The results of GABARAPL1 siRNA treatment were similar to ULK1, except the decrease of LC3B and P62. In H1975OR cells treated with each of ULK1 and GABARAPL1 siRNA, osimertinib treatment did not significantly change the cell viability compared to H1975 parental cells, but hydroxychloroquine (HCQ), an autophagy inhibitor, markedly decreased cell viability. In addition, p-Beclin1 protein expression was significantly increased in the tumor tissues of treatment failure status, when compared to pre-treatment status (13.0±10.9 vs. 59±7.2, P<0.018).

Conclusions: Taken together, our results suggest that ULK1 and GABARAPL1, two genes involved in osimertinib-induced autophagy, are closely related to the acquired drug resistance. Now, we are underway additional RNA profiling and functional studies to examine a possibility as potential targets for overcoming EGFR TKI resistance.

Keywords: EGFR TKI, Autophagy, NSCLC

P3.03I TUMOR BIOLOGY - TRANSLATIONAL BIOLOGY - TARGETED THERAPY/NOVEL THERAPY
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P3.03I.18 Optimizing Delivery of Anti-Cancer Therapeutics in Lung Adenocarcinoma Using Ultrasound-Induced Cavitation of Microbubbles

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Introduction: Methods that preferentially deliver anti-cancer drugs to tumor tissues are needed to enhance their efficacy which is often limited by dose-restricting toxicities. An innovative strategy that could circumvent this challenge involves using ultrasound and microbubbles (USMB). USMB can focus drugs administered intravenously along with microbubbles (MB) to tissues where ultrasound (US) is applied. Tumor-directed US causes MB circulating in the tumor vasculature to oscillate and/or burst, enhancing membrane permeability and drug uptake in cancer cells, thereby reducing systemic toxicity. While studies have demonstrated the feasibility of this approach in various pathologies including cancer, parameters for robust drug delivery and tumor regression in lung cancer (LC) remain to be established. Here, we aimed to develop a USMB-based approach for preferential delivery of molecular cargo and anti-cancer drugs to lung tumors in mice.

Methods: The LC cell lines, CMT167 and H1299, were used to optimize USMB parameters for in vitro delivery of molecular cargo including siRNA and chemotherapy. The in vitro USMB platform consisted of a 3D-printed water bath designed to fit a clinical US transducer at its base, and cells in suspension were mounted onto a 3D-printed coverslip holder positioned above the transducer at a fixed distance to ensure insonation at maximum intensity. Cells in suspension were exposed to an US beam in the presence of MB with Cy3-tagged non-targeting siRNA (Cy3-siRNA) or the intrinsically fluorescent chemotherapy drug, doxorubicin, and USMB-mediated uptake was evaluated using flow cytometry. The induction of apoptosis by USMB-mediated doxorubicin administration was also evaluated in H1299 cells using AnnexinV/DAPI staining. In vivo USMB parameters were investigated using orthotopic CMT167-Luc+ lung tumors grown in mice and delivery of rhodamine-labeled dextran as proof of concept. MB with dextran were given intravenously and US was applied to the chest. Dextran uptake in tumor tissues was then confirmed using flow cytometry on dissociated tumors.

Results: USMB facilitated siRNA uptake with efficiencies comparable to lipofection in LC cells in vitro. USMB also enhanced doxorubicin uptake in vitro, which was associated with an increase in apoptosis in H1299 cells compared to control cells treated with doxorubicin alone or doxorubicin with MB only. In vivo, flow cytometry on CMT167 lung tumors dissociated after USMB delivery of dextran indicated that dextran uptake was greater in lung tumor tissues treated with USMB (56%) compared to control tumors treated with dextran and MB alone (42%).

Conclusions: USMB enhanced in vitro uptake of siRNA and doxorubicin, which was associated with enhanced cytotoxicity. USMB also increased in vivo uptake of fluorescently-tagged dextran. These results highlight the potential of USMB for delivering various types of molecules to treat LC. Future experiments will include those to refine in vivo parameters for focusing delivery of molecular cargo to orthotopic lung tumors in mice and confirming the tissue specificity of USMB-mediated delivery. Subsequently, we will evaluate the anti-tumor efficacy and toxicity of LC therapeutics like doxorubicin delivered using USMB in comparison to conventional administration by intravenous injection.

Keywords: Ultrasound and Microbbubles (USMB), Lung adenocarcinoma, Drug delivery

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P3.03I.19 The International Pregnancy and Lung Cancer Registry at Dana-Farber Cancer Institute

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Introduction: For the first time in history, young women are getting lung cancer (LC) more than young men. As women increasingly postpone childbearing, we expect a growing number of women to be diagnosed with LC while pregnant or become pregnant during LC treatments. Launched in December 2023, the IRB-approved Pregnancy and Lung Cancer (PLC) Registry is the first international registry recording cases of pregnancy and lung cancer.

Methods: Clinicians and patients worldwide were invited via email or social media outreach to enter cases of pregnant patients with LC or patients diagnosed with LC <1 year post-delivery; a query was also developed to enter retrospective cases from DFCI. Descriptive statistics summarized characteristics from patients' baseline (immediate post-delivery) form.

Results: Between December 2023 and March 2024, a baseline form was completed for 22 women, 17 of whom are alive. Cases were entered from institutions in the United States (20) and Brazil (2). At the time of pregnancy and LC, most women were 31-34 years old. Nearly all (18) were diagnosed with Stage IV LC, mainly adenocarcinoma (20), and had an actionable biomarker (20). Three patients were diagnosed in first trimester, six in second, two in third, and three post-partum. Radiation was the most comment treatment during first trimester (3; range: 9-50 Gy), whereas targeted therapy was most common during second trimester (5; range: 3-5+ cycles), followed by chemotherapy (3; 1-3 cycles); in third trimester, four women received targeted therapy (5+ cycles) and three received chemotherapy (1-3 cycles). Treatment was deferred in the first, second, and third trimesters for three, one, and two women, respectively. Five patients reported accelerating their delivery to receive treatment sooner. Three patients terminated their pregnancy. Common radiographic imaging performed during pregnancy included CT scans (12) and MRIs (12). Most women experienced a partial treatment response during pregnancy and had a PFS for 1st line treatment of 6-9 months. Pregnancy complications included oligohydramnios/polyhydramnios (2), gestational hypertension or diabetes (2), stillbirth (1), and intrauterine growth restriction (1). Delivery complications included pre-eclampsia/eclampsia (4), bleeding (3), emergency caesarian section (2), umbilical cord avulsion (1), and fetal malpresentation due to spinal metastases (1). Maternal complications due to treatment during pregnancy included neutropenia (1) and thrombocytopenia (1); fetal complications included low birth weight (2) and icterus (1). Early infant gestational age (≤ 35 weeks) was reported for seven patients and a low APGAR score (<7) was reported for three (of nine) women. Five infants required the NICU post-birth and one required an operation; reported birth defects included respiratory (1) and GI (1) defects.

Conclusions: Among 22 cases, we observed a lack of uniformity in treatments utilized, treatment deferrals, and imaging modalities, demonstrating the lack of consensus in the treatment of pregnant women with LC. The Registry will continue to report data as more cases become available, including follow-up of maternal and fetal outcomes at 6 and 12-months post-delivery. We aim to ultimately create empirical guidelines and provide clinicians with an understanding regarding optimal therapies, potential adverse outcomes, and unique LC characteristics in this population.

Keywords: pregnancy, lack of consensus, young women

P3.03J TUMOR BIOLOGY - TRANSLATIONAL BIOLOGY - TUMOR MICROENVIRONMENT
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P3.03J.01 Genomic and Spatial Characterization of Neoadjuvant Efficacy Differences in Non-Small Cell Lung Cancer

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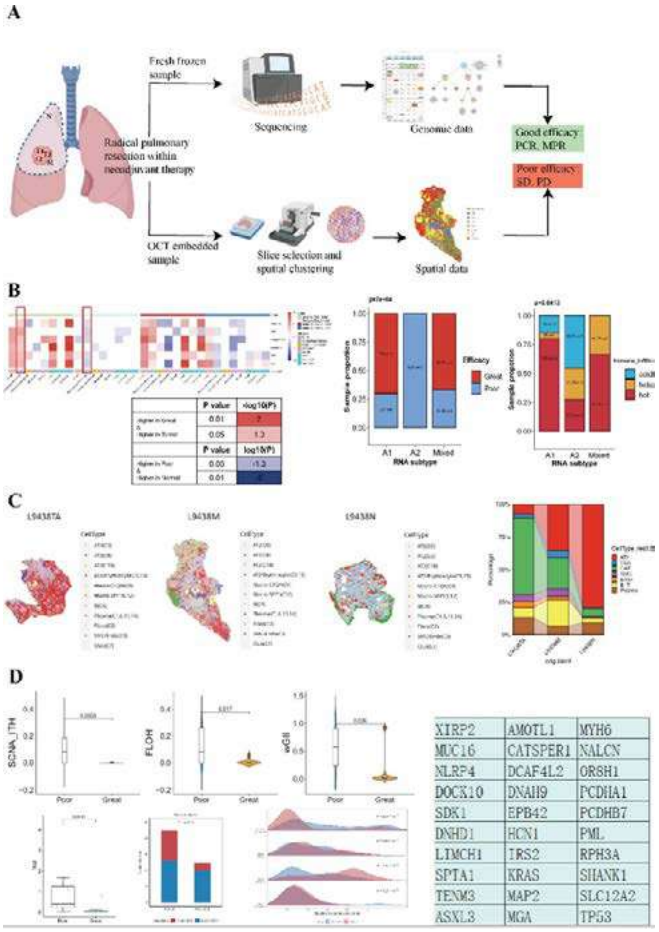
Introduction: Among a large cohort aimed at characterizing the features of early-stage NSCLC in the east Asian non-smoking dominant population, patients who had undergone neoadjuvant therapy were specifically chosen for separate analysis. Multiple sampling regions were selected within the tumor area. The elucidation of spatio-temporal heterogeneity, immune microenvironment composition, and genomic characterization holds promise for explaining the underlying mechanisms governing differential treatment efficacy (Figure 1.A).

Methods: This prospective cohort comprising 36 patients with 112 region WES data and paired 34 patients with 91 region RNA-Seq data. According to the results of unsupervised NMF rank survey, the RNA data were dichotomized, and the region level was divided into A1 and A2 clusters. We employed Ward's method, XCell, ssGSEA, random forest, and other analytical approaches to comprehensively investigate immunophenotypes and ascertain immune infiltration situation. The tumor, junction, and normal tissues were collected from neoadjuvant patients for the characterization of spatio-temporal heterogeneity in tumors using single-cell spatial transcriptome technology.

Results: Patients undergoing neoadjuvant chemotherapy exhibit a favorable response predominantly enriched in the A1 subtype. Conversely, patients displaying a suboptimal response to neoadjuvant treatment are more likely to exhibit enrichment in the A2 subtype (P<0.05). The findings of immunophenotyping were also in line with these results. Used nine immune cell infiltration assays and found that the consistent cell subsets affecting the efficacy of neoadjuvant immunotherapy were B cells, macrophages and T cells, which were all highly abundant in tumor tissues with good response. We will also focus on macrophages, with the increase of macrophages in tumor tissue is associated with good efficacy, while the increase of macrophages in normal tissue is associated with poor efficacy (Figure 1.B). By employing single-cell spatial transcriptome technology with enhanced resolution and more comprehensive positional information, we conducted further analysis exhibiting distinct therapeutic effects to corroborate the findings of the supplementary genomic analysis (Figure 1.C). The SCNA-ITH, FLOH, wGII, and TNB exhibited significantly higher levels in patients with poor response (P<0.05), indicating a potential association between genomic copy number alterations and genomic instability in the context of poor response. Patients with poor neoadjuvant response displayed a higher prevalence of overall gene mutations, and the top differentially expressed genes will be listed (Figure 1.D).

Conclusions: This study presents a comprehensive analysis of the spatio-temporal heterogeneity among neoadjuvant patients with varying treatment efficacy, providing an in-depth characterization of the tumor immune microenvironment at a higher resolution.

Keywords: NSCLC, Neoadjuvant treatment, Intratumor heterogeneity



P3.03J TUMOR BIOLOGY - TRANSLATIONAL BIOLOGY - TUMOR MICROENVIRONMENT
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P3.03J.02 Identification of CD200 as Potential Endothelia Target to Relieve the Immune Suppression in Precursor Lung Adenocarcinoma

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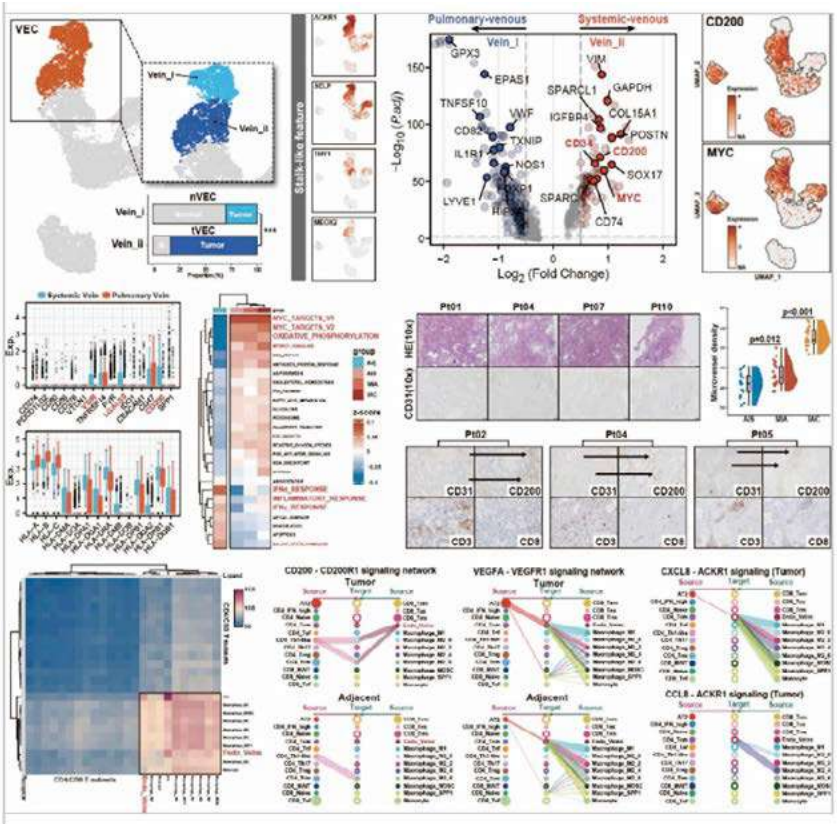
Introduction: Heterogeneity of endothelial cell phenotype in precursor lung adenocarcinoma and matched normal lung tissues remained poorly inventoried at the single-cell level. Understanding how these pivotal components involved in development of precursor lung adenocarcinoma could shed light on cancer initiation.

Methods: 31 patients with adenocarcinoma in situ (AIS), minimally invasive adenocarcinoma (MIA) and invasive adenocarcinoma (IAC) as well as match paired normal tissues were obtained for single-cell RNA sequencing. 10,668 high quality cells clustered as endothelia cells were analyzed. Multiple immunohistochemistry of CD3, CD8, CD31, CD34 and CD200 through continuous slides were performed. In-vivo experiments involving drug test were pending.

Results: 6 endothelia major phenotypes were identified including aerocytes, general capillary, lymphatics, arteries, immature and venous subtypes. Whether it stratified by histology subtypes or not, only immature (***) and venous (***) endothelia subtypes were significantly higher in tumor compared to matched normal lung tissues. A subtype of venous endothelia cell (VEC) was identified and defined as systemic-venous (SVs) which was highly enriched in tumor rather than normal tissue (***). SVs exhibited remarkably high expression of CD200, CD34 and MYC. Profiling of immune checkpoints confirmed high expression of CD200, VSIR and LGALS9 without CD276 and PD1/PD-L1 high expression. Function enrichment analysis also indicated SVs enriched MYC pathway and oxidative phosphorylation without inflammatory response and IFNy response compared to normal venous endothelia cells. By integrating CD31 and CD34 staining, we verified that these micro-vessels existed in precursor lung adenocarcinoma with significantly increased number in relatively late stage. Continuous staining of CD31, CD200, CD3 and CD8 further revealed highly enriched CD3+CD8+lymphocytes within CD31+CD200+endothelia hotspot area while limited CD3+CD8+lymphocytes within tumor. Cell-chat analysis also indicated highly interaction between VEC and macrophages. Specifically, a strong interaction of CD200-CD200R1 signaling between M2 macrophages and VEC was observed in tumor instead of normal lung tissues. Besides, M2 macrophages as well as tumor cells exhibited strong pro-angiogenesis through VEGFA-VEGFR1 signaling with VEC. Pseudotime analysis identified two major subsets involving immune regulation (CXCL10, ACKR1, CCL14) and stress (HSPB1, MEOX1, MYC) in SVs while immature endothelia subtype exhibited progenitor (VEGFC, PECAM1, CD93) and vascularization subtypes(VEGFR2, THY1, MMP2).

Conclusions: Distinct endothelia ecosystem has long been developed in precursor lung adenocarcinoma compared to normal lung tissue. CD200, specifically expressed in SVs, could highjack tumor infiltrating lymphocytes and interact with M2 macrophages which might be served as a potential treatment target.

Keywords: Lung adenocarcinoma, Endothelia cell, sing-cell RNA



P3.03J TUMOR BIOLOGY - TRANSLATIONAL BIOLOGY - TUMOR MICROENVIRONMENT
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P3.03J.03 Genetic Signature Derived from Single-Cell Defined Microenvironment Remodeling Correlate with Efficacy of Neoadjuvant Immunotherapy in LUSC

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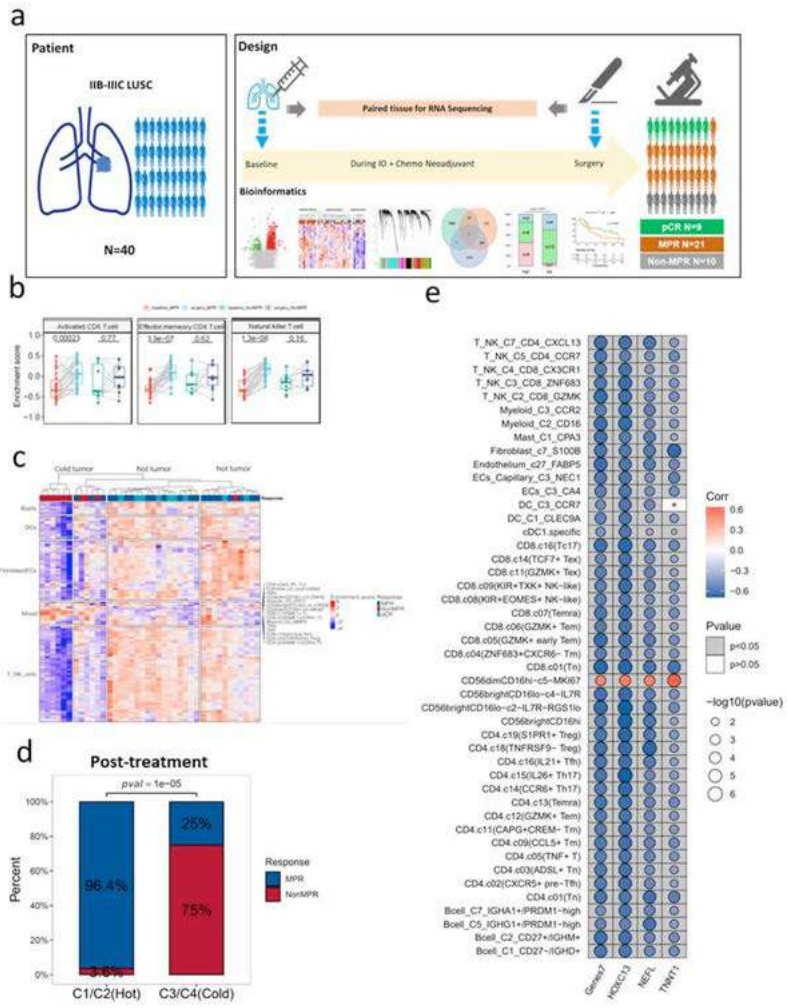
Introduction: Neoadjuvant therapy (NAT) of chemo-immunotherapy improved prognosis of LUSC patients. Treatment induced remodeling of tumor microenvironment may contribute to the therapeutic efficacy, but still largely unknown. This study aimed to disclose the dynamics of TME remodeling. And a TME remodeling genetic signature on pre-treatment sample was developed to predict response to chemo-immunotherapy.

Methods: Paired samples were collected pre- and post-NAI from 40 LUSC patients from 2019 to 2021. RNA was extracted and subjected to RNA-seq. scRNA-seq defined signatures of over 70 immune cell subtypes were curated from recent publications. ssGSEA was used to evaluate these signatures in each sample. Weighted gene co-expression network analysis (WGCNA) to identify hub genes associated TME remodeling by NAI (Fig.a).

Results: Out of 40 patients 30 achieved a major pathological response (MPR) (75%), with 9 cases (22.5%) achieving a complete pathological response (pCR). A significant increase in immune cell infiltration in patients with MPR following NAI.A significant “cold” to “hot” transition in the TME pre- and post- NAI was observed. Of note, activated CD8+ T cells (p<0.005), effector memory CD4+ T cells (p<0.005), and NK cells (p<0.005) (Fig.b), significantly increased post-treatment, a trend not observed in non-MPR patients. While Patients with ‘cold’ TME after NAI had a significantly lower proportion benefit from NAI (MPR, cold vs. hot, 25% vs. 96.4%, p<0.005) (Fig.c-d). Signature of seven genes (ASS1, HOXC13, KLK1, NEFL, FOXL2, TNNT1, and LMX1B), derived by WGCNA, represented ‘cold’ TME transition. Especially, it displayed negative correlation with infiltration of pro-inflammatory cells, like GZMK+ CD8+ effector memory T cell, GZMK+ CD4+ effector memory T cell (P<0.005) (Fig.e). Further, it also correlated with non-MPR (OR: 4.87, 95%CI: 1.61-14.73, P=0.005) and was validated to associate with dismal efficacy to immunotherapy in OAK cohort (HR=1.336, p=0.042).

Conclusions: “Hot”- “Cold” transition of TME was introduced by NAI, which may determine patients’ response and benefit in LUSC. A seven-gene signature, representing “cold” TME transition, may indicate poor therapeutic efficacy of NAI.

Keywords: Lung Squamous Cell Carcinoma, Microenvironment Remodeling, Neoadjuvant Immunotherapy



P3.03J TUMOR BIOLOGY - TRANSLATIONAL BIOLOGY - TUMOR MICROENVIRONMENT
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P3.03J.04 Single-Cell Landscape of Senescent Cells in the Lung Cancer Microenvironment Unveils Pivotal Roles of Senescent Cancer Cells

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Introduction: Aging is intricately linked to carcinogenesis, and cellular senescence, a known driver of aging, has been increasingly recognized as playing a critical role in immune editing. Evidence suggests that senescent macrophages and T cells can accelerate cancer growth and progression. However, the landscape of senescence in both normal and cancer cells, as well as the biological functions of senescent cancer cells within the tumor microenvironment, remain elusive.

Methods: Single-nucleus RNA sequencing was performed on surgically resected tissues from two normal lungs and three lung cancers across three patients. The InferCNV algorithm was employed to score each cell for the extent of copy number variation (CNV) signal. Malignant cells were identified using K-means clustering, with normal T cells and fibroblasts as references. Non-malignant cell clusters were labeled based on known canonical markers. The SenMayo gene set was utilized to calculate the senescence-associated secretory phenotype (SASP) score for each cell. The top 10% of malignant or non-malignant cells with the highest scores were recognized as senescent cells, respectively.

Results: Compared to normal lung tissues, lung cancer tissues exhibited increased infiltration of macrophages and plasma cells but reduced endothelial cell (EC) presence. In normal tissues, capillary or lymphatic ECs were the predominant subtypes, while tumor ECs maintained a consistent primary subtype across different tumors. Matrix fibroblasts were the major population in normal tissues, whereas myofibroblasts were predominant in tumors. Senescent scores based on SenMayo consistently correlated with CellAge and GeneAge, two independent senescence signatures, validating the identified senescent cells. Compared to non-senescent malignant cells, senescent malignant cells displayed higher expression of PLAUR, IL32, MMP1, AREG, ATF3, GEM, BMP2, TNFAIP2, and MMP7. Gene set enrichment analysis revealed that senescent cancer cells exhibited enrichment in cytokine-cytokine receptor interaction, IL-17 signaling pathway, TNF signaling pathway, and antigen processing and presentation. In non-malignant cells, 20-30% of arterial ECs, monocyte-derived macrophages, and inflammatory fibroblasts were senescent, with similar distribution in normal and tumor tissues. Cell-cell communication analysis demonstrated that senescent malignant cells played crucial roles in the tumor microenvironment, with enhanced communication from these cells to all other cell types.

Conclusions: Collectively, our study provides, for the first time, a comprehensive landscape of senescent cells, including both normal and cancer cells, within the tumor microenvironment of lung cancer patients at single-cell resolution, reinforcing the pivotal role of senescent cancer cells in lung cancer.

Keywords: cellular senescence, lung cancer, single nucleus RNA sequencing

P3.03J TUMOR BIOLOGY - TRANSLATIONAL BIOLOGY - TUMOR MICROENVIRONMENT
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P3.03J.05 Enhancement of Chemotherapy and Immunotherapy in LUSC Animal Models Through Tumor Microenvironment Remodeling by Losartan

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Introduction: Emerging research indicates the potential of Angiotensin Receptor Blockers (ARBs), particularly Losartan, in combating specific solid tumors. Our prior investigations, involving an analysis of the TCGA database, have established a correlation between AGTR1 expression and both Epithelial-Mesenchymal Transition (EMT) and immune-related pathways in Lung Squamous Cell Carcinoma (LUSC) patients. Preliminary in vitro studies with diverse LUSC cell lines have further revealed that a low dosage of Losartan can reduce LUSC migratory capabilities and amplify the cytotoxic effects of Cisplatin. Western blot analyses suggest Losartan's potential in suppressing EMT in tumor cells. To delve deeper into Losartan's therapeutic implications for LUSC, we have undertaken a series of animal experiments and subsequent mechanistic explorations.

Methods: For the evaluation of ARBs' anti-tumor efficacy, we established zebrafish models of LUSC and administered losartan treatment. Subsequently, we developed two distinct in vivo murine models of LUSC, which were treated with either losartan alone or in combination with chemotherapy, and chemoimmunotherapy. The underlying mechanism was investigated using Flow Cytometry and Western Blot to assess EMT and immune-related markers.

Results: Firstly, in the zebrafish tumor model experiments, we found that losartan treatment could reduce intra-tumor angiogenesis and inhibit tumor cell escape. Subsequently, in vivo drug experiments conducted in BALB/c nude mice revealed that combination therapy with losartan and cisplatin was more effective in inhibiting lung squamous cell carcinoma growth compared to cisplatin alone (P=0.0097). Finally, in vivo drug experiments in DBA/2 mice showed that combination therapy with losartan, cisplatin, and PD-1 antibody was more effective in suppressing lung squamous cell carcinoma growth compared to cisplatin combined with PD-1 antibody (P=0.0328). Flow cytometry analysis of tumor tissues and lymph nodes obtained from animal experiments revealed that losartan could ameliorate T cell exhaustion and upregulated CD8+ T cell in lymph nodes after chemoimmunotherapy (P<0.0001).

Conclusions: Our findings indicate that Losartan can bolster the effects of chemotherapy and chemoimmunotherapy in LUSC treatment. This study offers initial insights into the potential mechanisms of ARB in LUSC therapy, thereby endorsing its potential as a key component in a comprehensive therapeutic strategy for LUSC.

Keywords: Losartan, LUSC, Chemoimmunotherapy

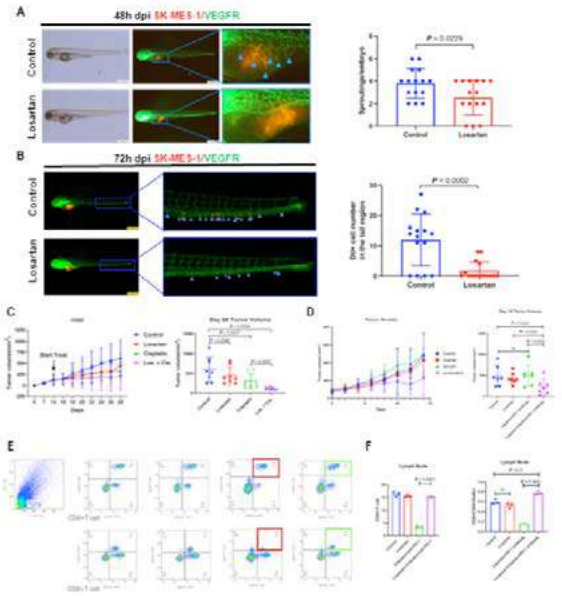

Figure: A. Impact of Losartan Treatment on Intestinal Angiogenesis in Zebrafish Embryo Tumor Model. Control (top) versus Losartan-treated (bottom) groups. T-test of intestinal vessel sprouting number shown on the right (n=15, P=0.0229). B. Impact of Losartan Treatment on Tail Vein Metastasis in Zebrafish Embryo Yolk Sac Injection Tumor Model. Control (top) versus Losartan-treated (bottom) groups. Statistical analysis of metastatic cell count in the tail region shown on the right (n=15, P=0.0002). C. Tumor Growth Curve and Tumor Volume Comparison on Day 28 of Losartan Combined with Cisplatin Therapy in Subcutaneous HS20 Mouse Tumor Model. The four groups include Control, Losartan, Cisplatin, and Losartan + Cisplatin. On Day 28, the tumor volume of the Losartan + Cisplatin group is significantly smaller compared to the Cisplatin group (t-test, n=8, P = 0.0097). D. Tumor Growth Curve and Inter-group Tumor Volume Comparison on Day 15 of Losartan Combined with Cisplatin and PD-1 Therapy in Subcutaneous KLN205 Mouse Tumor Model. The four groups include Control, Losartan, Cisplatin + PD-1, and Losartan + Cisplatin + PD-1. On Day 15, the tumor volume of the Losartan + Cisplatin + PD-1 group is significantly smaller compared to the Cisplatin + PD-1 group (t-test, n=7, P = 0.0328).E. Representative flow cytometry plots showing the immune cells within tumor-draining lymph nodes, including CD4+ T cells (CD3+, CD4+) and CD8+ T cells (CD3+, CD8+). F. Quantification of the level of CD8+ T cells, and the ratio of CD8+ T cells to CD4+ T cells by flow cytometry analysis (n=3).

P3.03J TUMOR BIOLOGY - TRANSLATIONAL BIOLOGY - TUMOR MICROENVIRONMENT
MONDAY, SEPTEMBER 9, 2024 - 12:00 - 14:00

P3.03J.06 The Co-Location of APOE+ Macrophages and MMP7+ Tumor Cells Contributed to Worse Immunotherapy Response in NSCLC

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Introduction: Intra-tumor immune infiltration is a crucial determinant affecting immunotherapy response in non-small cell lung cancer (NSCLC). However, its phenotype and related spatial structure have remained elusive.

Methods: To address these limitations, we undertook a comprehensive study comprising spatial transcriptomics (ST) data (28,712 spots from six samples).

Results: We identified two distinct intra-tumor infiltration patterns: immune exclusion (characterized by macrophages) and immune activation (characterized by plasma cells). The immune exclusion and immune activation signatures showed adverse and favorable roles in NSCLC patients' survival, respectively. Notably, APOE+ tumor-associated macrophages (TAMs) were recognized as the main cell type in immune exclusion samples, with increased epithelial-mesenchymal transition and decreased immune activities. The co-location of APOE+ TAMs and MMP7 +tumor cells was observed in both ST and bulk transcriptomics data, validated by multiplex immunofluorescence performed on twenty NSCLC samples. The co-location area exhibited the upregulation of proliferation-related pathways and hypoxia activities. This co-localization inhibited T cell infiltration and the formation of tertiary lymphoid structures. Both APOE+ TAMs and MMP7+ tumor cells were associated with worse survival. In an immunotherapy cohort from the ORIENT-3 clinical trial, NSCLC patients who responded unfavorably exhibited higher infiltration of APOE+ TAMs and MMP7+ tumor cells. Within the co-location area, the MK, SEMA3 and MIF signaling pathway was most active in cell-cell communication.

Conclusions: This study identified immune exclusion and activation patterns in NSCLC and the co-location of APOE+ TAMs and MMP7+ tumor cells as contributors to immune resistance.

Keywords: spatial transcriptomics, immunosuppression, spatial patterns

P3.06D PATHOLOGY AND BIOMARKERS - CTDNA
MONDAY, SEPTEMBER 9, 2024 - 12:00 - 14:00

P3.06D.01 Quantitative and Dynamic ctDNA as a Biomarker of Response and Survival in Treatment-Naive Patients with Advanced Lung Squamous Cancer

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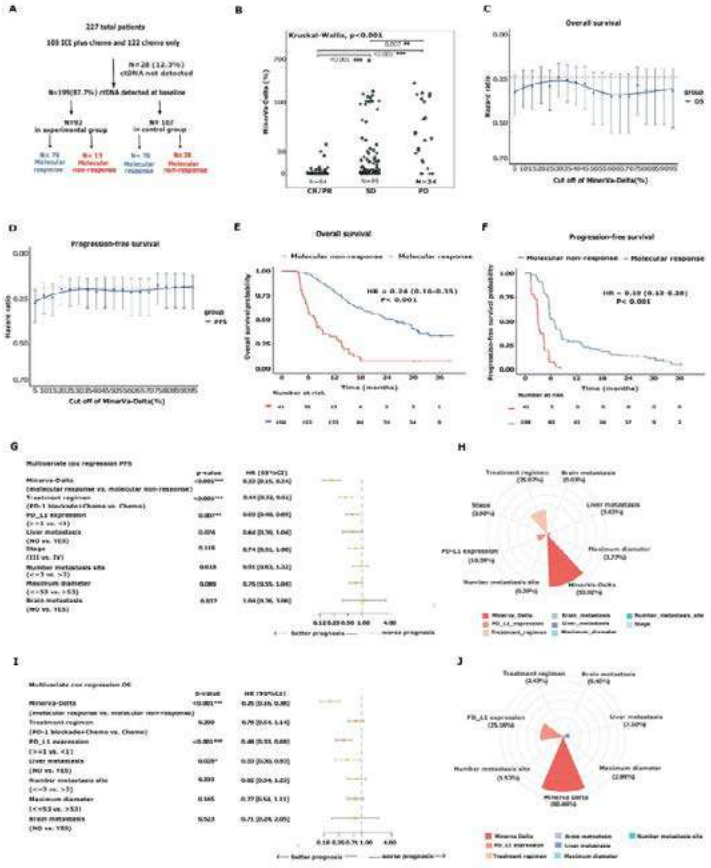
Introduction: Radiological imaging technologies have long been used to assess therapeutic response and track post-treatment outcomes in cancer patients. However, these imaging-based approaches have limitations, including inconsistency in image interpretation and technical limitations in visualizing malignancies in specific locations. Recently, circulating tumor DNA (ctDNA) has emerged as a viable tool for monitoring cancer treatment response. In this proof-of-concept study, we proposed MinerVa-Delta as a novel approach to accurately identify advanced lung squamous cell carcinoma (LUSC) patients who can benefit from first-line PD-1 blockade plus chemotherapy or chemotherapy.

Methods: This post-hoc analyses were performed in two independently conducted trials: Camel-Seq (NCT03668496) (Cohort A) and LIPUSU (NCT02996214) (Cohort B). Plasma samples were collected at two time points: pre-treatment baseline and post-treatment after 6 weeks or two cycles of treatments. MinerVa-Delta, a novel ctDNA dynamics quantification method, based on the differentially weighted sum of the ratio changes of variant allele frequencies of variants before and after treatment were developed. Variants de-novo called by a 769-gene based NGS panel in pre-treatment, serving as a basis for personalized variant tracking in post-treatment plasma. The established MinerVa-Delta model based on plasma-informed strategy was discovered from the Cohort A (discovery cohort) and was independently validated in cohort B (validation cohort).

Results: Using the MinerVa-Delta cutoff of 30%, patients with advanced LUSC receiving PD-1 blockade plus chemotherapy or chemotherapy alone were distinguishingly divided into “molecular responders” and “non-responders” groups. Patients in the molecular response group (MinerVa-Delta < 30%) exhibited significantly better PFS (HR 0.19 , 95% CI 0.13-0.28, p < 0.001) and OS (HR 0.24, 95% CI 0.16-0.35, p < 0.001) compared with those in the molecular non-response group (MinerVa-Delta ≥ 30%) (Fig 1). The results were further validated in the multivariate analysis model and in the validation cohort. More importantly, the MinerVa-Delta-defined molecular response but radiological stable disease (SD) group exhibited a significantly better PFS in comparison to molecular non-response and radiological SD group in both cohort A (HR = 0.28, p < 0.001) and cohort B (HR = 0.16, p = 0.007).

Conclusions: In summary, the current MinerVa-Delta tool provides useful insights into monitoring cancer treatment response. MinerVa-Delta effectively classified treatment-naïve LUSC patients into molecular responders and non-responders groups. More importantly, MinerVa-Delta is able to accurately identify SD patients, a heterogeneous patient population in clinic, who can benefit from the initial treatment. This makes it a valuable supplement to the current image-based RECIST classification system.

Keywords: ctDNA, PD-1 blockade plus chemotherapy, predictive and prognostic factors



P3.06D PATHOLOGY AND BIOMARKERS - CTDNA
MONDAY, SEPTEMBER 9, 2024 - 12:00 - 14:00

P3.06D.02 Dynamic ctDNA-mrd Indicates Pathological Benefits of Additional Neoadjuvant Chemoimmunotherapy Courses for Locally Advanced NSCLC

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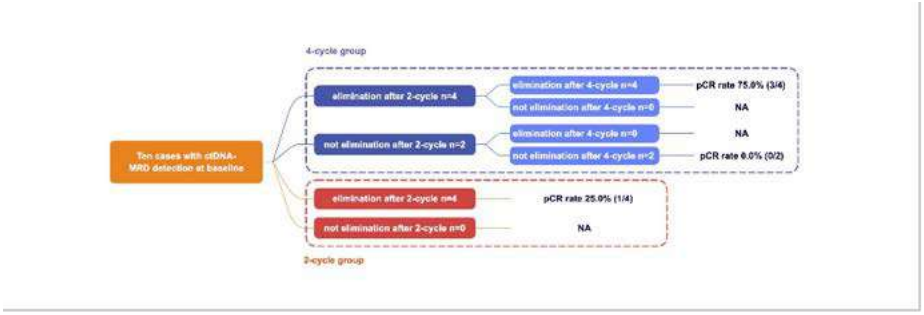
Introduction: Neoadjuvant chemoimmunotherapy (NCI) targeting the PD-1 pathway has proven effective for non-small-cell lung cancer (NSCLC). However, few studies have focused on the optimal cycles of NCI. This study introduced minimal residual disease (MRD) based on circulating tumor DNA (ctDNA), and investigated the association between ctDNA-MRD and NCI cycles and pathological response.

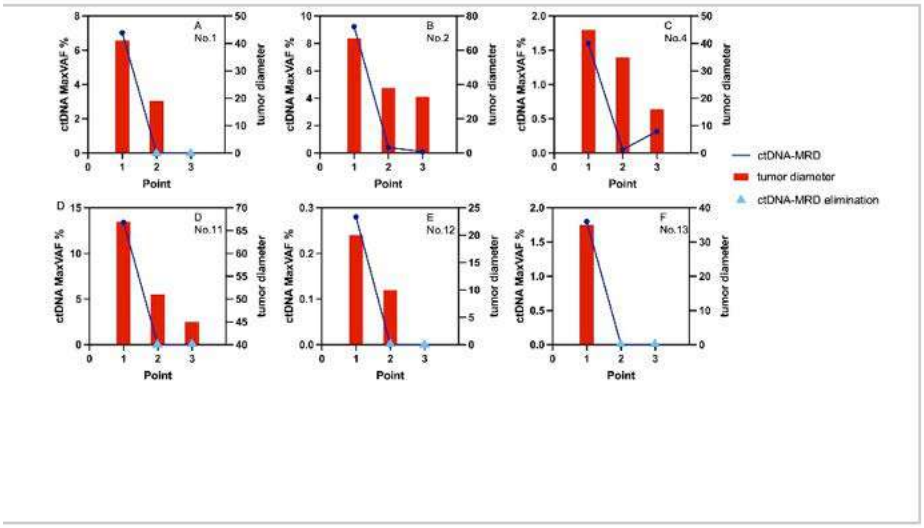
Methods: This study was based on a phase III trial (NCT05157776). The patients with IIIA NSCLC without driver genes were given two cycles of NCI (initial two-cycle NCI), after which they were 1:1 randomly assigned to the two-cycle NCI groups (no additional NCI) or four-cycle NCI group (with another two cycles of NCI). Peripheral blood was collected before each cycle and surgery for ctDNA-MRD detection via ultradeep-targeted next-generation sequencing.

Results: This study involved 13 patients. Six were in the four-cycle NCI group, and seven in the two-cycle group. At the start, ctDNA-MRD was detected in 10 patients (77%) (Figure.1). The pathologically complete response (pCR) rate was higher in the four-cycle group (3/6, 50%) than in the two-cycle group (1/7, 14.2%). Remarkably, the subgroup that achieved ctDNA-MRD elimination after two cycles and resisted elimination after additional two cycles had the highest pCR rate (3/4, 75.0%). The subgroup that did not achieve ctDNA-MRD elimination after two cycles and resisted existence after additional two cycles had the lowest pCR rate (0/2, 0%). Generally, in the four-cycle group, a strong correlation between ctDNA-MRD and radiological assessment was observed (5/6, 83.3%) (Figure.2).

Conclusions: According to the study, patients with locally advanced NSCLC who achieve ctDNA-MRD elimination after two-cycle NCI are more likely to benefit from additional two-cycle NCI, manifesting higher pCR rates.

Keywords: NSCLC, Immunotherapy, ctDNA-MRD





P3.06D PATHOLOGY AND BIOMARKERS - CTDNA
MONDAY, SEPTEMBER 9, 2024 - 12:00 - 14:00

P3.06D.03 Prognostic and Predictive ctDNA Signature for Patients on Targeted Therapy for Metastatic NSCLC: A Pathway-based Approach

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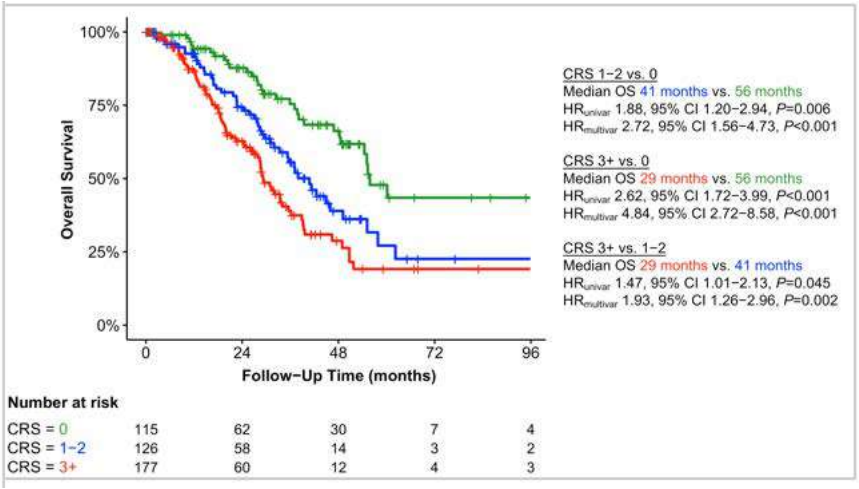
Introduction: Patients with metastatic non-small cell lung cancer (mNSCLC) harboring the same actionable genomic alterations (GAs) often display varying responses to targeted therapy. Co-occurring GAs related to growth signaling cascades, p53 co-interactions in DNA binding, and immunologic activation have been implicated. Given the vast combinatorics of GAs, we sought to develop a unifying biologic pathway-based risk score leveraging ctDNA.

Methods: From a previously reported multi-institutional cohort study of ctDNA-sequenced mNSCLC (NCT01775072), we identified genes with GAs (including non-synonymous mutations, structural variations, copy number alterations) for every patient. GAs were constructed into a ctDNA Risk Score (CRS) to reflect potential molecular pathway disturbances that lead to targeted therapy resistance: among affected genes that also belong to Gene Ontology terms for cell surface receptor signaling (GO:0007166), nucleotide binding (GO:0000166), or immune system response (GO:0006955), 2 points were accrued for every gene with a non-actionable GA and 1 point for every other gene.

Results: Between 2016 and 2020, 1127 patients enrolled in this study of whom 418 (65% female) received targeted therapy for mNSCLC (Table). On average, each unit increment of CRS was associated with shorter OS (HR 1.07, 95% CI 1.02-1.13, P=0.003). The rise in OS hazard ratio was most pronounced for CRS hikes from 0 to 1 and 2 to 3. These survival differences remained independently significant following multivariable adjustment for age, sex, ethnicity/race, smoking status, histology, presence of actionable GAs, history of prior treatment, and enrollment site (Figure). For patients without any actionable GAs, CRS was not predictive of OS (P>0.05).

Conclusions: The genomic landscape that accompanies actionable GAs in mNSCLC is crucial for outcomes inference and personalized surveillance. By leveraging ctDNA and known biologic pathway information, we developed a CRS that is both prognostic and predictive of treatment response on targeted therapy. Additional prospective external validation is warranted.

Keywords: ctDNA, Actionable mutations, Genomic landscape



	ctDNA Risk Score (CRS)	ctDNA Risk Score (CRS)	ctDNA Risk Score (CRS)	
	0 (n=115)	1-2 (n=126)	3+ (n=177)	*P-value*
Age				0.030
<70	83 (72)	97 (77)	150 (85)	
≥70	32 (28)	29 (23)	27 (15)	
Sex				0.141
Female	83 (72)	76 (60)	113 (64)	
Male	32 (28)	50 (40)	64 (36)	
Ethnicity/Race				0.068
Hispanic	2 (2)	3 (2)	5 (3)	
Non-Hispanic				
Asian	25 (22)	20 (16)	27 (15)	
Black	1 (1)	3 (2)	10 (6)	
White	45 (39)	52 (41)	93 (53)	
Other	2 (2)	2 (2)	1 (1)	
Unknown	40 (35)	46 (37)	41 (23)	
Smoking history				
Current/former	34 (30)	43 (34)	73 (41)	
Histology				0.058
Adenocarcinoma	110 (96)	118 (94)	171 (97)	
Squamous cell carcinoma	3 (3)	0 (0)	3 (2)	
Other	2 (2)	8 (6)	3 (2)	
Genes with actionable GAs*				<0.001
EGFR	38 (33)	63 (50)	111 (63)	
MET	14 (12)	22 (17)	31 (18)	
ALK	11 (10)	28 (22)	12 (7)	
ROS1	7 (6)	7 (6)	11 (6)	
HER2	5 (4)	9 (7)	23 (13)	
KRAS	3 (3)	5 (4)	30 (17)	
RET	2 (2)	5 (4)	18 (10)	
NTRK	2 (2)	7 (6)	9 (5)	
BRAF	1 (1)	4 (3)	13 (7)	
History of previous treatment				0.001
No	55 (48)	83 (66)	121 (68)	
Yes	60 (52)	43 (34)	56 (32)	
Enrollment site				0.002
New York, NY, USA	86 (75)	104 (83)	160 (90)	
Sydney, Australia	29 (25)	22 (17)	17 (10)	
*Does not sum to 100%, as some patients possess multiple actionable GAs.				

P3.06D PATHOLOGY AND BIOMARKERS - CTDNA
MONDAY, SEPTEMBER 9, 2024 - 12:00 - 14:00

P3.06D.04 Role of ctDNA Variant Allele Frequency in Predicting Response to Immune Checkpoint Inhibitors in Non-Small Cell Lung Cancer

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Introduction: The landscape of lung cancer therapy has been transformed with the advent of immune checkpoint inhibitors (ICIs). Biomarkers such as PD-L1 expression and tumor mutational burden (TMB) have been traditionally utilized to predict responses to these therapies, particularly with respect to non-small cell lung cancer (NSCLC). Recent insights suggest that the variant allele frequency (VAF) of individual mutations could serve as a predictor for the efficacy of immunotherapies in NSCLC. This study investigates the potential of using total VAF from somatic mutations in Circulating Tumor DNA (ctDNA) as a biomarker for predicting responses to ICIs in patients with NSCLC.

Methods: We conducted a retrospective analysis at a single center from January 2018 to March 2024, focusing on patients who underwent liquid biopsies. Participants included those with confirmed NSCLC at any disease stage, ascertained via tissue biopsy. Data collected included demographic information, histological subtype, PD-L1 % expression from initial tissue samples, and first-line treatments, including the use of ICIs. ctDNA was analyzed using Guardant360 reports, excluding genetic variants with a VAF greater than 40% to filter out germline mutations. The total VAF for each patient was calculated by summing the VAFs of all somatic mutations identified. Patients were then categorized into high (≥1%) and low (<1%) VAF groups. Logistic regression was used to explore the relationship between total VAF and PD-L1 % expression, while survival outcomes were analyzed using Kaplan-Meier curves and Cox proportional hazards models, adjusting for relevant clinical variables.

Results: Our cohort included 463 patients. PD-L1 % expression and VAF were reported in 350 (76.5%) and 306 (67.6%) of the cases, respectively. Regression analysis revealed a significant negative correlation between total VAF levels and PD-L1 % expression (p=0.02). No significant demographic differences were observed between the high and low VAF groups. Survival analysis was focused on patients receiving ICIs (n= 135, 29.6%). Of those, patients with high VAF (n= 73, 53.2%) had a mean VAF of 16.8%, while low VAF patients (n=31, 22.6%) had a mean VAF of 0.54%. It was found that patients with high VAF had significantly shorter overall survival compared to those with low VAF (6.16 months vs. 13.83 months, p=0.03). Furthermore, high VAF was associated with more than twice the risk of mortality (HR: 2.554, 95% CI: 1.206 to 5.408, p=0.02), according to the Cox model adjusted for smoking history, brain metastasis, histology, and ECOG performance status.

Conclusions: Our study found that higher levels of VAF in ctDNA are associated with lower levels of PD-L1 expression in tissue biopsies from patients with NSCLC. Moreover, a high VAF was correlated with a marked decrease in overall survival among patients treated with ICIs, across all stages of the disease. As liquid biopsy becomes more integrated into clinical practice, its potential for providing prognostic insights and enabling a more tailored therapeutic approach may become increasingly evident. Our findings highlight the potential role of total VAF in ctDNA as a predictive biomarker for ICI therapy outcomes in patients with NSCLC.

Keywords: liquid biopsy, PD-L1, Non-Small Cell Lung Cancer

P3.06D PATHOLOGY AND BIOMARKERS - CTDNA
MONDAY, SEPTEMBER 9, 2024 - 12:00 - 14:00

P3.06D.05 Stratifying Risk in Oligoprogressive EGFR-Mutated Non-Small Cell Lung Cancer: The Role of ctDNA

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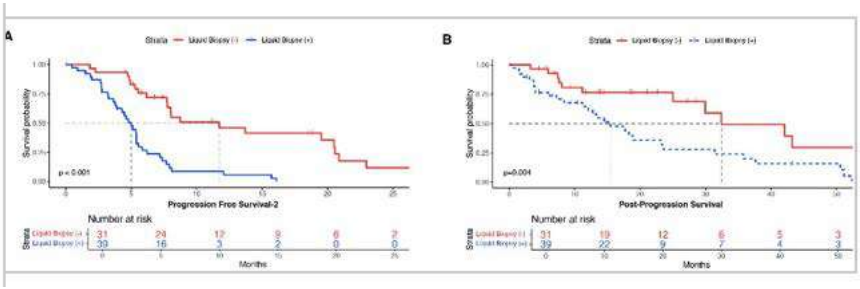
Introduction: EGFR-TKIs have markedly enhanced outcomes for non-small cell lung cancer (NSCLC) patients, but resistance development is virtually inevitable. In the context of oligoprogressive disease (OPD), local treatments can target resistant clones while EGFR-TKIs maintain systemic control, potentially extending the duration of therapy. However, a major challenge is distinguishing patients with true OPD from those with undetected micrometastatic spread using conventional imaging techniques. This distinction is crucial for identifying patients who are likely to benefit from the combined approach of local treatment and continued EGFR-TKI therapy. The present study aims to evaluate the prognostic impact of circulating tumor DNA (ctDNA) in this context.

Methods: We conducted a retrospective study (2013-2024) on advanced EGFR-NSCLC patients with OPD during first-line TKI therapy, treated with local therapy and continued TKI. Serum liquid biopsies for ctDNA EGFR mutations were performed at oligoprogression. We assessed the effect of ctDNA status on liquid biopsies and relevant clinical variables on progression-free survival-2 (PFS2), defined as the time from oligoprogression to the second disease progression or death. The effect of ctDNA on post-progression survival (PPS) was also assessed. Univariate analyses were conducted using Kaplan-Meier analysis, and multivariate analyses were performed with Cox-proportional hazard models.

Results: Among 84 patients, 70 (83%) underwent liquid biopsies at oligoprogression, with 56% testing positive for ctDNA. A positive ctDNA liquid biopsy was associated with worse PFS2 (4.99 vs. 11.73 months, p<0.001) and PPS (15.47 vs. 32.43 months; p=0.004). Stratified analysis showed that for patients with CNS oligoprogression (n=17), PFS2 did not differ based on ctDNA liquid biopsy status (4.47 vs. 4.73 months, p=0.75), while for patients with non-CNS oligoprogression (n=53), a significant difference in PFS2 was observed (5.13 vs. 13.70 months, p<0.001). In univariate analysis, shorter PFS1, CNS oligoprogression, poor performance status at oligoprogression, high carcinoembryonic antigen levels at oligoprogression, and non-SBRT radiotherapy were associated with worse PFS2. However, multivariate analysis identified positive ctDNA liquid biopsy status as the only independent factor associated with PFS2 (HR 3.57; 95% CI 1.68-7.59, p=0.001).

Conclusions: Detectable ctDNA is a significant prognostic marker in extracranial EGFR-oligoprogressive NSCLC, suggesting its potential in identifying patients who may benefit from continued TKI and local therapies. Further prospective studies are warranted to confirm these findings and explore alternative treatment strategies for OPD.

Keywords: Oligoprogression, Liquid Biopsy, EGFR



P3.06D PATHOLOGY AND BIOMARKERS - CTDNA
MONDAY, SEPTEMBER 9, 2024 - 12:00 - 14:00

P3.06D.06 Incremental Value of Liquid Biopsy in the Initial Evaluation of Non-Small Cell Lung Cancer Patients Undergoing Tissue Based Molecular Testing

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Introduction: Actionable genetic alterations (AGAs) are identified in 45% of patients with non-squamous metastatic non-small cell lung cancer (mNSCLC). Guidelines support the use of concurrent tissue (T) and plasma (P) -based next-generation sequencing (NGS) at initial diagnosis. This approach is associated with an improved sensitivity in detecting AGAs compared to either molecular profiling approach alone. However, the incremental value of P NGS in patients who have tissue analyzed for NGS testing has not been determined.

Methods: Patients in a single hospital system with newly diagnosed mNSCLC who underwent concurrent T+P NGS upon initial diagnosis were included in an IRB approved protocol. Patients with discordant results in AGAs between T+P NGS were reviewed. Patients with mutations detected in P alone were categorized into three groups with respect to T status; i.) true tissue negative (relevant tissue panels were completed, but the gene was missed by T testing), ii.) inadequate panel (limited T NGS panel ordered) and iii.) incomplete test (≥1 components of the T NGS panel not completed due to insufficient tissue).

Results: Of 552 patients evaluated between 01/01/19 and 03/31/22, 416 (75.4%) had orders placed for concurrent T+P NGS; 58 (13.9%) had inadequate tissue for T NGS and were excluded. The remaining 358 (86.1%) patients underwent T+P NGS, with 173 (48.3%) AGAs detected. 113 (65.3%) alterations were concordant in T+P NGS, 42 (24.3%) were identified in T NGS alone, and 18 (10.4%) were observed in P alone. Amongst patients with AGAs in P NGS only, most were female 61% (11/18), current or former smokers 66% (12/18), and ECOG PS <2 75% (14/18). P alone NGS alterations were identified across all actionable markers. 28% (5/18) of the cases were true tissue negative, 22% (4/18) had an inadequate T NGS panel, and 50% (9/18) had an incomplete test performed. 44% (8/18) of patients with alterations detected in P NGS alone received first-line targeted therapy.

Conclusions: Concurrent T+P NGS is included in current guidelines for molecular testing in advanced NSCLC and has been shown to improve overall detection rates of AGAs. We demonstrated that even amongst patients who undergo concurrent T testing, P NGS can improve AGA detection rates, compensating in part for inadequate or suboptimal tissue assays and thereby enhancing the comprehensiveness of molecular profiling. Our study demonstrates the benefit of P NGS for all patients with non-squamous mNSCLC, reinforcing the importance of concurrent T+P NGS testing at initial diagnosis.

Keywords: ctDNA, NSCLC, targeted therapy

Age	Gender	Race	ECOG PS	Smoking Hx	Type of Alteration	Gene Involved	Therapy Received	T-NGS Panel	Reason for Discrepancy	Targeted Tx
47	M	Black	0	Never	Insertion	ErbB2	Chemo+IO	DNA+FISH	True Tissue Negative	No
74	F	White	1	Current	Fusion	ALK	Targeted	DNA+RNA	True Tissue Negative	Yes
63	F	White	4	Former	Point	KRAS	Deceased	RNA	Inadequate Panel	No
58	M	Black	3	Current	Deletion	EGFR	Targeted	RNA+FISH	Incomplete Testing	Yes
68	F	Black	1	Former	Insertion	EGFR Exon 20	Chemo	RNA+FISH	True Tissue Negative	No
88	M	White	2	Former	Splice Site	MET Exon 14	Chemo	DNA	Incomplete Testing	No
68	M	White	1	Never	Fusion	ALK	Targeted	DNA	Incomplete Testing	Yes
62	M	Asian	0	Never	Deletion	EGFR	Targeted	DNA	Incomplete Testing	Yes
60	F	Unknown	1	Never	Fusion	RET	Targeted	DNA+FISH	Incomplete Testing	Yes
78	M	White	0	Former	Insertion	ErbB2	Chemo+IO	DNA+RNA+FISH	Incomplete Testing	No
79	F	White	1	Former	Insertion	ErbB2	IO	DNA+FISH	Inadequate Panel	No
59	F	White	0	Former	Splice Site	MET Exon 14	Targeted	DNA+RNA	True Tissue Negative	Yes
60	F	White	1	Current	Point	KRAS	Chemo+IO	RNA	Incomplete Testing	No
61	F	Black	0	Current	Point	KRAS	Chemo+IO	RNA	Incomplete Testing	No
78	F	White	3	Never	Point	BRAF	Targeted	DNA+FISH	Inadequate Panel	Yes
44	M	Asian	0	Former	Deletion	EGFR	Targeted	FISH	Inadequate Panel	Yes
66	F	Unknown	0	Never	Insertion	EGFR Exon 20	Chemo+IO	DNA+RNA+FISH	True Tissue Negative	No
62	F	White	1	Former	Insertion	ErbB2	Chemo+IO	DNA+FISH	Incomplete Testing	No

P3.06D PATHOLOGY AND BIOMARKERS - CTDNA
MONDAY, SEPTEMBER 9, 2024 - 12:00 - 14:00

P3.06D.07 Liquid Biopsy: Exploration of its Added Value in a Daily Practice

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Introduction: Non-small-cell lung cancer (NSCLC) is frequently driven by genetic mutations identified through next-generation sequencing (NGS) performed on tissue biopsies. Technological advancements enabled performing NGS on plasma circulating tumor DNA (ctDNA), offering viable alternative when tissue sampling is challenging and potentially reducing turnaround time (doi: 10.3390/cancers12041009; doi: 10.1158/1078-0432.CCR-19-0624).

We explored concordance between blood ctDNA NGS results and tissue NGS. We compared their respective turnaround times, evaluating efficiency and reliability of blood based NGS in the management of NSCLC.

Methods: Patients were recruited prospectively at the oncology service of the Geneva University Hospitals. All included patients had histological confirmation of metastatic NSCLC. NGS (hybrid capture custom panel) on tissue sample and liquid biopsy (FoundationOne®, LBx) were performed. Comparison and concordance between the two tests and their turnaround time were evaluated.

Results: We analyzed data from 37 patients, of which 26 were eligible. Tissue sample was not obtained in 3 patients. Liquid biopsy was not performed in one. Another patient was diagnosed with small cell lung cancer. The 6 other non-eligible patients only had limited molecular analysis performed on tissue sample (no NGS).

Mean concordance between tissue sample and LBx was 51% (range: 0-100%). LBx enabled changing treatment in 2 patients. The first was treated with BRAF-MEK inhibitors after finding BRAF V600E mutation in plasma only. No clinical response was observed, raising the question of whether this might have been just a subclonal mutation. The second had an exon 20 EGFR point mutation detected in the tissue, while LBx revealed concomitant L858R and exon 20 EGFR point mutations, enabling osimertinib treatment. One patient's tissue biopsy revealed an ALK translocation that was missed by LBx.

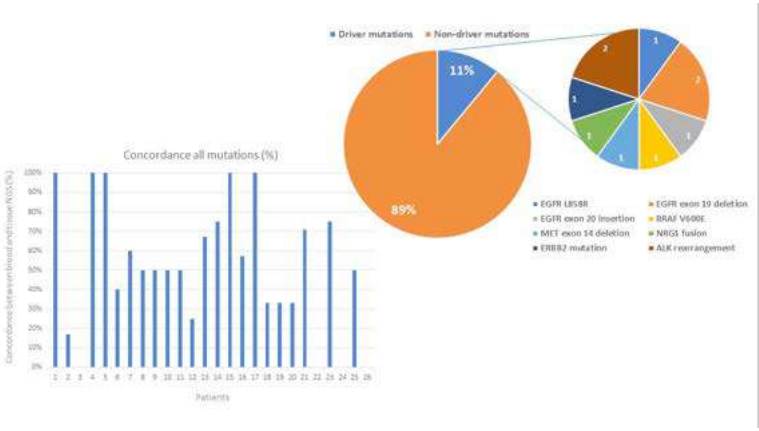
Turnaround time was quicker for tissue biopsy in 54% of cases, but median days was 13 for both (range LBx 10-26 and tissue 4-24).

62 likely pathogenic or pathogenic variants were identified in the tissue, and 76 in the LBx (excluding clonal hematopoiesis of indeterminate potential). 7 out of 10 driver mutations were identified in both samples.

Liquid biopsy was inconclusive in 3 patients.

Conclusions: LBx identified two driver mutations missed on tissue biopsy, enabling these patients to receive tyrosine kinase inhibitors as part of their treatment. One of them did not show any clinical benefit from BRAF-MEK inhibitors, suggesting a possible subclonal mutation. LBx failed to detect an ALK translocation, revealed only by tissue analysis. Turnaround time was similar between the two tests (median 13 days, range 4-26).

Keywords: Liquid biopsy, NGS, NSCLC



P3.06D PATHOLOGY AND BIOMARKERS - CTDNA
MONDAY, SEPTEMBER 9, 2024 - 12:00 - 14:00

P3.06D.08 ctDNA-NGS Assay (Liquid Biopsy) for Non-Small Cell Lung Cancer: Utility of Plasma Cell-Free DNA and Tissue NGS in Detecting Genetic Mutations

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Introduction: Liquid biopsy, specifically analyzing plasma cell-free nucleic acids, has emerged as a promising approach for NSCLC diagnosis and monitoring, particularly in advanced stages. This method enhances cancer diagnostics by enabling the assessment of tumor genetics and actionable biomarkers through a minimally invasive procedure that involves collecting peripheral blood for circulating tumor DNA (ctDNA) analysis. This is complementary to traditional tissue biopsies by allowing a comprehensive evaluation of tumor genetics, providing valuable insights into the molecular profile of NSCLC tumors enabling precision medicine with targeted therapies.

Methods: This is a prospective cohort study focused on the collection of ctDNA from patients suspected to have advanced NSCLC based on radiologic imaging. The blood samples were collected prior to any tissue obtaining procedure, ensuring a comprehensive analysis. The ctDNA was analyzed using the Oncomine Pan-Cancer Cell-Free Assay. The study was conducted at the Peter Brojde Lung Cancer Centre and received support from the McGill Rossy Cancer Network

Results: 73 ctDNA were obtained, with 61 analyzed. 51 cases were NSCLC, 4 SCLC, 1 mesothelioma and 5 hematologic malignancies. Mutation were found in 32/51 NSCLC, with 17/32 being targetable. EGFR (47%) and KRAS p.G12C (35%) were the most frequently observed, accounting for a significant portion of the targeted mutations identified. Other rare and non-targetable mutations are presented in the table. The study identified TP53 mutation in all 4 SCLC , indicating the potential utility of liquid biopsy across different lung cancer subtypes. This finding underscores the value of liquid biopsy in capturing genetic information from various tumor types, guiding treatment decisions across the lung cancer spectrum. The concordance between the ctDNA-NGS assay and standard of care (SOC) methods for detecting actionable mutations showed relatively high agreement rates for EGFR and KRAS G12C, 80% and 85% respectively. Discordances attributed to heterogeneity that is not captured in tissue, as well as low ctDNA shedding. The study also revealed 9 inconclusive results due to low amounts of ctDNA.

Conclusions: ctDNA represents a valuable tool in NSCLC management. Its potential benefits include early detection, personalized treatment strategies based on tumor genetics, and minimally invasive sample collection, which reduces patient discomfort and risk compared to traditional tissue biopsies. Ongoing improvements in technology and methodology, may help address challenges related to sensitivity detection limitations. By being complementary or when tissue is not available, liquid biopsy has great potential in lung cancer management, ultimately improving patient outcomes and treatment efficacy.

Keywords: ctDNA, mutations, NSCLC

Mutations	Targetable n(%)	Non-targetable n(%)
EGFR	8 (47.1)	
KRAS	6 (35.2)	4 (26.6)
BRAF	1 (5.9)	1 (6.7)
ERBB2	1 (5.9)	
MET ex 14	1 (5.9)	
FGFR4		1 (6.7)
GNAS		2 (13.3)
RET		1 (6.7)
MAP2K1		1 (6.7)
TP53		5 (33.3)

P3.06D PATHOLOGY AND BIOMARKERS - CTDNA
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P3.06D.09 Reciprocal DNA Fusions and their Association with DNA Damage Response Genes in Patients with NSCLC Through cfDNA NGS

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Introduction: Patients (pts) with non-small cell lung cancer (NSCLC) harboring activating gene rearrangements of ALK, ROS1, or RET derive clinical benefit from targeted tyrosine kinase inhibitors (TKIs). Assessment of gene rearrangements can be conducted by many methods, including next-generation sequencing (NGS) of tumor tissue or cell-free DNA (cfDNA). The most common driver rearrangement in NSCLC is EML4-ALK. However, reciprocal fusions, such as ALK-EML4, also occur and may be detected by NGS. We explored the genomic profiles of lung tumours that shed activating and/or reciprocal gene rearrangements into plasma and the prevalence of co-mutations in genes associated with DNA damage repair (DDR).

Methods: NSCLC pts with a cfDNA NGS report (Guardant360) from October 2016 to September 2022 indicating the presence of a gene rearrangement (involving ALK, RET, or ROS1) were categorized by the type of rearrangement detected: activating, reciprocal, or both. The presence of co-mutations in genes associated with DDR (TP53, BRCA1, BRCA2, ATM, ARID1A and MLH1) was assessed within each category.

Results: We analyzed a cohort of 2,385 patients with advanced-stage NSCLC, as described in Table 1. Among the entire patient population, 72% exhibited solely activating rearrangements, while 6% displayed exclusively reciprocal rearrangements, and 23% had both types concurrently. ALK rearrangements were identified in 63.4% of the patient subset, with 75.5% exclusively displaying activating rearrangements, 5.4% showing solely reciprocal rearrangements, and 19.1% presenting both. RET rearrangements were observed in 25.3% of patients, among whom 61.9% had activating rearrangements only, 4.3% exhibited solely reciprocal rearrangements, and 33.8% displayed both types. ROS1 rearrangement occurred in 11.3% of cases, with 71.8% exhibiting activating rearrangements exclusively, 9.3% showing only reciprocal rearrangements, and 18.9% displaying both activating and reciprocal rearrangements concurrently. In the analysis of co-mutations involving rearrangement subtypes and genes associated with DDR, we have observed that co-mutations in ALK rearrangements occurred at consistent frequencies regardless of the rearrangement subtype. Conversely, when considering RET or ROS1 rearrangements, variations are apparent in co-mutations involving TP53, ATM, and ARID1A between reciprocal-only and activating (with or without reciprocal) rearrangements.

Conclusions: In advanced NSCLC patients with gene rearrangements identified through cfDNA NGS, 6% exhibited only the reciprocal fusion. Notably, individuals with exclusive reciprocal rearrangements of RET or ROS1 might be less prone to co-mutations in TP53, ATM, and ARID1A, than are those with detectable activating rearrangements. This emphasizes the significance of evaluating co-mutations in DNA repair genes alongside fusions to refine treatment approaches.

Keywords: Reciprocal rearrangements, NSCLC, ALK, RET, ROS1

Table 1. Demographics and co-mutations prevalence of DNA damage repair genes on kinases fusions.

Rearrangement cohorts	ALK (n=1512)			RET (n=603)			ROS1 (n=270)		
	Activating	Reciprocal	Both	Activating	Reciprocal	Both	Activating	Reciprocal	Both
Cases	1142 (76%)	82 (5%)	288 (19%)	373 (62%)	26 (4%)	204 (34%)	194 (72%)	25 (9%)	51 (19%)
Median age (range), years	60 (16-94)	60 (19-87)	60 (19-92)	63 (23-94)	64 (31-88)	60 (22-94)	57 (23-89)	61 (22-76)	53 (27-78)
Sex, n (%)									
Male	487 (42.64%)	34 (41.46%)	133 (46.18%)	156 (41.82%)	12 (46.15%)	81 (39.71%)	81 (41.74%)	11 (44.00%)	15 (29.41%)
Female	655 (57.36%)	48 (58.54%)	155 (53.82%)	217 (58.18%)	14 (53.85%)	123 (60.29%)	113 (58.25%)	14 (56.00%)	36 (70.59%)
Histology, n(%)									
ADC	1021 (89.4%)	74 (90.2%)	261 (90.62%)	331 (88.74%)	22 (84.62%)	175 (85.78%)	169 (87.11%)	20 (80.00%)	42 (82.36%)
SCC	19 (1.66%)	1 (1.22%)	4 (1.39%)	6 (1.61%)	0 (0%)	3 (1.48%)	3 (1.55%)	2 (8.00%)	2 (3.92%)
ASC	2 (0.18%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (1.03%)	(0%) 0	0 (0%)
LCC	11 (0.96%)	1 (1.22%)	3 (1.04%)	5 (1.34%)	0 (0%)	2 (0.98%)	2 (1.03%)	(0%) 0	0 (0%)
NSCLC	71 (6.22%)	5 (6.10%)	15 (5.21%)	25 (6.70%)	4 (15.38%)	22 (10.78%)	16 (8.25%)	3 (12.00%)	6 (11.76%)
Unknown	18 (1.58%)	1 (1.22%)	5 (1.74%)	6 (1.61%)	0 (0%)	2 (0.98%)	2 (1.03%)	0 (0%)	1 (1.96%)
DNA Damage Repair Related Genes co-mutations (%)									
TP53	523 (45.8%)	41 (50.0%)	156 (54.2%)	228 (61.1%)	11 (42.3%)	106 (52.0%)	100 (51.5%)	17 (68.0%)	27 (52.9%)
ARID1A	83 (7.3%)	9 (11.0%)	23 (8.0%)	36 (9.7%)	1 (3.8%)	22 (10.8%)	23 (11.9%)	(0.0%)	8 (15.7%)
ATM	95 (8.3%)	9 (11.0%)	33 (11.5%)	45 (12.1%)	4 (15.4%)	17 (8.3%)	21 (10.8%)	5 (20.0%)	7 (13.7%)
BRCA1	46 (4.0%)	3 (3.7%)	18 (6.3%)	16 (4.3%)	2 (7.7%)	10 (4.9%)	16 (8.2%)	1 (4.0%)	4 (7.8%)
BRCA2	67 (5.9%)	8 (9.8%)	20 (6.9%)	19 (5.1%)	2 (7.7%)	12 (5.9%)	16 (8.2%)	(0.0%)	5 (9.8%)
MLH1	1 (0.1%)	1 (1.2%)	3 (1.0%)	1 (0.3%)	(0.0%)	1 (0.5%)	(0.0%)	(0.0%)	(0.0%)

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P3.06D.10 Concordance of Liquid Biopsy and Tissue Biopsy for the Detection of EGFR Mutation in Stage III NSCLC in the United States

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Introduction: Molecular profiling is empirical in NSCLC to guide appropriate treatment selection. Although tissue sampling remains the gold standard approach for detection of oncogenic driver mutations, there are innate limitations associated with tissue biopsy (TBx). Liquid biopsy (LBx) could offer a practical alternative for investigation of tumor-derived somatic mutations. Clinical application of LBx is established for metastatic NSCLC with guidelines recommending combination of tissue and plasma testing concurrently or in sequence. Nonetheless, the clinical utility of LBx in stage III NSCLC remains unclear. We present the findings on the concordance rate between LBx and TBx and the effectiveness of LBx to detect EGFR mutations in stage III NSCLC.

Methods: This retrospective study of Flatiron EDM database included adult patients (aged ≥18 years) diagnosed with stage III NSCLC between January 2017 and August 2023 with receipt of both LBx and TBx for detection of EGFR mutations in the United States. Patients must have received LBx and TBx between stage III diagnosis date and date of metastasis (if patient metastasized) with no missing EGFR test results to be eligible for inclusion. Descriptive statistics were used to summarize the study outcomes including concordance rate and performance of LBx against TBx.

Results: A total of 425 patients were included in the study. Median age was 67 years; 51% were males, 83% were current/former smokers, 69% had adenocarcinoma, and 43% had stage IIIA, while 41% and 9% had stage IIIB and IIIC NSCLC, respectively. Tumor PD-L1 expression was negative (<1%), low (1-49%), high (≥50%), and unknown in 37%, 33%, 20%, and 11% of patients, respectively. A total of 494 LBx and 499 TBx tests were performed. LBx was performed using next generation sequencing (NGS) method (74%), real-time polymerase chain reaction (RT-PCR) method (23%), and other methods (3%). TBx testing was performed using NGS (67%), RT-PCR (5%), and other methods (29%). Concordance rate between LBx and TBx was 93.0% (95% confidence interval [CI]: 90.6-94.9). The sensitivity and specificity of LBx were 45.3% (95% CI: 31.6-59.6) and 97.7% (95% CI: 96.1-98.8), respectively. PPV and NPV of LBx were 66.7% (95% CI: 49.0-81.4) and 94.7% (95% CI: 92.5-96.4), respectively. In the analysis limited to LBx NGS versus TBx NGS, the concordance rate was 94.1%. Furthermore, NGS performed in patients diagnosed between 2020 and 2023 had numerically higher concordance rates (95.7%) relative to NGS performed in patients diagnosed between 2017 and 2019 (90.6%). In other subgroups, numerically higher concordance rates were observed in patients with unresectable stage III NSCLC (98.1%) versus patients not classified as having unresectable stage III NSCLC (91.0%); stage III B/C (95.7%) versus stage IIIA (90.2%); PD-L1 high (98.2%) versus PD-L1 negative (90.7%) and PD-L1 low (95.8%); and LBx performed prior to initiation of chemotherapy (97.3%) versus after initiation of chemotherapy (95.3%).

Conclusions: Our findings suggest LBx could be an additional tool for detection of EGFR mutations in stage III NSCLC. However, negative LBx results should be considered inconclusive due to lower sensitivity. Further work to confirm specificity in EGFRm patients is warranted.

P3.06D PATHOLOGY AND BIOMARKERS - CTDNA
MONDAY, SEPTEMBER 9, 2024 - 12:00 - 14:00

P3.06D.11 Faster Treatment Decision-Making Using Liquid Biopsies NGS in Non-Small Cell Lung Cancer

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Introduction: Recent advancements in identifying key molecular markers have revolutionized non-small cell lung cancer (NSCLC) treatment with therapies boosting survival rates for patients with targetable mutations. The introduction of Next Generation Sequencing (NGS) into clinical practice has provided methods to examine the genetic profile of the tumor and identify possible targets for treatment. Traditionally, tissue biopsies have been the benchmark for tumor profiling despite being invasive; yet, plasma-based "liquid biopsies" have emerged as a faster and less invasive means to evaluate circulating tumor DNA. This technology has challenged prior paradigms and optimized treatment decisions with demonstrated improvements in patient outcomes, particularly as part of a comprehensive testing paradigm with tissue biopsy. This study evaluated a real-world, community cohort of NSCLC patients tested with both tissue and liquid biopsies done at the same time to examine testing features related to treatment decision-making, initiation, and outcomes.

Methods: This was a retrospective review of adults with advanced NSCLC treated at Memorial Cancer Institute with both a tissue and liquid NGS ordered between July 1, 2015 to December 31, 2022. We analyzed demographics, clinical features, and qualities of each biopsy, including biopsy turnaround time (TAT), time to treatment decision (TtT), frequencies of on-label alteration detection, and outcomes (progression free survival (PFS) and overall survival (OS). TAT and TtT were analyzed with unpaired t-tests. Descriptive statistics for outcomes were conducted via a Log Rank (Mantel-Cox) test. The choice of NGS used for treatment decision was conducted based on available sample report, i.e., sample failed due to 'quality not sufficient' (QNS)), presence of on-label alterations, and TAT.

Results: The study cohort (N=331 NSCLC patients) predominantly consisted of white (79.5%), non-Hispanic (65.65), women (53.8%) with a median diagnosis age of 65 who were largely former smokers (65.3%) and diagnosed with adenocarcinoma (89.7%). Liquid biopsy NGS demonstrated a significant 12-day advantage in TAT vs. tissue biopsy with a median of 8 versus 20 days ($p<0.0001$). On-label alterations were detected in both biopsies with concordance >96% across genes. Liquid biopsy NGS also demonstrated a significantly faster TtT than tissue biopsy in patients with any treatment (24 vs. 34 days $p=0.0003$) and specifically with targeted therapy (18 vs. 36 days $p= 0.0007$). Of note, 13.6% of tissue samples were not reported due to QNS, while all liquid biopsy samples reported. In this cohort, 80.5% of samples used a liquid biopsy NGS for treatment decision. In comparing outcomes, there were no statistical differences in PFS or OS depending on type of biopsy NGS used for treatment decision ($p\geq0.67$).

Conclusions: This study demonstrates the utility of NGS liquid biopsy to support comprehensive genomic profiling in a community based, real-world cohort. Liquid biopsy demonstrated faster TAT, TtT, and sample success as compared to tissue biopsy, while demonstrating high concordance and similar outcomes (OS and PFS). This data supports liquid biopsy alongside tissue biopsy to streamline diagnostic processes and enhance the practice of precision medicine in patients with advanced NSCLC.

Keywords: liquid biopsy, NGS, Targeted Therapy

P3.06D PATHOLOGY AND BIOMARKERS - CTDNA
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P3.06D.12 Racial Differences in ALK Gene Alterations Detected by Tissue and Liquid Biopsy Across Patients with Lung Cancer.

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Introduction: Racial and ethnic differences in incidence are well-reported in lung cancer associated with Tobacco smoking. ALK gene alterations as driver genetic alterations occur in 2-4% of lung cancer patients. Racial differences in ALK gene-altered lung cancer are not well defined. The objective of this study was to assess the frequency and type of ALK alterations observed in lung cancers across races.

Methods: Patients with a primary lung cancer diagnosis (histology and stage agnostic) that underwent testing with the Tempus xT/xR (tissue) or xF (liquid biopsy) assays (n=27,991) and had a confirmed pathogenic ALK gene alteration (SNVs, CNAs, or fusions) were retrospectively identified within the Tempus database (n=377). Race was determined based on abstracted clinical records, and patients were stratified as either white, Black or African American (BAA), Asian Pacific Islander (API), unknown or other. Somatic pathogenic co-mutations were compared across races using Chi-squared/Fisher's Exact tests with FDR correction.

Results: Among tissue-tested lung cancer patients (n=17,482), ALK alterations occurred in 1.4% (n=135) white, 1% (n=13) BAA, 3.4% (n=15) API, 3.1% (n=16) other, and 2% (n=108) unknown, which differed across race (p<0.001). The most common ALK alterations were fusions, as detected by DNA or RNA-seq, which also differed across race (p<0.001), with the lowest frequency in BAA patients (0.9%, n=12). EML4-ALK fusions were most common, occurring in 86% (n=116) of white patients with an ALK alteration, 62% (n=8) BAA, 87% (n=13) API, 100% (n=16) other, and 93% (n=100) unknown race (p=0.013). Atypical gene fusion partners ACYP2, RMND5A, BABAM2, MYT1L, and TPR were observed only in BAA, and SOS1, KLC, NPM1, PRKAR1A were observed only in white patients. Interestingly, a subset of patients with ALK fusions also harbored ALK amplifications (n=28), SNVs (n=11), or both (n=2). Similar results were observed in the smaller cohort of patients harboring ALK gene alterations as detected by liquid biopsy (n=90). There were no significant differences in co-mutated genes across races in ALK-altered tumors, including TP53, CDKN2A, or SETD, as detected by liquid or tissue testing.

Conclusions: In this large cohort of lung cancer patients, ALK fusions were more commonly observed in API and "other" groups compared to white or BAA patients, with the lowest frequency in BAA. Some atypical fusion partners were observed in white and BAA that were not observed in other races. These data emphasize the importance of testing lung cancer patients with assays that allow for unbiased fusion detection and identification of novel fusion partners across racially diverse populations to better understand racial and ethnic differences in ALK-rearranged lung cancers.

Keywords: Racial Differences, ALK Gene Alterations, co-mutations

P3.06D PATHOLOGY AND BIOMARKERS - CTDNA
MONDAY, SEPTEMBER 9, 2024 - 12:00 - 14:00

P3.06D.13 Patterns of Tissue NGS Alterations are Associated with ctDNA Shedding in Non Small Cell Lung Cancer Tumors Harboring EGFR Mutations

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Introduction: The presence ctDNA at baseline in Non Small Cell Lung Cancer (NSCLC) tumors harboring EGFR mutations is a negative prognostic factor. While it is already known that ctDNA is associated with disease burden, low Performance Status and brain metastasis, it is still unknown if it is associated with particular molecular alterations in the tumor.

Methods: We reviewed all patients with NSCLC and EGFR exon 19 or 21 mutations treated at University of Chicago from 2011 to 2022 for whom Next-Generation Sequencing (NGS) both on tissue and liquid biopsy was available. NGS on tissue samples was performed using Oncoplus, an in-house panel targeting 168 genes, while liquid biopsy was performed with Guardant360 assay. ctDNA shedders were defined as having an identical EGFR mutation identified both on tissue biopsy and liquid biopsy sequencing. Differences among predefined groups of mutations on tissue and shedding were evaluated with $\chi 2$ test for heterogeneity and test for trend when appropriate and by means of multivariate logistical model.

Results: We analyzed 84 patients with EGFR exon 19 or 21 mutations treated with EGFR tyrosine kinase inhibitors (TKI). Results are described in Table1. Median age at diagnosis was 66 and 64 years for ctDNA shedders and non-shedders respectively. Females were 86% (n= 18) in the non-shedders' cohort and 70% (n= 44) in the shedders'- of the latter, two of them did not have available genomic data beyond EGFR mutations. 51 (61%) patients had metastatic disease at diagnosis, of which 42 (82%) were shedders.The multivariate analysis controlled for stage (early vs. metastatic) showed an association between ctDNA shedding and specific groups of co-mutations (p value for heterogeneity= 0.048) and with the increasing number of additional gene mutations (p value for trend = 0.056).

Conclusions: These are the first data showing that ctDNA at baseline is associated with a specific pattern of mutations found on tissue NGS. This suggests that ctDNA shedding might be associated with some underlying tumor biology, reflective of a more aggressive phenotype. Given the small sample size, validation using a larger cohort should be performed.

Keywords: Non Small Cell Lung Cancer, ctDNA, EGFR

	Shedders (n=63)	Non-Shedders (n=21)	R/R
Combination of significant mutations			
EGFR alone	6 (7.4%)	3 (3.7%)	2.0
EGFR + p53 +/- mutations other than RB1	35 (43.2%)	10 (12.4%)	3.5
EGFR + p53 + RB1	10 (12.3%)	0 (0.0%)	Not Applicable
EGFR + mutations other than p53	9 (11.1%)	8 (9.9%)	1.1
EGFR + Not Available	3	0	
Number of EGFR + Additional Gene Mutations			
EGFR + 0 mutations	5 (6.2%)	3 (3.7%)	1.7
EGFR + 1-5 mutations	36 (44.4%)	16 (19.8%)	2.2
EGFR + >5 mutations	19 (23.3%)	2 (2.5%)	9.3
EGFR + Not Available	3	0	

P3.06D PATHOLOGY AND BIOMARKERS - CTDNA
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P3.06D.14 Liquid Biopsy-Based Single T-Cell Dynamic Polyfunctionality Profiling as a NSCLC Immunotherapy Biomarker

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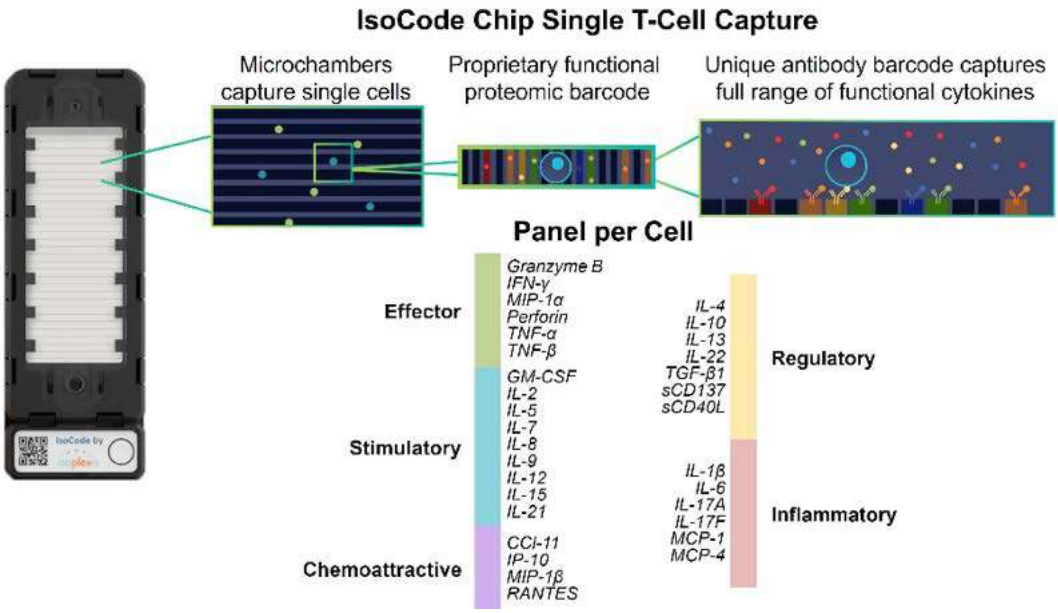
Introduction: Predictive biomarkers for immune checkpoint inhibitors (ICI), such as PD-L1 expression tumor proportional score (TPS), remain limited in clinical applications in NSCLC immunotherapy. Improved novel ICI predictive biomarkers are urgently needed. Currently available NSCLC ICI predictive biomarkers require invasive tumor biopsy procedures to obtain the tissues for testing and are practically challenging to follow longitudinally on ICI treatment course. Importantly, the clinical utility of tissue-based PD-L1 tumor proportion score also becomes diluted when the ICI is combined with cytotoxic chemotherapies.

Methods: We evaluated a novel live single-cell functional liquid biopsy cytokine profiling platform to track ICI treatment response and clinical outcomes. Peripheral blood mononuclear cell samples of healthy donors and NSCLC patients undergoing ICI-based therapies were collected longitudinally pre-/post-treatment under IRB-approved protocols. Samples were enriched for CD4+ and CD8+ T-lymphocytes and analyzed on the IsoLight platform. The single T-cells were captured in microchambers on IsoCode chips for proteomic immune cytokines profiling (Fig.). Functional polyfunctionality data from 55,775 single cells were analyzed using the IsoSpeak software, 2D- and 3D-tSNE analyses, kappa coefficient, and Kaplan-Meier survival plots.

Results: Pre-treatment baseline polyfunctionality profiles could not differentiate NSCLC patients from healthy subjects. Neither baseline overall polyfunctionality (PolyFx) nor polyfunctionality strength index (PSI) of NSCLC patients differentiated ICI responders from non-responders. Conversely, we found a statistically significant difference between responders and non-responders in CD8+ T-cells' changes in overall polyfunctionality (ΔPolyFx) and polyfunctional strength index (ΔPSI) in our dynamic pre-/post-treatment single cell measurements. In the 3D-tSNE analysis, there were subpopulations of post-treatment CD8+ T-cells in ICI responders that displayed distinct immune cytokine profiles from those of the pre-treatment cells. Conversely, this was not evident in the non-responders analysis. ΔPSI score in CD8+ T-cells performed better than PD-L1 TPS in ICI response correlation. Moreover, when combined with PD-L1 TPS, ΔPSI score strongly correlated with early ICI treatment response with a robust kappa coefficient of 1.0 (p=0.003), which was statistically established to indicate a perfect agreement between the prediction and actual response status. Interestingly, high CD4+ T-cells ΔPSI was found to correlate with a strong trend of improved progression-free survival (3.9-fold) and overall survival (3-fold) in ICI-treated NSCLC patients.

Conclusions: In conclusion, our study nominates single peripheral T-cell polyfunctionality dynamics analysis to be a promising liquid biopsy profiling platform to determine ICI predictive biomarker in NSCLC. It warrants further studies in larger prospective clinical cohorts to broaden available tools to further optimize lung cancer immunotherapy clinical adoption.

Keywords: Single cell analysis, Immune cytokine profiling, T-cell polyfunctionality



P3.06E PATHOLOGY AND BIOMARKERS - IO
MONDAY, SEPTEMBER 9, 2024 - 12:00 - 14:00

P3.06E.01 Evaluation of the Immune Landscape of Patients with Adenosquamous NSCLC (LUAS)

M. Lee[1], T. Adeyelu[2], S. Wang[1], A. Elliott[2], A. Vanderwalde[2], L. Villaruz[3], H. Khan[4], B. Herzberg[5], S.Y. Kim[6], P. Ma[7], S. Liu[8], B. Halmos[1], H. Cheng[1], [1]Montefiore Einstein Comprehensive Cancer Center (MECCC), The Bronx/NY/USA ,[2]Caris Life Sciences, Phoenix/AZ/USA ,[3]UPMC Hillman Cancer Center, Pittsburgh/PA/USA ,[4]Brown University Legorreta Cancer Center, Providence/RI/USA ,[55]. Columbia University Herbert Irving Comprehensive Cancer Center (HICCC), New York City/NY/USA ,[6]Yale Cancer Center, New Haven/CT/USA ,[7]Penn State Cancer Institute, Hersey/PA/USA ,[8]Georgetown Lombardi Comprehensive Cancer Center, Washington D.C./DC/USA

Introduction: Adenosquamous lung cancer (LUAS) is a rare subset of non-small cell lung cancer (NSCLC) characterized by at least 10% of both adenocarcinoma (AC) and squamous (SCC) components, comprising up to 4% of NSCLC cases. Given limited investigations into LUAS's genomic and immune characteristics, this study aimed to delineate molecular and immune variances between LUAS, AC, and SCC, as well as between primary and metastatic sites of LUAS, while examining associated clinical outcomes. Such insights may help to address the significant clinical challenges in LUAS management.

Methods: NSCLC samples (n=35404) underwent DNA (592 genes or whole exome)/RNA (whole transcriptome) sequencing at Caris Life Sciences. Cell infiltration in the tumor microenvironment was estimated by quanTIseq. Primary and metastatic samples included lung and extra-pulmonary biopsies, respectively. Real-world overall survival (rwOS) was obtained from insurance claims data, calculated from either time of biopsy, or start of immunotherapy to last contact. Mann-Whitney U and X2/Fisher-Exact tests were applied, with p-values adjusted ($p < .05$).

Results: Among NSCLC samples, 72.5% (n=25665) AC, 26.5% (n=9365) SCC, 1.0% (n=374) were LUAS. Of the LUAS, 74.9% were from primary and 25.1% from metastatic sites. PD-L1 expression (TPS >1%) was significantly higher in LUAS compared to AC and SCC but there was no significant difference between LUAS primary and metastatic sites. PD-L1 high (TPS >50%) was significantly more in LUAS compared to SCC but not LUAD. Analysis of the tumor microenvironment showed significantly higher cell fractions of neutrophils, NK cells, T cells CD8 and Dendritic cells in LUAS compared to either AC or SCC, particularly prominent in primary LUAS sites compared to LUAS metastatic sites. There was also significantly higher expression of immune-related genes in LUAS compared to either AC or SCC, but no difference in LUAS primary vs metastatic sites (Table 1).

No significant difference in rwOS from start of immunotherapy between LUAS and AC ($p = 0.928$) or SCC ($p = 0.928$). However, prolonged rwOS was noted in LUAS compared to SCC (HR = 0.79 CI 0.70 - 0.89, $p < 0.001$) from time of biopsy to last contact.

Conclusions: This study provides unique insights into LUAS. Although our results revealed multiple significantly higher immune environment factors in LUAS, still there were no significant OS differences when treated with immunotherapy. This suggests that additional factors beyond the immune environment may also influence immunotherapy responses in LUAS, highlighting the need for further investigation.

Keywords: Adenosquamous, Immunotherapy, Actionable Alterations

		Adenosquamous (LUAS, n =374)	Squamous (SCC, n = 9635)	Adenocarcinoma (AC, n = 25665)	p-value (SCC vs LUAS)	p-value (AC vs LUAS)
Overall Actional Alteration Prevalence	*EGFR, ALK, ROS1, RET* fusions /rearrangements, *METex 14, BRAF V600E, KRAS G12C, NTRK* fusions, *HER2*	110 (29.4%)	343 (3.67%)	9267 (36.22%)	<0.001	0.0065
Immune landscape factors	PD-L1 positive (IHC 22c3: ≥1%)	228 (65.5%)	5293 (59.8%)	12789 (53.7%)	0.033	<0.001
	PD-L1 High (≥50%)	110 (31.6%)	2119 (26.3%)	6218 (31.2%)	0.0293	0.1843
	PD-L1 low (1-49%)	112/348 (33.9%)	3009/8045 (37.8%)	6177/20023 (30.8%)	0.048	0.512
	No PDL1 (0%)	126/348 (36.2%)	2917/8045 (35.9%)	7628/20023 (38.1%)	0.984	0.3621
	TMB High (≥10 Mut/MB)	112 (30.6%)	3488 (38.47%)	8159 (32.94%)	0.002	0.344
Tumor microenvironment		LUAS Median cell fraction (%)	SCC Median cell fraction (%)	AC Median cell fraction (%)	p-value (SCC vs LUAS)	p-value (AC vs LUAS)
	Monocytes	0.02	0.06	0.10	0.138	0.017
	T cells CD4	0.04	0.07	0.11	0.274	0.130
	Neutrophils	5.57	5.23	4.85	0.165	0.020
	NK cells	2.68	2.49	2.94	0.005	<0.001
	T cells CD8	0.39	0.11	0.27	<0.001	0.164
	Macrophages M2	6.08	4.65	6.19	<0.001	0.172
	Macrophages M1	4.57	2.64	5.12	<0.001	0.005
	B cells	4.08	4.19	3.87	0.092	0.160
	Dendritic cells	0.61	1.07	0.54	<0.001	0.049
	Tregs	2.92	1.75	2.76	<0.001	0.365
Immune-related genes		LUAS Median Gene expression median ((Log2 (TPM+1))	SCC Median Gene expression median ((Log2 (TPM+1))	AC Median Gene expression median ((Log2 (TPM+1))	p-value (SCC vs LUAS)	p-value (AC vs LUAS)
	PDCD1LG2	1.447	1.319	1.284	0.009	<0.001
	PDCD1	0.817	0.711	0.790	0.003	0.251
	CTLA4	1.914	1.629	1.638	<0.001	0.001
	CD86	3.534	3.218	3.482	<0.001	0.337
	ID01	2.850	2.300	2.241	<0.001	<0.01
	CD274	3.210	3.122	3.031	0.717	0.132
	CD80	2.888	2.569	2.798	<0.001	0.453
	HAVCR2	4.511	3.999	4.499	<0.001	0.739
	LAG3	1.037	1.043	0.865	0.466	0.001
	IFNG	0.841	0.697	0.691	0.026	0.025

P3.06E PATHOLOGY AND BIOMARKERS - IO
MONDAY, SEPTEMBER 9, 2024 - 12:00 - 14:00

P3.06E.02 Serum NY-ESO-1 And XAGE1 Antibodies Are Diagnostic and Cancer-Specific Immunomonitoring Markers in NSCLC

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Introduction: NY-ESO-1 and XAGE1 cancer/testis antigens are exclusively expressed in cancer and germ cells only. These antigens are highly immunogenic and elicit spontaneous humoral and cellular immune responses in NSCLC patients. Notably, NY-ESO-1 is broadly expressed in various cancers, but XAGE1 expression is comparatively specific in lung adenocarcinoma. Thus, antibodies (Abs) against these antigens are cancer-specific immune response biomarkers. We previously reported that serum NY-ESO-1/XAGE1 Abs were detected in approximately 25% of advanced NSCLC and potentially predicted clinical response to immune checkpoint inhibitor (ICI) regardless of tumor PD-L1 status. Although ICI therapy has been a standard care of NSCLC, immune responses against cancer antigens remain unexplored in the treatment of NSCLC. Here, cancer-specific immunomonitoring using NY-ESO-1/XAGE1 Abs was performed in various NSCLC treatments.

Methods: This retrospective biomarker study included 543 patients with NSCLC and 36 with non-malignant pulmonary diseases at Kawasaki Medical School Hospital, between 2015 and 2023. This NSCLC cohort was composed with 331 (61%) adenocarcinoma, 151 (28%) squamous cell carcinoma, and 61 (11%) others. The patients' sera were obtained at diagnosis, and serum NY-ESO-1 and XAGE1 Abs were quantitatively measured by ELISA. The cutoff value of the positive Abs was defined as ≥ 100 titer. For immunomonitoring, the Abs in 83 NSCLC patients were serially measured after the treatments including 20 surgery, 20 chemotherapy, 17 targeted therapy, and 25 ICI therapy.

Results: NY-ESO-1/XAGE1 Abs were never detected in non-malignant patients. In NSCLC, the positive rate of the Abs was 19% (105/543) overall, and it was 13% (73/543) in XAGE1 Ab, 6% (32) in NY-ESO-1 Ab, and 0.1% (4) in both Abs. According to disease stage (8th ed), the Ab-positive rate was 5% (8/150) in stage I, 16% (10/63) in stage II, 21% (26/126) in stage III, and 30% (60/199) in stage IV. The Ab-positive rate was 23% and 11%, in adenocarcinoma and squamous cell carcinoma, respectively, and especially it was the highest 33% in advanced adenocarcinoma of stage IIIB and stage IV. In systemic therapy, the Ab dynamics showed three patterns according to clinical responses (CR, PR, SD, PD); the Ab levels were gradually decreased or became negative in CR/PR, not changed in SD, and increased in PD. However, the Abs even in CR never disappeared in targeted therapy for EGFR and ALK, indicating cytostatic activity. In surgery, the Ab dynamics showed three patterns after resection; the Abs completely disappeared without recurrence and were decreased with recurrence and increased at recurrence only.

Conclusions: This study detected serum Ab against cancer-specific antigens in NSCLC patients and first monitored cancer-specific Ab response in the treatment of NSCLC. Our results indicate that NY-ESO-1/XAGE1 Abs are diagnostic markers in NSCLC, especially XAGE1 Ab in lung adenocarcinoma. NY-ESO-1/XAGE1 Ab levels were increased in association with disease progression, suggesting potential response biomarkers of immunotherapy, as we previously reported. In addition, immunomonitoring using NY-ESO-1/XAGE1 Abs are probably useful to monitor response to various treatments and predict postoperative recurrence in clinical practice. Recently, we developed a fully automated immunoassay measuring NY-ESO-1/XAGE1 Abs for clinical application.

Keywords: biomarker, immunotherapy, cancer antigen

P3.06E PATHOLOGY AND BIOMARKERS - IO
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P3.06E.03 Anlotinib Mediated Inflammation Response Through NFKB/TNFRSF11A Cascade in Lung Cancer

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Introduction: Anlotinib is a highly promising anti-tumor drug in advanced non-small cell lung cancer (NSCLC). Previous studies have shown that Anlotinib plays a significant role in anti-angiogenesis and proliferation inhibition in the treatment of advanced NSCLC. These anti-tumor effects may be attributed to the selective inhibition of tyrosine kinase receptors by Anlotinib, including VEGFR (2/3), PDGFR (α/β), FGFR (1-4), and others. Recent studies have also revealed some potential biomarkers associated with anti-angiogenesis used for stratifying Anlotinib. However, due to the complex structure of angiogenesis signal transduction and the direct anti-tumor effects of Anlotinib being discovered, further exploration is needed to predict potential biomarkers of NSCLC patients responsive to Anlotinib.

Methods: Establish a patient-derived xenograft (PDX) model of NSCLC and treat it with Anlotinib. Transcriptome analysis to study the changes in gene expression profiles and molecular pathway activation levels underlying the anticancer effects of Anlotinib. In vitro cell experiments confirm the anti-cancer effects of Anlotinib are related to NFκB activation and cytokines IL1B and TNFRSF11A. Collect patient serum, ELISA experiments confirm the relevance of IL1B and TNFRSF11A to the anticancer effects of Anlotinib.

Results: After 14 days of Anlotinib gavage treatment in PDX mice, there were 621 differentially expressed genes and 2168 different transcripts between the Anlotinib group and the control group tissues. Functional analysis using GO and KEGG on differentially expressed genes revealed differences in 1616 pathways. Among them, changes in the NFκB pathway affected by Anlotinib were particularly prominent, with significantly reduced expression of NFκB-related cytokines IL1B and TNFRSF11A. Furthermore, Kaplan-Meier survival analysis on TCGA cohort showed that NSCLC patients with higher mRNA levels of NFKB pathway-related genes (including IL1B and TNFRSF11A) had a poorer prognosis. Subsequently, in vitro cell experiments verified that Anlotinib can downregulate NFκB expression and downregulate the expression of immune-related cytokines IL1B and TNFRSF11A in the NFκB pathway. In vivo experiments confirmed a significant decrease in the expression of IL1B and TNFRSF11A in patient serum after Anlotinib treatment.

Conclusions: The expression levels of immune-related genes IL1B and TNFRSF11A in the NFKB pathway have potential clinical applications and can be used to predict the response to Anlotinib.

Keywords: Non-small cell lung cancer, Anlotinib, Transcrip-tomics

P3.06E PATHOLOGY AND BIOMARKERS - IO
MONDAY, SEPTEMBER 9, 2024 - 12:00 - 14:00

P3.06E.04 Genetic and Immunological Backgrounds in Advanced NSCLC Patients Treated with Immunotherapy - NGS and Flow Cytometry Analysis

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Introduction: The treatment of non-small-cell lung cancer (NSCLC) patients at advanced stages of the disease relies on immunotherapy. Programmed death ligand 1 (PD-L1) expression on tumor cells and tumor mutational burden (TMB) are used to predict the response to immune checkpoint inhibitors treatment and qualify patients to the therapy, but in some cases those biomarkers are not efficient enough. Discovering new predictive markers would therefore allow clinicians to modify therapy course for the patient's benefit. We performed a preliminary analysis aimed at describing genetic and immunological background of immunotherapy course and discovering factors possibly related to clinical benefit or lack of response.

Methods: We applied next generation sequencing (NGS) of tumor tissue and flow cytometry analysis of peripheral blood lymphocytes' subpopulations. Both materials were obtained from 20 patients with advanced NSCLC just before treatment. Nine patients received pembrolizumab in monotherapy and 11 people received pembrolizumab combined with chemotherapy (carboplatin and pemetrexed). Then, bioinformatic and statistical analysis were performed.

Results: Based on progression-free survival (PFS) time, the study group was divided into short (n=11) and long (n=9) responders (PFS ≤6 months or >6 months, respectively). In short responders, the most frequently altered genes were NOTCH4 (55%), H3-3A (45%) and KDR (36%), while in long responders KDR and TP35 genes were the most commonly mutated in 44% and 33% samples, respectively. Then, 22% of long responders had KRAS, NOTCH4, PDGFR, JAK2 and PMS2 gene mutations, and none had H3-3A gene mutations. Moreover, the co-occurrence between KRAS/STK11 genes occurred in short responders, while PMS2/NOTCH4 and PDGFRA/JAK2 overlaps were significantly often observed in long responders. Flow cytometry analysis results revealed a higher baseline CD4+/GATA3+ cells percentage and higher baseline T regulatory cells (CD4+/CTLA-4+/FoxP3+) percentage in long responders. High CD62L expression on CD8+ cells and high CD4+/GATA3+ cells percentage turned out to be favorable in terms of PFS in Kaplan-Meier analysis. Considering the whole analysis, the following molecules appear relevant: CD62L, GATA3, CTLA-4, TIM-3, LAG-3, CXCR3, PD-1, and EOMES.

Conclusions: Even though the complexity of molecular and immunological landscape in cancer disease is not entirely understood, our work indicates that NGS and flow cytometry analysis of tumor tissue in NSCLC may constitute a useful tool providing an overview of the background affecting the response to immunotherapy. In our study, some of the alterations and immunological features detected appear to be favorable, whereas other seem to be disadvantageous and this is not always in consistency with literature data. Therefore, there is much more research to be conducted in this matter in order to understand the anti-cancer response and discover new predictive factors. We continue our research to elucidate the interplay between genetic and immunological processes in lung cancer.

Keywords: immunotherapy, next generation sequencing, flow cytometry

P3.06E PATHOLOGY AND BIOMARKERS - IO
MONDAY, SEPTEMBER 9, 2024 - 12:00 - 14:00

P3.06E.05 The Inflammation Induced by Neoadjuvant Immunotherapy Facilitated Favorable Clinical Outcomes

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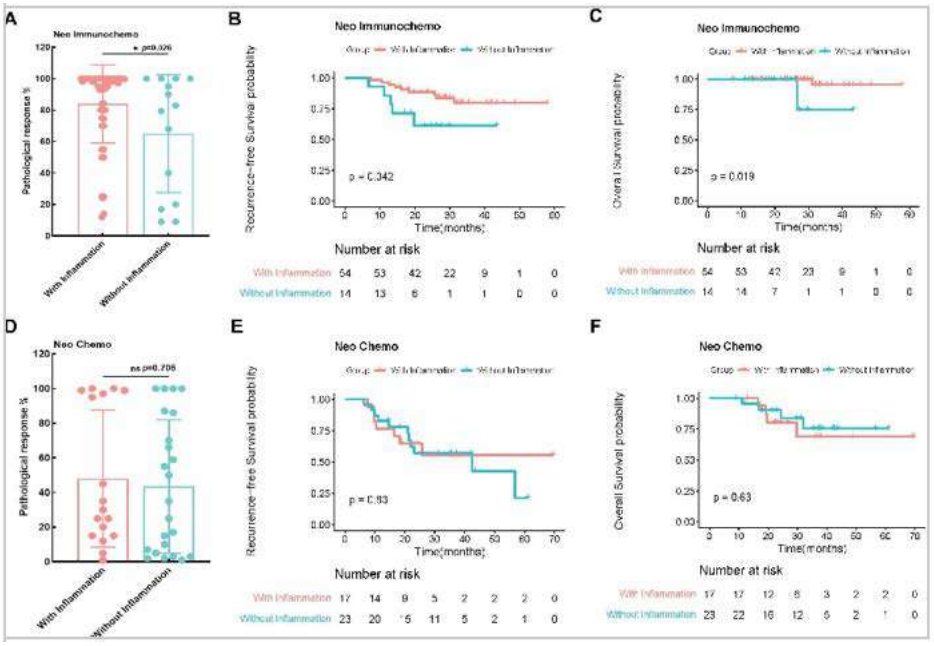
Introduction: After neoadjuvant therapy for non-small cell lung cancer (NSCLC), resected tumors exhibit varying degrees of inflammation formation. Usually, the inflammatory reactive changes in non-neoplastic lung must be separated when defining the tumor bed. However, the relationship between inflammation around the tumor bed and treatment response and prognosis in NSCLC with neoadjuvant therapy is yet to be elucidated.

Methods: We retrospectively collected hematoxylin and eosin-stained slides from patients with NSCLC (stage IA-IIIB) from two cohorts based on neoadjuvant immunochemotherapy(N=68) and neoadjuvant chemotherapy(N=41). Inflammation surrounding the tumor bed in different treatment groups was assessed and its' relationship with treatment response and prognosis was also analyzed.

Results: Peritumoral inflammation were identified in 79.4% of the patients with neoadjuvant immunochemotherapy and 42.5% of the patients with neoadjuvant chemotherapy, respectively. A higher proportion of peritumoral inflammation was found in neoadjuvant immunochemotherapy group (p<0.001). Inflammation surrounding the tumor bed was significantly correlated with pathological response in patients with neoadjuvant immunochemotherapy, while there was no significant correlation between peritumoral inflammation and pathological response in neoadjuvant chemotherapy group. Kaplan-Meier analyses revealed that the presence of inflammation around tumor bed was significantly associated with improved recurrence-free survival (RFS, p=0.042) and overall survival (OS, p=0.019) for patients with neoadjuvant immunochemotherapy. However, the presence of inflammation around tumor bed was not significant correlated with neither recurrence-free survival (RFS, p=0.83) nor overall survival (OS, p=0.63) for patients with neoadjuvant chemotherapy.

Conclusions: This study for the first time elucidates the correlation between inflammation surrounding tumor bed and treatment response and prognosis for NSCLC patients with neoadjuvant therapy. The findings reveal that peritumoral inflammation was more frequently induced by immunotherapy. Notably, the inflammation surrounding the tumor bed was correlated with favorable treatment response and prognosis in patients who received neoadjuvant immunochemotherapy. Improving the clinical outcomes through the induction of increased inflammation represents a significant benefit of neoadjuvant immunotherapy.

Keywords: Non-small cell lung cancer, Neoadjuvant immunotherapy, Inflammation



P3.06E PATHOLOGY AND BIOMARKERS - IO
MONDAY, SEPTEMBER 9, 2024 - 12:00 - 14:00

P3.06E.06 Angiogenesis and Immune-Related Biomarkers in Advanced Non-Small Cell Lung Cancer Treated with Immune Checkpoint Inhibitors

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Introduction: Previous data have shown that immune cells may interact with angiogenesis-related factors in the tumor microenvironment, regulating the development and progression of cancer, and that angiogenesis and immune checkpoint-related biomarkers may be useful as predictors of prognosis and treatment response in immunotherapy-treated solid tumors. We herein aimed to investigate the prognostic and predictive value of baseline and post-treatment levels of serum VEGF-A, VEGF-B and soluble programmed cell death-1 (sPD-1) and programmed cell death-ligand 1 (sPD-L1) in patients with advanced non-small cell lung cancer (NSCLC) treated with immune checkpoint inhibitors (ICIs).

Methods: 55 patients with advanced NSCLC eligible to receive immunotherapy (as monotherapy or in combination with chemotherapy) were prospectively enrolled. A group of sex- and age-matched healthy controls (n=16) was also recruited, for determination of the optimal cut-off value of the examined biomarkers. Serum VEGF-A, VEGF-B, sPD-1 and sPD-L1 levels were measured in peripheral blood samples using ELISA, both at baseline and at the time of treatment response evaluation, and were correlated with prognosis (PFS, OS), treatment response and the remaining clinicopathological features of patients.

Results: Mean age of patients was 66.5 years (SD=8.0 years); 65,5% of patients received chemotherapy and pembrolizumab combination while the remaining patients received pembrolizumab monotherapy. VEGF-B and sPD-1 levels were significantly decreased and increased, respectively, after treatment (p=0,028 and p<0,001, respectively). VEGF-A and sPD-L1 levels were also decreased and increased, respectively, albeit without reaching statistical significance. Univariate Cox regression analysis showed that increased pre-treatment values of sPD-1 (HR=10.96; p=0.037) and sPD-L1 (HR=1.68; p=0.040) and increased post-treatment levels of VEGF-B (HR=2.99; p=0.049) were all significantly associated with reduced OS. VEGF-B and sPD-L1 retained their prognostic significance in multivariate analysis (HR=3.37; p=0.032 and HR=2.10; p=0.014, respectively).

Conclusions: sPD-L1 and VEGF-B may represent independent biomarkers of prognosis in advanced-stage NSCLC patients treated with ICIs.

Keywords: non-small cell lung cancer, immunotherapy, biomarkers

P3.06F PATHOLOGY AND BIOMARKERS - PROFILING
MONDAY, SEPTEMBER 9, 2024 - 12:00 - 14:00

P3.06F.01 Proteomic Profiling Reveals Distinct Biological Characteristics of EGFR L858R Mutation and a Prognostic Model in Lung Adenocarcinoma

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Introduction: EGFR (epidermal growth factor receptor) gene mutations are among the key molecular drivers of lung adenocarcinoma. The L858R subtype, in particular, is often associated with more aggressive biological behavior and poorer prognosis compared to the 19DEL subtype and wild-type (WT), but its underlying mechanisms remain elusive.

Methods: To investigate the biological differences between EGFR mutation subtypes and their impact on patient prognosis, we established isogenic NCI-H520 cell line models harboring EGFR WT, 19DEL, or L858R mutations through stable lentiviral transfection. Comparative proteomic profiling using liquid chromatography-mass spectrometry (LC-MS) was performed to reveal proteome variations between the L858R mutation and other subtypes. Subsequent bioinformatic analyses were conducted to construct potential prognostic models for predicting recurrence in EGFR-mutated lung adenocarcinoma patients.

Results: Proteomic data revealed 11 proteins with significantly higher expression levels in L858R compared to 19DEL and WT, including TERF2IP, CDCA5, MRPL1, ACOT13, AKTIP, ROMO1, NFKBIL1, AKR1C3, NDUFAF4, GUSB, and PPME1. Conversely, 9 proteins, namely MTFP1, ENTPD8, PTRH2, KTN1, KANK2, PRIM1, PNPLA4, FBXO18, and ISY1, exhibited lower expression in L858R. Gene set enrichment analysis indicated common enriched pathways between 19DEL and L858R, such as ribosome and antigen processing and presentation, while L858R uniquely enriched metabolism-related pathways like lysine degradation and oxidative phosphorylation. Integrative analysis of our proteomic data and a clinical RNA-array dataset identified 28 differentially expressed genes (DEGs) between EGFR-mutated and WT samples. Lasso-Cox regression analysis yielded a 4-gene prognostic model effectively predicting disease-free survival (DFS) in EGFR-mutated lung adenocarcinoma patients. Higher expressions of BAG4 (HR(95%CI): 2.764 (1.215 - 6.288), P= 0.015), PLGRKT (HR(95%CI): 2.589 (1.383 - 4.846), P= 0.003), and PRIM1 (HR(95%CI): 2.960 (1.526 - 5.740), P= 0.001) correlated with worse DFS, while higher MOCS2 expression associated with improved DFS (HR(95%CI): 0.398 (0.168 - 0.945), P= 0.037). Multivariate analysis confirmed PRIM1 as an independent prognostic factor for DFS in EGFR-mutated lung adenocarcinoma (HR(95%CI): 2.225 (1.029 - 4.811) , P= 0.042).

Conclusions: In summary, this study uncovered proteomic variations and biological behavior differences among classical EGFR mutations in lung adenocarcinoma cell line models, highlighting distinct characteristics of the L858R mutation. The constructed risk model effectively predicted DFS in EGFR-mutated patients, with PRIM1 identified as a potential prognostic biomarker warranting further investigation.

Keywords: EGFR, lung adenocarcinoma, L858R

P3.06F PATHOLOGY AND BIOMARKERS - PROFILING
MONDAY, SEPTEMBER 9, 2024 - 12:00 - 14:00

P3.06F.02 Role of GOLT1B and PTGES3 In Suppressing Lung Adenocarcinoma Progression

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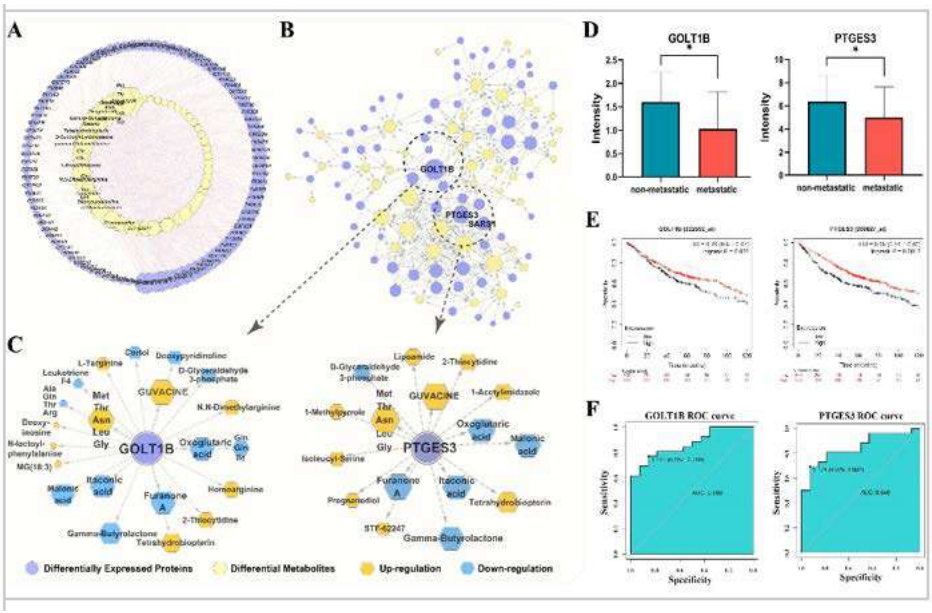
Introduction: The current clinical diagnosis of cancer metastasis relies mainly on pathology and genetic tests, due to the lack of practical diagnostic biomarkers, early clinical diagnosis and treatment are hindered, which consequently leads to poor prognosis. Herein we applied proteomics and non-targeted metabolomics to identify biomarkers associated with lung adenocarcinoma progression.

Methods: In this study, analysis of cancer tissues and adjacent tissues was conducted based on proteomics and untargeted metabolomics. Patients were categorized into two groups based on long-term follow-up data: those with metastasis and those without. Pearson correlation analysis was used to calculate the correlation between clinical outcomes of metastasis and differentially expressed proteins (DEPs) and metabolites (DEMs). Cytoscape was utilized to construct a network diagram of DEPs/DEMs related to metastasis, and the cytoHubba plugin was used to select the top 2 central genes, GOLT1B and PTGES3. The inhibitory effect of overexpressed GOLT1B and PTGES3 on tumors was determined through in vitro and in vivo experiments. Furthermore, the correlation between GOLT1B and PTGES3 and the degradation of HIF1-α was explored and validated based on transcriptome sequencing.

Results: Based on proteomic and metabolomic analyses of 40 patients, 99 differentially expressed proteins and 58 metabolites related to postoperative metastasis of lung adenocarcinoma were identified. The core genes GOLT1B and PTGES3, along with 27 metabolites, were considered highly associated with lung adenocarcinoma metastasis. Preliminary results from in vitro and in vivo experiments demonstrated the inhibitory effect of GOLT1B and PTGES3 overexpression on the malignant behavior of lung adenocarcinoma. Furthermore, preliminary validation indicated that GOLT1B and PTGES3 promote the degradation of HIF1-α.

Conclusions: Our findings suggest that the alterations in GOLT1B and PTGES3, along with 27 related metabolites, may be highly associated with the metastasis of lung adenocarcinoma. Preliminary results from in vitro and in vivo experiments indicate that the overexpression of GOLT1B and PTGES3 exerts an inhibitory effect on the malignant progression of lung adenocarcinoma by promoting the degradation of HIF1-α.

Keywords: multi-omics, metastasis, biomarkers



P3.06F PATHOLOGY AND BIOMARKERS - PROFILING
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P3.06F.03 Unbiased Proteomics and Multi-Omics Discovery of a Peripheral Blood-Based Classifier for Early Lung Cancer Detection

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Introduction: Blood-based approaches to detect early-stage cancer provide an opportunity to improve survival rates for lung cancer. Multiple approaches for blood-based cancer detection using molecular analytes derived from individual 'omics (cell-free DNA, RNA transcripts, proteins, metabolites) have been developed and tested, generally showing significantly lower sensitivity for early- versus late-stage cancer. We hypothesized that using a multi-omic approach, including broad and untargeted coverage of proteins using the Proteograph™ Product Suite (Seer Inc., Redwood City, CA), could potentially improve detection of early-stage lung cancer.

Methods: This report describes an observational case-control study of 2513 subjects enrolled from 77 unique clinical sites in the US. 2094 subjects were clinically eligible, including 816 with histopathologically confirmed lung cancers and 1278 non-cancer controls.

Study subjects were assigned into either a training or hold out set such that clinical sites were separated between these two sets. Sample processing was done in a blinded fashion for all subjects.

K2 EDTA plasma samples were processed with the Proteograph in conjunction with liquid chromatography-mass spectrometry following the manufacturer's protocol. 1623 subjects (1225 in training and 398 in validation) were profiled across all molecular assays and passed QC checks. Metabolomics and RNA sequence data were also collected.

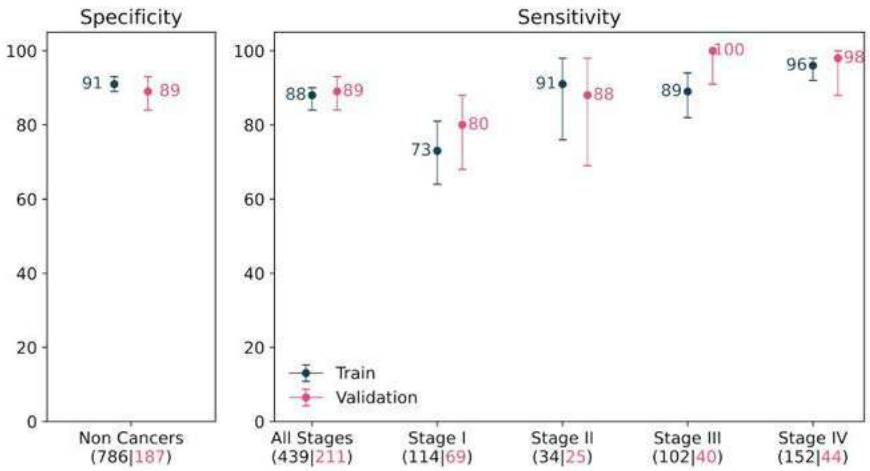
A regularized, tree-based gradient boosted model (XGBoost) was fitted to the training data using hyperparameters optimized across 10 repeats of 10-fold cross validation. The trained classifier was used for inference on the hold out set.

Results: Multi-omics profiling detected 113,671 peptides corresponding to 8385 protein groups, 219,729 RNA transcripts, 71,756 RNA introns, and 1801 metabolites across all subject samples.

The machine learning-based multi-omics classifier for lung cancer detection was comprised of 682 of these analytes and demonstrated 89%, 80%, 88%, 100% and 98% sensitivity for all-stage, stage I, stage II, stage III, and stage IV lung cancer, respectively, at 89% specificity in the hold out set.

Conclusions: The application of a multi-omics platform for discovery of blood-based disease biomarkers, including proteins and complementary molecular analytes, enables the detection of early-stage lung cancer with the potential for downstaging at initial diagnosis and the improvement of clinical outcomes.

Keywords: lung cancer, biomarkers, multi-omics



Performance of the validated multi-omics classifier. Stage-wise sensitivity and specificity of the multi-omics classifier for subjects from training (black) and validation (pink) datasets. Error bars indicate 95% Clopper-Pearson confidence intervals. The number of subjects in each sub-group is denoted in parentheses.

P3.06F PATHOLOGY AND BIOMARKERS - PROFILING
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P3.06F.04 Multi-Omics Analysis of SMARCA4-Deficient Tumors

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Introduction: SMARCA4 (BRG1) encodes an ATPase subunit of the evolutionary conserved SWI/SNF chromatin remodeling complex. SMARCA4-deficient thoracic-origin tumors exhibit high malignancy and currently lack effective treatment options, whereas most patients are diagnosed at an advanced stage, and miss the chance of surgery. A comprehensive understanding of the landscape of SMARCA4-deficient tumors is needed.

Methods: Pan-cancer surgical samples suspected BRG1 loss from the National Cancer Center collected retrospectively between 2019 and 2023 were subjected to BRG1 IHC staining, whole-exomes sequencing (WES), and RNA-sequencing. The BRG1 protein deficient status, categorized as total-deficient (TD) or partial-deficient (PD), was twice-confirmed independently. Additionally, samples from lung cancer were acquired as control group for comparative analysis.

Results: A total of 66 patients were included in this study, with tumors originating primarily from various sites: lung (43), kidney (6), stomach (5), uterus (3), ovary (2), liver (2), colon (2), cervix (1), thyroid (1), and salivary (1). Among TD (n=38) and PD (n=11) groups, 39 out of 49 (79.6%) patients were heavy smokers, with TTN (68%), TP53 (57%), and SMARCA4 (41%) being the top three frequently mutated genes. Notably, no SMARCA4 mutations were detected in the control group (n=17), and SMARCA4 mutations were significantly more frequent in TD group than PD group (18/38, 47.4% vs. 2/11, 18.2%, P<0.05). SMARCA4 loss of heterogeneity (LOH) was only observed in TD group, while copy number amplification/deletion was observed in all three groups. Class I SMARCA4 mutations were exclusively present in the deficient groups, particularly more frequent in TD group than PD group (15/38, 39.5% vs. 2/11, 18.2%, P<0.05). Moreover, tumor mutational burden (TMB) was significantly higher in the deficient groups compared to the control group (P<0.05), with no significant variation observed between TD and PD groups. PD-L1 IHC staining did not show differences among the three groups. Regarding DNA damage response (DDR) pathways, mutations were significantly more common in all pathways, as well as the MMR, NER, and BER pathways in the deficient group compared to the control group (P<0.05). Conversely, mutations in the NHEJ and TLS pathways of PD group were significantly more common than those in TD group (P<0.05). Notably, for other subunits of SWI/SNF, the expressions of SMARCC1, ARIDA1, PHF10, GLTSCR1L, SS18L1, ACTL6A, and PBRM1 in PD group were significantly higher than those in TD group (P<0.05), suggesting a possible functional compensatory effect. The expression of SMARCA4 or SMARCA2, another ATPase subunit of SWI/SNF, was significantly higher in the deficient group than in the control group (P<0.05), with no significant difference observed between PD and TD groups. Further analysis revealed a positive correlation between SMARCA4 expression and SMARCA2 expression regardless of BRG1 status. Additionally, the expression of SOX-2, a biomarker distinguishing SMARCA4-deficient undifferentiated tumors from SMARCA4-deficient non-small cell lung cancer, was highest in TD group compared to PD and the control groups.

Conclusions: Discrepancies between SMARCA4 mutation and BRG1 status persist, calling a further exploration in mechanisms. Additionally, tumors exhibiting varying degrees of BRG1 integrity demonstrate distinct characteristics and potentially divergent biological behaviors. Further studies are underway.

Keywords: Multi-Omics Analysis, SMARCA4-Deficient Tumor, Surgical Samples

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P3.06F.05 Spatial Profiling of the Tumor Microenvironment of SMARCA4-Mutant NSCLCs Using Whole-Slide Multiplex Fluorescence Imaging

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Introduction: SMARCA4 alterations are found in ~10% of non-small cell lung carcinomas (NSCLC), predominantly in adenocarcinomas among patients with a smoking history. Patients with these tumors may derive limited benefit from immune checkpoint inhibitor (ICI) therapy. The etiology of ICI primary resistance remains uncertain, as these tumors demonstrate high tumor mutational burden (TMB) and an inconsistent association with PD-L1 tumor proportion score (TPS) across studies. Frequent co-occurring mutations (e.g. STK11 mutations), may contribute to ICI resistance. To explore our hypothesis that lack of sensitivity to ICI in SMARCA4-deficient NSCLCs may be attributable to impaired immune infiltration, we investigated the tumor immune microenvironment of these tumors in relation to STK11 co-mutation status.

Methods: We conducted a retrospective study of patients diagnosed with NSCLC who underwent a lung surgical resection or a large surgical biopsy. Patients were selected based on SMARCA4 and STK11 alteration status detected using a 447-gene next generation sequencing panel (OncoPanel). Patients with SMARCA4/STK11 wild-type NSCLC served as a control group. Clinical and pathological data was collected from medical records, and additional molecular alterations were retrieved from OncoPanel reports. Immunohistochemistry (IHC) for SMARCA4/BRG1 and STK11/LKB1 was used to confirm loss of protein expression and to assess SMARCA2/BRM and PD-L1 expression. High-plex fluorescent spatial profiling using cyclic immunofluorescence (CyCIF) was performed to analyze the tumor immune composition with a 60-plex panel covering tumor, lineage, and immune, and checkpoint markers.

Results: We included 40 samples from 38 patients: 24 SMARCA4/STK11 mutant, 10 SMARCA4 mutant/STK11 wild-type, and 6 SMARCA4/STK11 wild-type (controls). Among the patients, 63% were female (mean age: 63.2 years; range 34-80 years). Adenocarcinoma was diagnosed in 90% of cases, and 72.5% of samples were from primary lung tumors. The cohort included seven patients with SMARCA4 missense mutations, and 25 with truncating mutations, including 10 nonsense mutations, 6 frameshift, and 6 splice site alterations. SMARCA4 loss of heterozygosity occurred in 9 (36.0%) patients with truncating mutations and in 6 (85.7%) with missense mutations. Complete or partial loss of SMARCA2/BRM was seen in 6 (17.6%) SMARCA4-mutant tumors and all had a loss of SMARCA4/BRG1 expression. TMB was higher in SMARCA4-mutant NSCLCs (SMARCA4/STK11 mutant: 13.2, SMARCA4 mutant/STK11 wild-type: 12.4, control: 4.6), with no significant difference in PD-L1 TPS between groups. Initial findings from CyCIF profiling indicate that SMARCA4-mutant NSCLCs exhibit significantly increased infiltration of myeloid cells (CD14 p=0.003) and macrophages (CD163 p=0.002).

Conclusions: SMARCA4-deficient NSCLCs has a distinct tumor immune microenvironment characterized by increased myeloid cell and macrophage infiltration, potentially contributing to resistance to immune checkpoint inhibitors. Additional work is underway to profile and spatially analyze the tumor immune microenvironment and to characterize its relation to STK11 co-mutation status.

Keywords: SMARCA4-deficient non small cell carcinoma, Tumor immune microenvironment, High-plex spatial fluorescence imaging

P3.06F PATHOLOGY AND BIOMARKERS - PROFILING
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P3.06F.06 Spatial Transcriptomic Profiling Reveals Molecular Patterns Associated with Poor Prognosis in ALK-Rearranged NSCLC Patients

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Introduction: ALK-rearranged NSCLC patients typically exhibit a median overall survival of 4-5 years. The pateint's response to treatment is influenced by factors including baseline and on-treatment genetic alteration, comorbidities, and the patient's age. Given the varying risks of poor prognosis among patients, early identification of high-risk profiles becomes imperative. Recently the interaction of tumors and their microenvironment has gained importance as determinants of treatment response in cancer. Therefore, this study employs Spatial transcriptomics (ST)-based molecular analysis of tumor and tumor microenvironment to characterize the risk landscape in ALK-rearranged NSCLC patients.

Methods: Retrospectively, 16 ALK-rearranged NSCLC FFPE tumor blocks (2016-2022) with clinical details and 3 control FFPE blocks (Normal: Brain, Lung, Lymph Node: LN) were collected. A tumor microarray consisting of 20 cores from 19 blocks were subjected to ST (NanoString GeoMx DSP). Immunohistochemical markers including PanCytokeratin for tumor, SYTO 13 for nuclei, and CD45 for immune cells were used to select 20 Regions of Interest (ROI) and 36 Areas of Illumination (AOI). RNA sequencing data was analyzed using various bioinfomatics tools

Results: Out of 16 ALK-rearranged NSCLC cases, six cases were in the High-risk patient/poor treatment responder (PTR) category, who succumbed to their disease in less than 1.5 years of the diagnosis (2 Brain metastasis and 4 LN metastasis) and the 10 cases were in Treatment Responder (TR) category, who survived for more than 1.5 years. ST data showed distinct immunological features linked with PTR and TR. TR stromal segment of LN metastasis shows enriched B cell markers in comparison to PTR, and the stroma of brain metastasis PTR showed enriched Effector cell and Tumor-Associated macrophage Markers in comparison to TR. The Differential gene expression analysis (DGEA) in the tumor segment of LN metastasis of TR and PTR showed 30 differentially expressed genes (DEG), the top upregulated genes (TUGs) in PTR were related to surfactant, epithelial barrier, and immune response. The top-downregulated genes (TDGs) in TR were related to immune response and angiogenesis. Similarly, the DGEA of stromal lymph node metastasis of TR and PTR showed 29 DEG, the TUGs in PTR were related to tumor proliferation, whereas the TDGs in TR were related to inflammation and angiogenesis.

Conclusions: This study reveals distinct gene expression patterns in tumor and stroma segments for immune response, angiogenesis, and tumor proliferation TR and PTR. This signifies its application in the early detection of PTR-related gene expression patterns, enabling tailored clinical management.

Keywords: ALK-Rearranged NSCLC, Spatial Transcriptomics, Poor treatment respoders

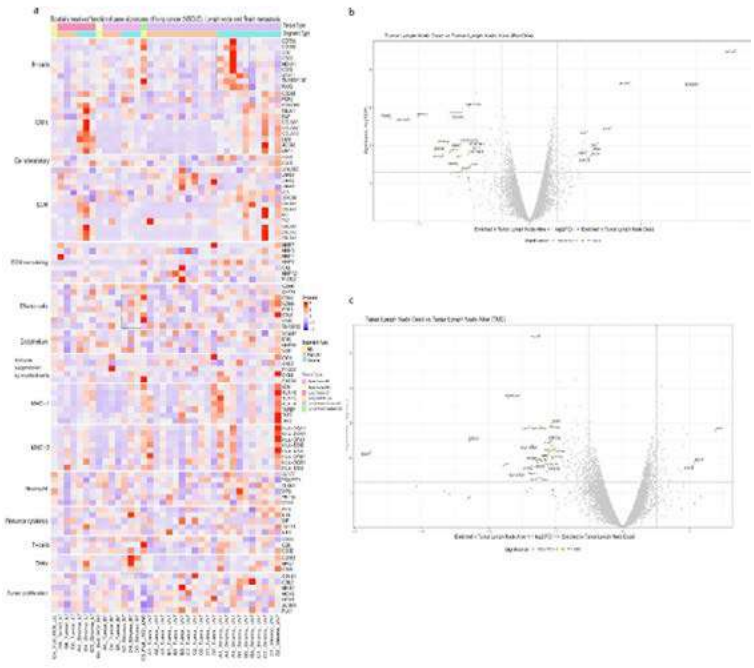

Fig 1: Spatial transcriptomics in ALK-rearranged NSCLC a)Spatially functional gene expressions in lung cancer, Lymph Node metastasis and Brain metastasis depicted through a heatmap, illustrating alterations in cellular or extracellular elements across primary and metastatic tumor regions. b) Volcano plot illustrating differentially expressed genes between the tumor(PanCK+) segments of poor treatment responders (Dead) and treatment responders (Alive).c) Volcano plot illustrating differentially expressed genes between the stroma (TME) segments of poor treatment responders (Dead) and treatment responders

P3.06F PATHOLOGY AND BIOMARKERS - PROFILING
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P3.06F.07 Effect of Neoadjuvant Chemotherapy on the Spatial Landscape of Regulatory T Cells in Non-Small Cell Lung Cancer Patients

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Introduction: It is crucial to decipher the modulation of regulatory T cells (Tregs) in tumor microenvironment (TME) induced by chemotherapy, which may contribute to improving the efficacy of neoadjuvant chemoimmunotherapy in resectable non-small lung cancer (NSCLC).

Methods: We retrospectively collected specimens from patients with II-III NSCLC, constituting two cohorts: a neoadjuvant chemotherapy (NAC) cohort (N =141) with biopsy (N = 58) and postoperative specimens (N = 141), and a surgery-only cohort (N =122) as the control group. Then, the cell density (Dens), infiltration score (InS), and Treg-cell proximity score (TrPS) were conducted using multiplex fluorescence staining (Foxp3, CD4, CD8, CK, CD31, αSMA). Subsequently, the association of Tregs with cancer microvessels (CMVs) and cancer-associated fibroblasts (CAFs) was analyzed.

Results: Patients with NAC treatment have a higher density of Tregs in both paired (P < 0.001) and unpaired analysis (P = 0.022). Additionally, patients with NAC treatment showed higher infiltration score (paired, P < 0.001; unpaired, P = 0.014) and more CD8+T cells around Tregs (paired/unpaired, both P < 0.001). Multivariate analysis identified that the Dens(Tregs), InS(Tregs) and TrPS(CD8) were significantly associated with better chemotherapy response [OR= 8.54, 95%CI (1.69, 43.14), P = 0.009; OR= 7.14, 95%CI (1.70, 30.08), P = 0.024; OR= 5.50, 95%CI (1.09, 27.75), P = 0.039, respectively] and positive recurrence-free survival [HR = 3.23, 95%CI (1.47, 7.10), P = 0.004; HR = 2.70; 95%CI (1.27, 5.72); P = 0.010; HR = 2.55, 95%CI (1.21, 5.39), P = 0.014, respectively]. Moreover, TrPS(CD8) and TrPS(CD4) were negatively correlated with the CMVs and CAFs.

Conclusions: These discoveries have deepened our comprehension of the immune-modulating impact of chemotherapy and underscored that the modified spatial landscape of Tregs after chemotherapy should be taken into account for personalized immunotherapy, aiming to ultimately improve clinical outcomes in patients with NSCLC.

Keywords: Regulatory T cell, Spatial architecture, Non-small cell lung cancer

P3.08E LOCAL-REGIONAL NON-SMALL CELL LUNG CANCER - BIOMARKERS FOR NEOADJUVANT
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P3.08E.01 Perioperative Chemoimmunotherapy Rescue Cold HLA-Deficient Tumors Inducing Strong Immune Responses and Long-Term Survival

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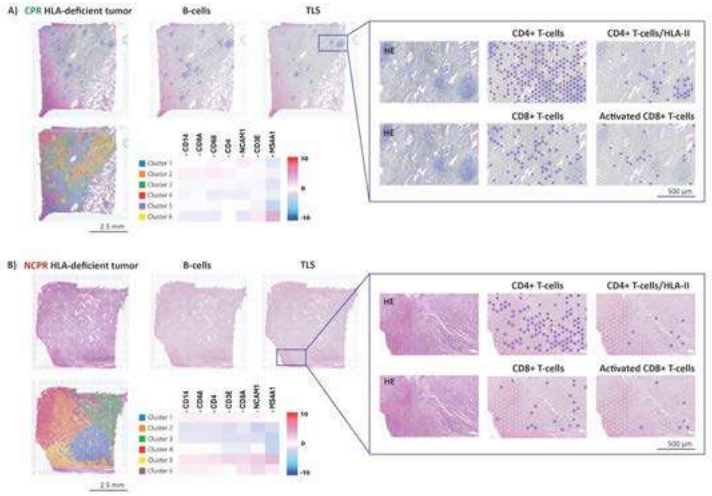
Introduction: Human leukocyte antigen (HLA) class I molecules present antigenic peptides to T-lymphocytes, favoring specific responses. Loss of HLA expression and loss of heterozygosity (LOH) are common events in cancer development that could be implicated in antigen diversity presentation and primary resistance to immunotherapy. Here, we studied the relationship of HLA-I tumor status at diagnosis, with tumor microenvironment and clinical outcomes of NSCLC patients treated with perioperative nivolumab plus chemotherapy (ChIO) from NADIM clinical trial (NCT03081689).

Methods: Diagnostic tissue from 24 patients were analyzed. Baseline HLA tumor status (HLA-deficient or -proficient) was determined by DNA LOH (ImmunoArray-24.v2) combined with immunohistochemistry for protein levels. PD-L1 and TMB were measured in pretreatment FFPE tissue samples. Immune cell populations were determined in baseline and surgery samples by multiplex immunofluorescence. Spatial transcriptomics was performed in posttreatment HLA-deficient tumors using Visium Spatial FFPE Gene Expression and Space Ranger pipeline 2.1.1 with Loupe Browser 7.0.1 analysis (10X Genomics).

Results: Baseline LOH and/or decreased HLA protein levels occurred in 41.7% of tumors and were categorized as HLA-deficient status. HLA-deficient tumors showed a desert-like tumor microenvironment at baseline, with lower PD-L1 levels and immune cell infiltrate, supporting the key role of HLA status in tumor development and immune microenvironment coevolution. Despite their "cold" microenvironment, perioperative ChIO induced similar Complete pathological response (CPR) rates in both HLA-deficient and proficient tumors (50% and 60% respectively, p=0.670). Similarly, ChIO induced high 3-year PFS and OS rates in both HLA-deficient (PFS 70% [95%CI 32.9-89.2] and OS 70% [95%CI 32.9-89.2]) and HLA-proficient (PFS 71.4% [95%CI 40.6-88.2] and OS 92.9% [95%CI 59.1-99.0]) (PFS p=0.909, OS p=0.137). In fact, the study of the post-treatment tumor bed microenvironment of an CPR HLA-deficient tumor showed a strong immune response, supporting observed long-term benefit of ChIO in some patients with HLA-deficient tumors. Focusing on reactive stroma, CPR HLA-deficient tumor had B-cell aggregates (MS4A1/CD19) forming tertiary lymphoid structures (TLS, MS4A1/CD19/CXCL13/CR2), while these were absent in non-CPR HLA-deficient tumor. Additionally, CD4+ T-cells were present in both CPR and Non-CPR HLA-deficient tumors, but CD4+ T-cells/HLA-II colocalization occurred mainly inside TLS of CPR tumor (CD4/CIITA/CD80). Similarly, CD8+ T cells were identified in both HLA-deficient tumors, but activation was only detected in CPR HLA-deficient tumor (CD8A/GZMB/KLRK1).

Conclusions: Our findings highlight the activity of perioperative ChIO in NSCLC HLA-deficient tumors, and the potential role of TLS, as well as the coordinated action of helper and cytotoxic T-cells, in tumor resolution.

Keywords: NADIM CLINICAL TRIAL, cold HLA-deficient, Perioperative Chemoinmmunotherapy



P3.08E LOCAL-REGIONAL NON-SMALL CELL LUNG CANCER - BIOMARKERS FOR NEOADJUVANT
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P3.08E.02 An Artificial Intelligence Driven Approach to Predict Pathological Response to Neoadjuvant Chemoimmunotherapy for Non-Small Cell Lung Cancer

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Introduction: Neoadjuvant chemoimmunotherapy has been evident to play critical roles in perioperative Non-small Cell Lung Cancer (NSCLC). Increased neoadjuvant cycles have been found to be associated with improved pathological response, albeit at the potential of higher adverse effects. To date, it is unlikely to make precise pathological evaluation at the preoperative setting. The aim of our study is to develop an artificial intelligence driven radiomics approach to estimate the pathological response before surgery, optimizing the individualized neoadjuvant strategies.

Methods: 314 patients with II to IIIB NSCLC who received neoadjuvant therapy of anti-programmed death-1(PD-1) combined with chemotherapy in five medical centers in China from May 2019 to August 2023 were retrospectively included. We constructed a training set (n=202), an internal validation set (n=51) and an external validation set (n=61). Radiomic features were extracted from regions of interest delineated on pre- and post-neoadjuvant therapy chest CT imaging. The change in radiomics features, termed as delta features was calculated. The Mann-Whitney U test was employed to eliminate redundant features. Major pathological response (MPR) and non-MPR statuses served as outcome labels. Feature selection within the training set was performed using LASSO regression through a process of 10-fold cross-validation. The predictive model was developed employing eXtreme Gradient Boosting (XGBoost), with the AUC being computed to assess model performance. All statistical analyses were executed using Python (Version 3.11).

Results: Among 314 patients (mean [SD] age,63.2[8.7] years) included, squamous cell carcinoma (209, 66.6%) and stage III disease (212, 67.5%) were predominantly presented. MPR was achieved in 198 patients (63.1%). Over a median follow-up time of 17.0 months, the HR of event-free survival (EFS) between patients achieving MPR and non-MPR was 0.36 (95%CI: 0.20, 0.65, P < 0.01). 4 pre-treatment features, 30 post-treatment features and 11 delta features were selected by LASSO regression. By utilizing these features, we developed pre-treatment, post-treatment, and delta radiomics prediction models based on XGboost algorithm. Of note, compared with pre-treatment and post-treatment model, the delta model demonstrated superior performance in predicting MPR achievement (AUC for internal validation and external validation, respectively: delta model 0.86 and 0.87; pre-treatment model 0.70 and 0.58; post-treatment model 0.83 and 0.65). Moreover, there was significant difference in EFS between MPR and non-MPR predicted by the delta model across training plus internal validation set, as well as external validation set, yielding an HR of 0.31 (95% CI: 0.15, 0.62, P < 0.01) and 0.30 (95% CI: 0.10, 0.94, P = 0.03), respectively.

Conclusions: The establishment of an artificial intelligence based radiomics approach can precisely predict the pathological response to neoadjuvant chemoimmunotherapy, facilitating the identification of the optimal timing for surgery.

Keywords: Neoadjuvant therapy, Non-small Cell Lung Cancer, radiomics

P3.08E.03 Dynamics of Peripheral Blood Inflammatory Index Predict Response of Neoadjuvant Immunotherapy in Non-Small Cell Lung Cancer

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Introduction: Static tumor features before treatment were insufficient to select responding tumors under the selective pressure of immunotherapy. Herein, we investigated the value of longitudinal dynamics of peripheral blood inflammatory indexes (dPBI) in predicting major pathological response (MPR) in non-small cell lung cancer (NSCLC).

Methods: 147 NSCLC patients underwent neoadjuvant immunochemotherapy were reviewed as training cohort and 26 NSCLC patients from a phase II trial were validation cohort. dPBIs were calculated as posttreatment values of PBI minus their baseline values. Least absolute shrinkage and selection operator algorithm was utilized to screened out predictors for MPR and integrated a MPR score. We constructed a model incorporating this MPR score and clinical predictors for predicting MPR and evaluated its predictive capacity via the area under the curve (AUC) of the receiver operating characteristic and calibration curves. Furthermore, we sought to interpret this MPR score in the context of micro-RNA transcriptomic analysis in plasma exosomes for 12 paired samples (baseline and posttreatment) obtained from training cohort.

Results: Longitudinal dynamics of monocyte-lymphocyte ratio, platelet-to-lymphocyte ratio, platelet-to-albumin ratio, and prognostic nutritional index were screened out as significant indicators for MPR and integrated a MPR score, an independent predictor of MPR. Then, a predictive model incorporating MPR score, histology and differentiated degree, discriminated MPR and non-MPR patients well in both training and validation cohorts with an AUC of 0.803 and 0.817, respectively. Furthermore, micro-RNA transcriptomic analysis revealed the association between our MPR score and immune regulation pathways. And significantly better event-free survival was seen in subpopulations with high MPR score.

Conclusions: dPBI reflected responses to neoadjuvant immunochemotherapy for NSCLC. The MPR score, a non-invasive biomarker integrating four dPBIs, captured the miRNA transcriptomic pattern and distinguished MPR from non-MPR for neoadjuvant immunochemotherapy, which could support the clinical decisions on the utilize of ICIs-based treatments in NSCLC patients.

Keywords: non-small cell lung cancer, neoadjuvant immunotherapy, dynamics

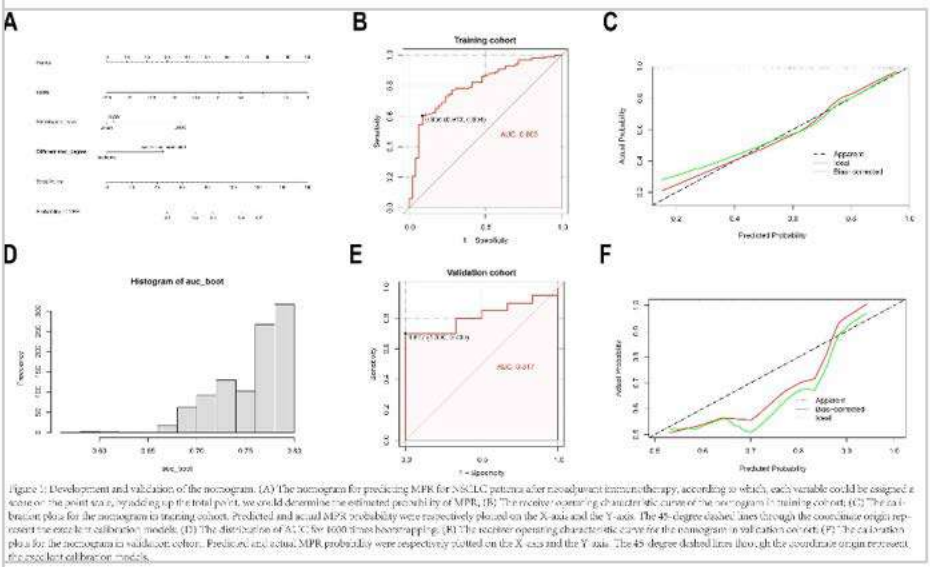


Figure 1: Development and validation of the nomogram. (A) The nomogram for predicting MPR for NSCLC patients after neoadjuvant immunotherapy, according to which, each variable could be assigned a score on the point scale, by adding up the total points, we could determine the estimated probability of MPR; (B) The receiver operating characteristic curve of the nomogram in training cohort; (C) The calibration plots for the nomogram in training cohort. Predicted and actual MPR probability were respectively plotted on the X-axis and the Y-axis. The 45-degree dashed lines through the coordinate origin represent the excellent calibration models; (D) The distribution of AUC for 1000 times bootstrapping; (E) The receiver operating characteristic curve for the nomogram in validation cohort; (F) The calibration plots for the nomogram in validation cohort. Predicted and actual MPR probability were respectively plotted on the X-axis and the Y-axis. The 45-degree dashed lines through the coordinate origin represent the excellent calibration models.

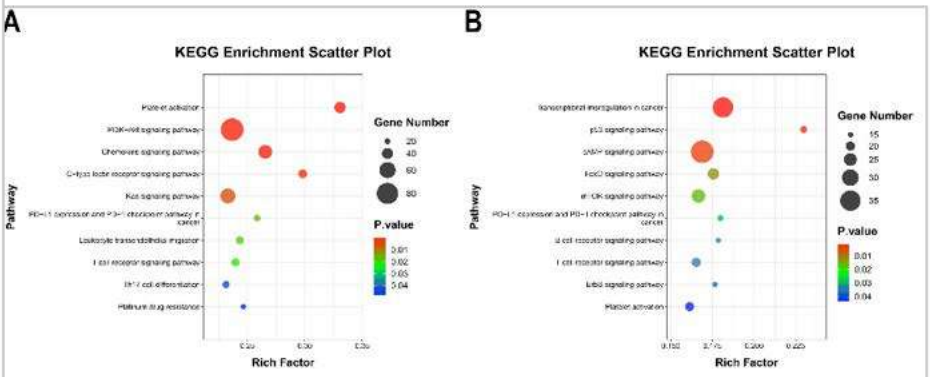


Figure 2: The scatter plot of KEGG enrichment analysis. (A) The pathways involved in immune regulation and signal transduction of 3 miRNAs which positively correlated with MPR signature; (B) The pathways of involved in immune regulation and signal transduction 2 miRNAs which negatively correlated with MPR signature.

P3.08E.04 TCR Metrics as Predictive Biomarkers of Response and Survival after Perioperative Chemoimmunotherapy. NADIM & NADIM II Trials

C. Martínez-Toledo[1], B. Sierra[1], M. Molina-Alejandre[1], M. Casarrubios[1], V. Calvo[1], E. Nadal[2], M.R. García Campelo[3], A. Martínez-Martí[4], A. Garrido[5], B. Massutí[6], A. Insa[7], J. De Castro[8], M. Dómine[9], J.L. González-Larriba[10], M. Majem[11], S. Ponce[12], I. Barneto[13], A. Aguilar[14], J. Martín-López[1], M. Provencio[1], A. Cruz- Bermúdez[1], [1]Hospital Universitario Puerta de Hierro-Majadahonda, Madrid/ES ,[2]Institut Català d'Oncologia L'Hospitalet de Llobregat, Hospitalet de Llobregat (Barcelona)/ES ,[3]Complexo Hospitalario Universitario A Coruña, A Coruña/ES ,[4]Hospital Universitario e Instituto de Oncología Vall d´Hebron (VHIO), Barcelona/ES ,[5]Complexo Hospitalario Universitario de Vigo, Pontevedra/ES ,[6]Hospital General Universitario Dr. Balmis de Alicante, Alicante/ES ,[7]Fundación INCLIVA, Hospital Clínico Universitario de Valencia, Valencia/ES ,[8]Hospital Universitario La Paz, Madrid/ES ,[9]Hospital Universitario Fundación Jiménez Díaz. IIS-FJD, Madrid/ES ,[10]Hospital Clínico San Carlos, Madrid/ES ,[11]Hospital de la Santa Creu i Sant Pau, Barcelona/ES ,[12]Hospital Universitario [12] de Octubre, Madrid/ES ,[13]Hospital Universitario Reina Sofia, Córdoba/ES ,[14]Instituto Oncológico Dr. Rosell. Hospital Universitario Quiron Dexeus, Grupo QuironSalud,, Barcelona/ES

Introduction: T-cell Receptor (TCR) repertoire metrics have shown potential as efficacy biomarkers for immunotherapy treated patients. In NADIM trial (NCT03081689), higher TCR repertoire clonality in tumors at baseline, were associated to hot microenvironment, improved rates of complete pathological responses (CPR), and survival after perioperative nivolumab plus chemotherapy (ChIO) in locally-advanced NSCLC. In this study, we aimed to confirm our previous results increasing the patient cohort and follow-up, including patients from NADIM and NADIM II (NCT03838159) trials.

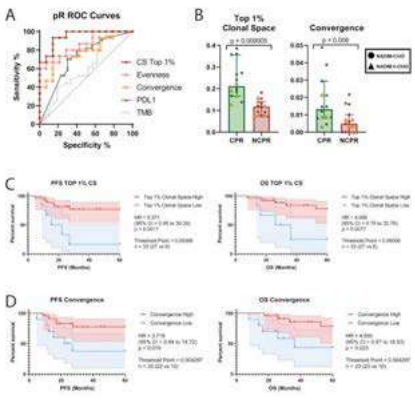
Methods: TCR data from FFPE tissue samples obtained before and after neoadjuvant treatment was available from 71 patients (NADIM-ChIO, n=42; NADIM-II-ChIO, n=19; NADIM-II-Ch, n=10). TCR repertoire was determined using the NGS Oncomine TCR Beta-SR assay. The association of different TCR metrics (Convergence, Evenness and TOP1% clonal space (CS) with pathological response and survival, were performed by U-Mann Whitney test and Kaplan-Meier with log-rank analysis, respectively. ROC curves and best likelihood ratio were used to determine cut-off points in survival analyses. Analyses were performed on the pooled ChIO-treated patients (NADIM+NADIM-II-ChIO), and individually in NADIM-ChIO, NADIM-II-ChIO, and NADIM-II-Ch arms.

Results: The median follow-up time was 27 and 60 months for NADIM II and NADIM trials, respectively. Regarding pathological responses in NADIM+NADIM-II-ChIO, metrics derived from baseline TCR repertoire analysis presented a relevant ROC curve for predicting CPR (Convergence AUC=0.79, p=0.0078; Evenness AUC=0.86, p=0.0011; TOP1% CS AUC= 0.95, p<0.0001) compared with PD-L1 or TMB (PD-L1 AUC=0.71, p=0.0037; TMB AUC=0.61, p=0.226). CPR tumors showed increased levels of baseline TCR convergence (p=0.008), TOP1% CS (p=0.000005), PD-L1 (p=0.0024) and reduced Evenness (p=0.001). Concerning survival, baseline TCR metrics were associated to PFS and OS. Thus, patients harboring tumors with higher TCR evenness, or lower TOP1%CS or convergence, showed higher risk of disease progression (Hazard Ratio (HR)=4.38, p=0.0096; HR=5.37, p=0.0017; HR=3.72, p=0.019; respectively), or death (HR=3.08, p=0.093; HR=4.96, p=0.0077; HR=4.06, p=0.023; respectively). Patients with negative PD-L1 tumors or TMB-low (<3.8 mut/Mb) showed a trend for increased risk of disease progression or death (PD-L1 PFS HR=2.32, p=0.054; PD-L1 OS HR=1.83, p=0.284; TMB PFS HR=3.62, p=0.069; TMB OS HR=5.84, p=0.043. Similar results for biomarkers were observed in NADIM and NADIM II ChIO cohorts analyzed separately, and were not predictive of patients' outcomes when analyzed in posttreatment samples or in chemotherapy treated patients.

Conclusions: Baseline TCR metrics, particularly convergence, evenness, and TOP1% CS, demonstrate robust predictive value for CPR and survival in locally-advanced NSCLC patients undergoing perioperative nivolumab plus chemotherapy, warranting further investigation in larger cohorts.

Keywords: NADIM and NADIM II Clinical trials, TCR metrics, Perioperative Chemoinmmunotherapy

IMAGE



P3.08F LOCAL-REGIONAL NON-SMALL CELL LUNG CANCER - CLINICAL TRIALS IN PROGRESS
MONDAY, SEPTEMBER 9, 2024 - 12:00 - 14:00

P3.08F.01 Interim Analysis of a Phase 2 Prospective Trial of Induction Lorlatinib in Locally Advanced ALK-Positive NSCLC (LORIN)

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Introduction: Induction ALK-TKIs in locally advanced NSCLC remained an emerging area for further exploration. Although lorlatinib has exhibited superb clinical benefit in advanced NSCLC, no corresponding date regarding locally advanced disease was reported. Herein, we report an interim analysis of a phase 2 prospective trial (NCT05740943).

Methods: This is an open-label, phase 2 prospective trial with Simon two-stage design. 13 patients with confirmed stage III through PET scan as well as brain MRI and ALK fusion were estimated to enroll for stage I cohort. Patients would be provided with 3 cycles (90 days) induction lorlatinib and evaluated by multidisplenary team to determine the subsequent local treatment. The primary endpoint was pathological complete response (pCR). At least 3 patients achieved pCR could allow for initiation of stage II cohort. Longitudinal tumor-naive MRD and large panel NGS were performed.

Results: By March 1, 2024, 13 patients were consecutively enrolled and 11 patients had completed induction treatment and surgery. 2 patients refused surgery and local radiotherapy due to patient's willingness and sever toxicity, respectively. 4, 8 and 1 patients diagnosed as stage IIIA, IIIB and IIIC disease, respectively. PD-L1 positive was found in 69.2% patients and 30.8% had PD-L1 high expression. The overall response rate was 76.9% and disease control rate was 100%. The most common treatment-related adverse events included hypercholesterolemia, hypertriglyceridemia and weight gain. For patients who underwent surgery, one patient received 4 cycles induction treatment while others completed 3 cycles treatment. In terms of the baseline evaluation, 7 patients (53.8%) had unresectable disease due to N3 metastasis and the surgical conversion rate was 85.7% with pathologically confirmed N3 negative after induction treatment. pCR and MPR for ITT and PP cohort was 23.1% vs. 27.3% and 76.9% vs. 90.9%, respectively. LN-pathologically downstaging rate was 63.6%. All patients had undergone minimally invasive lobectomy except for one patient had conversion to open thoracotomy. 3 patients had mild surgical difficulties while others (72.7%) had moderate to severe surgical difficulties regarding fibrosis and adhesion. Baseline PD-L1 expression did not impact treatment efficacy and all patients with MRD positive (46.2%) at baseline had ctDNA clearance after induction treatment.

Conclusions: Induction lorlatinib was clinically feasible and tolerable in stage III ALK-mutant NSCLC regardless of PD-L1 expression, leading to high surgical conversion. Short-term lorlatinib could efficiently eliminate ctDNA though sensitivity for fusion detection warranted further improvement.

Keywords: Phase 2 Prospective Trial, Lorlatinib, ALK-Positive NSCLC

P3.08F.02 MRD Guiding Treatment after Aumolertinib Induction Therapy for EGFRm+ Stage III NSCLC in the MDT Diagnostic Model (APPROACH)

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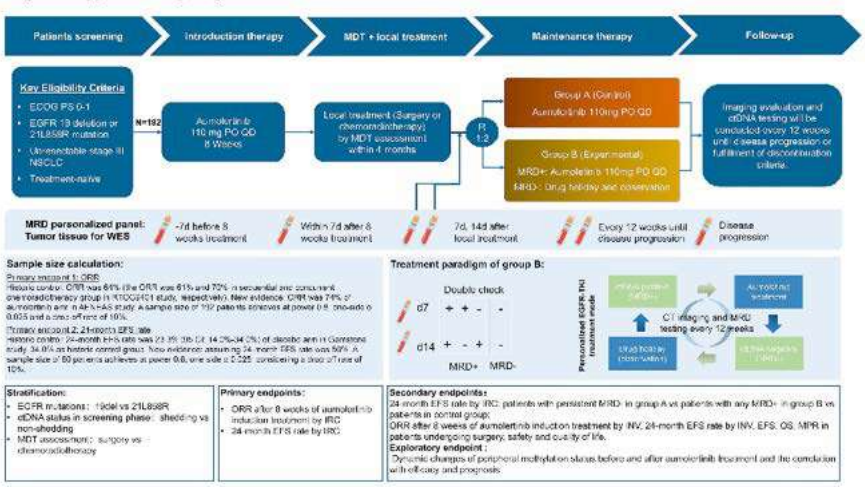
Introduction: The current standard therapy for patients with unresectable stage III non- small cell lung cancer (NSCLC) is concurrent or sequential chemoradiotherapy followed by immune-maintenance therapy (Pacific). However, the recent studies have shown that EGFRm+ stage III unresectable NSCLC who received epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs) after chemoradiotherapy had longer survival. Our study aims to firstly evaluate the efficacy and safety of aumolertinib induction therapy in EGFRm+ patients with unresectable stage III NSCLC and dynamic minimal residual disease (MRD) guided maintenance therapy with aumolertinib after local therapy (surgery or chemoradiotherapy) evaluated by multidisciplinary team (MDT) (NCT04841811/CTONG2101).

Methods: This is an open-label, multi-center, randomized, phase III study. Patients have histopathology or cytology confirmed Stage III non-squamous NSCLC and investigator confirmed unresectable. The performance status (Eastern Cooperative Oncology Group) is 0 or 1. This trial is prepared to enroll 192 patients (Figure 1). Eligible patients receive aumolertinib 110 mg QD for 8 weeks, followed by local treatment (surgical or chemoradiotherapy) which is evaluated by MDT assessment. Patients are randomized (1:2) to group A or B. Stratification factors include EGFR exon 19 deletion or 21L858R mutation, shedding or non-shedding ctDNA at baseline, surgery or chemoradiotherapy under MDT. Patients in group A receive aumolertinib 110 mg QD. Patients in group B receive aumolertinib 110 mg QD guided by dynamic MRD monitoring: aumolertinib treatment or drug holiday (only observation) in the first cycle is determined by the d7 and d14 MRD status after local therapy; after that, when ctDNA positive (MRD+), patients receive aumolertinib 110 mg QD until ctDNA turns to negative (MRD-); at this time, patients stop aumolertinib until ctDNA turns to positive and restart aumolertinib. Imaging evaluation and ctDNA testing will be conducted every 12 weeks. The treatment paradigm of group A and B will be continued until disease progression or fulfillment of discontinuation criteria. Primary endpoints are objective response rate after 8 weeks of aumolertinib induction therapy and 24-month event-free survival (EFS) rate assessed by independent review committee between group A and B. Secondary endpoints are comparison of 24-month EFS rate among three cohorts (patients with longitudinal negative MRD in group B vs patients with any positive MRD in group B vs group A), overall survival, EFS, major pathological response rate in patients undergoing surgery, safety and quality of life. The trial initiated on June, 2022. Now is ongoing.

Keywords: EGFRm+ stage III NSCLC, aumolertinib introduction followed by MDT, personalized EGFR-TKI with MRD monitoring

Figure 1: Key points of study design of CTONG2101/APPROACH



P3.08F LOCAL-REGIONAL NON-SMALL CELL LUNG CANCER - CLINICAL TRIALS IN PROGRESS
MONDAY, SEPTEMBER 9, 2024 - 12:00 - 14:00

P3.08F.03 NRG LU008: Phase III Randomized Trial of Primary Tumor SBRT Followed by Concurrent Mediastinal Chemoradiation for LA-NSCLC

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Introduction: Outcomes remain poor for unresectable LA-NSCLC treated with concurrent chemoradiation followed by immunotherapy. The primary tumor is the most common site of non-metastatic failure, and local failure (LF) directly correlates with overall survival (OS). While local control (LC) and OS have improved by increasing the biological effective dose with SBRT in early-stage NSCLC, SBRT use in LA-NSCLC has largely been limited to primary tumor boost after chemoradiation, which has high morbidity. A recent phase II trial of SBRT to the primary tumor and chemoradiation to involved lymph nodes demonstrated lower rates of pulmonary and cardiac toxicities relative to historical controls, while improving LC, progression-free survival (PFS), and OS. We hypothesize that replacing conventionally fractionated radiotherapy with SBRT to the primary tumor followed by concurrent chemoradiation to the mediastinum will be associated with lower rates of toxicity and improved QOL, while also improving LC, PFS, and OS.

Methods: LU008 is a phase III randomized trial in stage II-III NSCLC conducted by NRG Oncology (NCT05624996). Patients are randomized to chemoradiation to all disease (60/2 Gy) (control arm) or SBRT to the primary (BED ≥100 Gy in 3-5 fractions) followed by chemoradiation to nodal disease (60/2 Gy) (experimental arm). Standard concurrent chemotherapy regimens are allowed in both arms. Maintenance therapy is pragmatic, with most patients expected to receive durvalumab for up to 12 months. Inclusion criteria include node-positive stage II-III NSCLC, medically inoperable or refuse surgery, identified primary tumor ≤7 cm, ECOG performance status (PS) 0-2, and ≤4 cycles of systemic therapy prior to registration. Key exclusion includes central primary tumor location that is <2cm from involved nodal disease. The primary objective is to compare OS and PFS. Secondary objectives are response rate, LC, patterns of failure, pulmonary function changes, QOL, and toxicity. Exploratory objectives include biospecimen analyses, regional lung ventilation, and proton vs. photon differences. Real-time pre-treatment reviews are conducted

Results: LU008 was activated nationally on 5/10/23. As of 4/3/24, 40 patients have been accrued, and 280 sites have the trial open to accrual. Final target accrual is 474 subjects, with an expected 9.5 accruals per month after an initial 6-month ramp up.

Conclusions: LU008 is poised to change the standard of care in inoperable LA-NSCLC by improving LC, PFS, and OS. It is the most pragmatic thoracic NCI National Clinical Trial Network (NCTN) trial, with no lab/PFT cutoffs, no CT chest/MRI brain/lab time windows, and allowing patients with actionable mutations and ECOG PS 2. LU008 is the only phase III NCTN trial accruing for inoperable LA-NSCLC, and robust accrual is expected.

Keywords: Lung cancer, Locally advanced unresectable NSCLC, SBRT

P3.08F LOCAL-REGIONAL NON-SMALL CELL LUNG CANCER - CLINICAL TRIALS IN PROGRESS
MONDAY, SEPTEMBER 9, 2024 - 12:00 - 14:00

P3.08F.04 Developing Circulating and Imaging Biomarkers Towards Personalised Radiotherapy in Lung Cancer: An Update on the VIGILANCE Study

A. Horne[1], H. Crawford[2], C. Dempsey[1], C. Faivre-Finn[1], [1]University of Manchester, Manchester/GB ,[2]The Christie NHS Foundation Trust, Manchester/GB

Introduction: Multi-modality radiotherapy-based treatments are available to treat patients with stage III non-small cell lung cancer and are associated with improved clinical outcomes. However, not all patients benefit from these complex treatments and there is a paucity of biomarkers supporting treatment decisions tailored to the individual patient.

The VIGILANCE study's primary aim is to build a prognostic model using longitudinal novel health technology data collected before, during and for 1 year after completion of radiotherapy in patients with stage III non-small cell lung cancer. This includes blood samples for methylated circulating tumour DNA analysis, electronic patient reported outcome measures (ePROMs) and radiomic analysis of standard of care imaging.

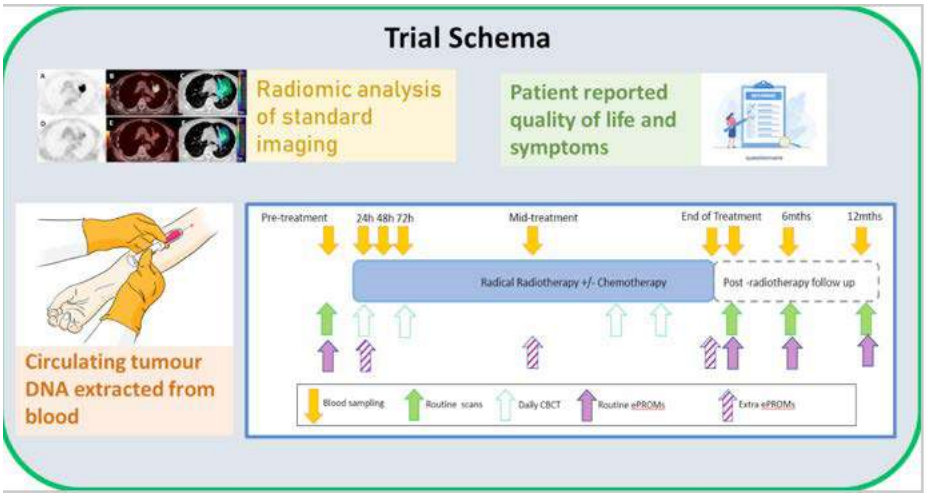
The study is sponsored by the University of Manchester and funded by CRUK, a Rosetree Grant and AstraZeneca.

Methods: The VIGILANCE study opened to recruitment on 24th March 2023 for 18 months. Up to 80 patients will be enrolled. Key eligibility: Inoperable stage III NSCLC planned to be treated with either radical radiotherapy, sequential chemoradiotherapy and concurrent chemoradiotherapy +/- consolidation immunotherapy. Participants will have additional blood samples and ePROMs performed and their standard of care imaging will be acquired as per schema (see Image 1 below).

As of 06/04/2024, 35 patients have been registered: 21 patients were treated with concurrent chemoradiotherapy, 5 patients with sequential chemoradiotherapy, 5 patients with radiotherapy alone, 1 patient died of a pneumonia prior to starting treatment, 1 patient progressed and was no longer ineligible and 2 patients withdrew their consent.

The study continues to recruit and further information is available: https://clinicaltrials.gov/study/NCT06086574

Keywords: Exploratory study, Circulating tumor DNA, Radiomics



P3.08F LOCAL-REGIONAL NON-SMALL CELL LUNG CANCER - CLINICAL TRIALS IN PROGRESS
MONDAY, SEPTEMBER 9, 2024 - 12:00 - 14:00

P3.08F.05 Four-Cycle Compared with Two-Cycle Neoadjuvant Chemoimmunotherapy Achieved a Higher Rate of pCR: Preliminary Results of a Phase III Trial

D. Lin, X. Wang, X. Li, J. Fan, Shanghai General Hospital, Shanghai/CN

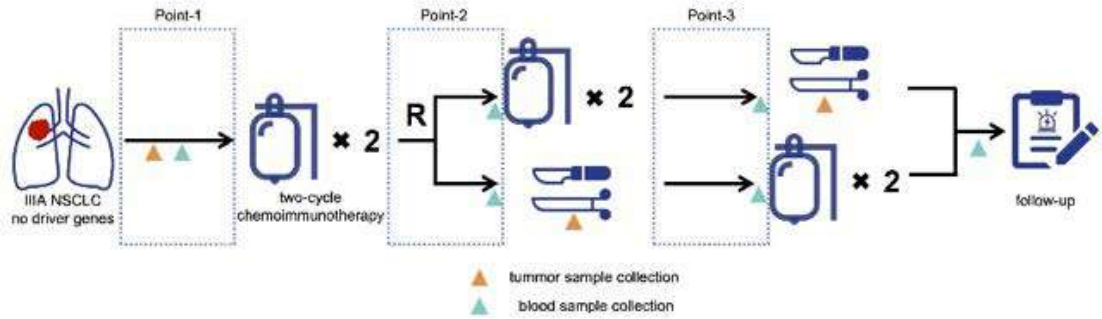
Introduction: Neoadjuvant chemoimmunotherapy (NCI) targeting the PD-1/PD-L1 pathway is effective for non-small-cell lung cancer (NSCLC). However, few studies have focused on the optimal cycles of NCI. We have launched a prospective, multicenter, phase III randomized controlled clinical study to evaluate the safety and efficacy of two-cycle versus four-cycle neoadjuvant PD-1 antibody plus chemotherapy followed by surgery in resectable stage IIIA non-small cell lung cancer (NCT05157776).

Methods: The patients with IIIA NSCLC without driver genes were given two cycles of NCI (initial two-cycle NCI), after which they were 1:1 randomly assigned to the two-cycle NCI groups (no additional NCI) or four-cycle NCI group (with another two cycles of NCI) (Figure.1). The primary endpoint is pathological complete regression (pCR) rate.

Results: Of the 26 patients that had completed neoadjuvant NCI, surgical resection and pathological re-evaluation, the pCR rate was 23.1% (3/13) in the two-cycle group, and it was 53.8% (7/13) in the four-cycle group. These were mostly consistent with the pre-estimated rates. The incidences of immunotherapy-related accidental events (AEs) were comparable between the groups. And no new AE was observed.

Conclusions: Compared with two-cycle NCI, four-cycle NCI achieved a higher rate of pCR, with comparable incidences of immunotherapy-related AEs. More data is needed to further validate it.

Keywords: NSCLC, Immunotherapy, Neoadjuvant Cycles



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MONDAY, SEPTEMBER 9, 2024 - 12:00 - 14:00

P3.08F.06 PLATINUM Trial: Preliminary Analysis of Lazertinib Therapy in Locally Advanced, Unresectable, EGFR Mutation(+) NSCLC Following CCRT

S.Y. Lee[1], J. Choi[1], T.W. Jang[2], S.H. Lee[3], D.W. Park[4], S.I. Choi[5], S.H. Yoon[6], J.H. Lim[7], J.E. Lee[8], S.Y. Lee[9], S.H. Park[10], I-J. Oh[11], E.Y. Kim[12], J.C. Lee[13], [1]Korea University Guro Hospital, Seoul/KR ,[2]Kosin University Gospel Hospital, Busan/KR ,[3]Kyung Hee University Hospital, Seoul/KR ,[4]HanYang University Hospital, Seoul/KR ,[5]Korea University Anam Hospital, Seoul/KR ,[6]Pusan National University Yangsan Hospital, Busan/KR ,[7]Inha University Hospital, Incheon/KR ,[8]Chungnam National University, Daejeon/KR ,[9]Kyungpook National University Chilgok Hospital, Daegue/KR ,[10]Keimyung University Dongsan Hospital, Daegu/KR ,[11]Chonnam National University Medical School and Hwasun Hospital, Hwasun/KR ,[12]Yonsei University Severance Hospital, Seoul/KR ,[13]Ulsan University Asan Medical Center, Seoul/KR

Introduction: The PACIFIC trial has demonstrated sustained overall survival (OS) benefit with durvalumab as consolidation therapy after concurrent chemoradiation therapy (CCRT). In a subgroup analysis, the effect was not proven in EGFR mutation positive patients. Lazertinib is 3rd generation EGFR TKI as osimertinib and shows good anti-cancer effect in EGFR sensitive mutations in LASER 301 trial. PALTINUM trial is an ongoing, phase II trial, evaluating the efficacy and safety of lazertinib as consolidative treatment after CCRT in patients who had EGFR mutation positive NSCLC (E19del/L858R, Stage III). We present data from the preliminary efficacy and safety data.

Methods: Eligible patients (≥18 years) with inoperable stage III EGFR mutation positive NSCLC (AJCC 8th edition), who have not progressed following CCRT, received lazertinib as consolidation therapy. Primary endpoint is PFS and 2ndary endpoints are OS, the objective response rate, the duration of response, the time to death or distant metastasis, and safety.

Results: Twenty-five patients enrolled in this analysis. At the 29 Feb 2024 database lock (median follow-up, 12.7 mo), the median age was 67 years, 56% were females, 56% were never smokers. The objective response rate and disease control rate were 72%, 100%, respectively. Among never or former smokers, 50% demonstrated a partial response to lazertinib, indicating significant tumor regression. Conversely, all current smokers exhibited only stable disease, with no cases of partial response observed. Median PFS was not reached. The most common treatment-related Grade 3 adverse events (AEs) were dermatitis (8%), paraesthesia (4%), asthenia (4%) and pulmonary embolism (4%). Treatment-related AEs leading to discontinuation occurred in 16% of patients. Grade 2 radiation pneumonitis developed in three patients (12%), but no lazertinib-related pneumonitis was observed (table).

Conclusions: In this preliminary analysis from PLATINUM trial, consolidative lazertinib demonstrated clinically meaningful efficacy and no new safety signal was detected at interim analysis.$$graphic_{D3846C3D-AA63-41BE-8D4B-0BA4522B9029}$$

Keywords: EGFR mutation, CCRT, Lazertinib

P3.08F LOCAL-REGIONAL NON-SMALL CELL LUNG CANCER - CLINICAL TRIALS IN PROGRESS
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P3.08F.07 Efficacy and Safety of Envafolimab Plus Platinum-based Chemotherapy as Neoadjuvant Therapy in Resectable Stage II-IIIB NSCLC

H. Zhang, G. Zhao, J. Gu, D. Ge, Zhongshan Hospital, Fudan University, Shanghai/CN

Introduction: Multiple clinical trials have reported the striking benefit for PD-1/PD-L1 monoclonal antibody combined with chemotherapy neoadjuvant therapy for non-small cell lung cancer (NSCLC), while the efficacy of subcutaneous injection of anti-PD-L1 Envafolimab combined with chemotherapy neoadjuvant therapy for NSCLC patients has not been demonstrated yet. Envafolimab is a novel recombinant protein of a humanized camel-derived single-domain anti-PD-L1 antibody fused with a human IgG1 Fc fragment designed for subcutaneous injection, making it easy to administer and improving patient compliance. This study aims to investigate the efficacy and safety of Envafolimab plus platinum-based chemotherapy as neoadjuvant therapy in resectable stage II-IIIB NSCLC.

Methods: In this prospective, open-label, single-arm study aims to enroll histologically confirmed, potentially resectable stage II-IIIB NSCLC patients. Eligible patients will receive concurrent 300 mg Envafolimab and chemotherapy (cisplatin 50~100mg/m2 or carboplatin AUC = 4~6 plus pemetrexed 500mg/m2 or docetaxel 60-75mg/m2) on day 1 for three 21-day cycles. Radical surgery was scheduled within 4-6 weeks after the last dose of neoadjuvant therapy, followed by optional adjuvant therapy. Follow up will last for three years unless the subject withdraws. The primary endpoint was pathological complete response (pCR) rate. The secondary endpoints included event-free survival (EFS), major pathologic response (MPR) rate, R0 resection rate, safety and quality of life.

Results: Thirteen patients were enrolled. The pCR rate was 30.7%, and the MPR rate was 53.8%. R0 resection rate reached 92.3%. Two patients (15.4%) had at least one grade 3 or 4 related treatment-emergent adverse event. No grade 5 treatment-emergent adverse events related to Envafolimab were reported.

Keywords: Envafolimab, Resectable NSCLC, Neoadjuvant chemoimmunotherapy

P3.08F LOCAL-REGIONAL NON-SMALL CELL LUNG CANCER - CLINICAL TRIALS IN PROGRESS
MONDAY, SEPTEMBER 9, 2024 - 12:00 - 14:00

P3.08F.08 NEOLA: Phase II Study of Osimertinib Treatment Before and after Chemoradiotherapy in Unresectable Stage III EGFRm NSCLC

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Introduction: Epidermal growth factor receptor (EGFR) mutations are detected in up to one third of patients with unresectable stage III NSCLC. Osimertinib - a third-generation, central nervous system-active EGFR-tyrosine kinase inhibitor (TKI) - is recommended in advanced and early-stage surgically-resectable EGFR mutation-positive (EGFRm) NSCLC. The Phase III LAURA study (NCT03521154) is evaluating osimertinib efficacy and safety in patients with unresectable stage III EGFRm NSCLC after definitive CRT. A number of small studies have shown EGFR-TKIs may be effective as induction treatment prior to CRT in unresectable stage III EGFRm NSCLC; however, further investigation is required. NEOLA (NCT06194448) is a global Phase II, open-label, single-arm study assessing the efficacy and safety of induction osimertinib followed by chemoradiotherapy (CRT) and osimertinib maintenance in patients with unresectable stage III EGFRm NSCLC.

Methods: Approximately 70 patients ≥18 years of age with unresectable stage III (International Association for the Study of Lung Cancer Staging v8) EGFRm (exon 19 deletion or exon 21 L858R mutation) NSCLC, who are eligible for curative-intent CRT, will be enrolled in the NEOLA study. Patients will receive osimertinib (80 mg once daily [QD]) as induction treatment for 8 weeks (±1 week). After a minimum 5-day washout, patients will receive sequential/concurrent platinum-based CRT. Within 6 weeks post-CRT, patients without progressive disease (PD) will receive osimertinib (80 mg QD) until PD (per Response Evaluation Criteria in Solid Tumors v1.1) or another discontinuation criterion. The primary endpoint is 12-month progression-free survival rate. The secondary endpoints are: objective response rate and disease control rate at the end of the induction phase; overall survival; eventfree survival; and safety, including the incidence and characterization of interstitial lung disease, pneumonitis, and radiation pneumonitis. The exploratory endpoints include description of target volumes, radiological exposure, and dosimetric variables. Recruitment for NEOLA will begin in early 2024.

Keywords: Osimertinib, Induction, Maintenance

P3.12C METASTATIC NON-SMALL CELL LUNG CANCER - TARGETED THERAPY - BRAF/ HER2 / MET / NOVEL TARGETS
MONDAY, SEPTEMBER 9, 2024 - 12:00 - 14:00

P3.12C.01 BRAF Mutation Diversity and Impact on Clinical Outcomes in Non-Small Cell Lung Cancer

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Introduction: Both the combinations of dabrafenib with trametinib and more recently encorafenib with binimetinib have been FDA approved for the management of BRAF V600E-mutant advanced non-small cell lung cancer (NSCLC). However, questions remain regarding how targeted therapies and immunotherapies should be incorporated into the overall treatment regimen for this subset population. BRAF V600E mutations account for 50% of BRAF mutations in NSCLC and some, but not all, non-V600E BRAF alterations can be oncogenic. Prior investigations have classified BRAF mutations into three distinct functional classes. In this study, we analyze the therapeutic implications of class variants on targeted and immunotherapy strategies.

Methods: Here we retrospectively evaluate a multi-institutional cohort of BRAF-mutant NSCLC patients (n=97) and conduct chemical screens of class II and class III BRAF-mutant cell lines to better understand pathway dependencies for each mutational class. We utilize a clinco-genomic database (n=342) to identify co-occurring genetic alterations and tumor mutation burden (TMB) associated with each class.

Results: Class I BRAF mutations were detected in 46 of 97 patients (47%), class II mutations in 12 patients (12%), and class III in 17 patients (18%). Of the class I BRAF-mutant patients, 22 were treated with combination BRAF-MEK inhibitor therapy. We identified that class I BRAF mutation treated with BRAF-MEK inhibitors at any line had greater overall survival compared to those without targeted treatment regardless of immunotherapy treatment (median OS 40.0 vs 10.0 months, Log-rank p=0.043). From our clinico-genomic database analysis, we observed that tumors with class II BRAF variants were significantly more likely to harbor concurrent MAPK pathway alterations relative to class I and III (Chi Square p<10-4). A total of 33 RAS alterations (15 NRAS, 15 KRAS, 3 HRAS) were seen in class II and III tumors in contrast to two in class I tumors. In addition, BRAF class I mutant tumors had significantly lower median TMB (4.8 mut/Mb) compared to class II (8.65 mut/Mb, Wilcoxon p = 1.77e-9) and class III (10.8 mut/Mb, Wilcoxon p<10-10). Computational modeling demonstrated a stereochemical impediment to stable binding between vemurafenib and the class III BRAF mutations G466V, G596R, and D594H. In vitro testing identified that some class II mutant cells were pharmacologically inhibited by pan-RAF, MEK, and pan-EGFR inhibitors.

Conclusions: We conclude that BRAF variants have distinct functional and genomic signatures that have therapeutic implications. Receiving combination BRAF-MEK inhibitor therapy for class I mutations was associated with superior overall survival compared to those patients who did not receive the medicines. Class II and III tumors have higher TMB which may suggest the role of immunotherapy in this subset population. In vitro drug testing in class II and III cell lines demonstrates cell death in select lines for pan-RAF, ERK, MEK, and pan-EGFR inhibitors. Further analyses are needed to determine the clinical value of EGFR, ERK, MEK, and pan-RAF inhibition in class II and III patients.

Keywords: BRAF, NSCLC, Targeted Therapy

P3.12C METASTATIC NON-SMALL CELL LUNG CANCER - TARGETED THERAPY - BRAF/ HER2 / MET / NOVEL TARGETS
MONDAY, SEPTEMBER 9, 2024 - 12:00 - 14:00

P3.12C.02 MET Fusions in NSCLC: Prevalence, Oncogenicity, and Resistance Mechanism

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Introduction: Molecular testing is part of the standard diagnostic algorithm of advanced non-small cell lung cancer (NSCLC). As a result, MET fusions are increasingly detected, with reports demonstrating clinical response to MET tyrosine kinase inhibitors (TKIs). We aimed to characterize MET fusions in NSCLC both as a primary oncogenic alteration and as a mechanism of acquired resistance to targeted therapy.

Methods: Clinicopathological features of NSCLC with MET fusions were queried from three datasets (cBioportal; GENIE; and Dana-Farber Cancer Institute). We describe a clinical case of advanced NSCLC harboring a MET fusion treated with a MET TKI. This index case of MET fusion was modeled in vitro for oncogenicity, resistance, and activating mechanisms. This MET fusion was also modelled as a mechanism of acquired resistance to EGFR TKI in the context of EGFR-mutant NSCLC.

Results: Among the three pooled cohorts, MET fusions were observed in 0.13% of NSCLC (43/33, 927). ST7 was the most common fusion partner gene (19%, 8/43), followed by HLA-DRB1 (14%, 6/43), and KIF5B (9%, 4/43). The median age of patients was 66 years (range: 25-89), 54% (N=23) were female; and the most common histology was adenocarcinoma (77%, 33/43), followed by squamous cell carcinoma (9%, 4/43). Co-occurring driver alterations were seen in 33% (14/43) of cases, including EGFR mutations (57%, 8/14), KRAS mutations (29%, 4/14), ALK fusion (7%, 1/14), and METex14 alteration (7%, 1/14). Co-occurring MET amplification was detected in 35% of cases. Within the DFCI cohort, a MET fusion was detected after targeted therapy in other oncogene-driven NSCLC (1 case of ALK fusion-positive NSCLC after alectinib and crizotinib treatment; and 1 case of EGFR-mutant NSCLC after osimertinib treatment), suggesting the potential implication of MET fusion in conferring resistance to targeted therapy in the setting of other oncogene-driven NSCLC. Our index case harbored a HLA-DRB1::MET fusion and showed a clinical response to a type Ib MET TKI, APL-101. Biopsy at disease progression revealed a D1228V mutation in the tyrosine kinase domain of MET. The oncogenicity of HLA-DRB1::MET was confirmed in Ba/F3 cells. The MET D1228V mutation led to resistance to type I MET TKIs (i.e. crizotinib, APL-101, capmatinib, tepotinib). Both homo- and hetero-dimerization of HLA-DRB1::MET were observed in vitro, suggesting diverse mechanisms of transactivation. Transduction of HLA-DRB1::MET in an EGFR-mutant NSCLC cell line resulted in resistance to an EGFR TKI, which was overcome by the addition of a MET TKI.

Conclusions: MET fusions are detected in 0.13% of NSCLC, and concomitantly to another driver gene alteration in one-third of cases. We present a clinical case of NSCLC harboring a MET fusion, with in vitro modeling suggesting that MET fusions can be an actionable oncogenic driver. Similar to NSCLC with MET exon 14 skipping alterations, a mutation in the kinase domain of the MET fusion could conferred resistance to a MET TKI. Additionally, MET fusions were detected at resistance after targeted therapy for other oncogene-driven NSCLC, with in vitro modeling showing that it could be overcome by combinatorial treatments with TKIs.

Keywords: MET, fusion gene, NSCLC

P3.12C METASTATIC NON-SMALL CELL LUNG CANCER - TARGETED THERAPY - BRAF/ HER2 / MET / NOVEL TARGETS
MONDAY, SEPTEMBER 9, 2024 - 12:00 - 14:00

P3.12C.03 Efficacy and Safety of Brigimadlin, a MDM2-p53 Antagonist, in Patients with Advanced Lung Adenocarcinoma

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Introduction: Mouse double minute 2 homolog (MDM2) amplification occurs in 4-6% of cases of lung adenocarcinoma (LUAD) and is associated with poor survival. There is frequent co-occurrence of MDM2 amplification with known genomic alterations: in patients with LUAD with mutated METex14, EGFR, or KRAS, MDM2 is amplified in 36%, 8%, and 5% of cases, respectively. The MDM2-p53 interaction represents a potential therapeutic target. Brigimadlin, a potent oral MDM2-p53 antagonist, has shown encouraging early efficacy in patients with MDM2-amplified solid tumors.

Methods: We present an analysis of data from patients with LUAD treated in 3 trials of brigimadlin in patients with advanced solid tumors (Phase Ia/Ib monotherapy trial, NCT03449381; Phase Ia/Ib trial of brigimadlin in combination with ezabenlimab [anti-PD-1], NCT03964233; Phase IIa/IIb monotherapy trial, NCT05512377). Across trials, eligible patients had advanced/metastatic solid tumors, MDM2 amplification (monotherapy Phase Ib and Phase IIa/IIb only), ECOG PS 0-1, ≥1 measurable target lesion (RECIST v.1.1) and adequate organ function. Prior treatment with MDM2-p53 or MDMX/MDM4-p53 antagonists was not permitted. Patients received brigimadlin 45 mg on Day 1 of 21-day cycles (once every 3 weeks [q3w]). Patients in the combination trial also received ezabenlimab 240 mg q3w.

Results: 16 patients were included in this analysis, most had received prior treatment and had documented MDM2 amplification (Table). In 7 patients treated in the Phase Ia/Ib monotherapy trial (median 3 [range 0-7] prior lines of treatment), all evaluable patients (n=4) achieved stable disease (SD; unconfirmed partial response [PR] in one patient). 6 patients were treated in the Phase Ia/Ib combination trial (median 3 [range 1-6] prior lines of treatment); of 5 evaluable patients, 1 patient achieved a PR (tumor shrinkage 56%) and 3 achieved SD. In 3 patients treated in the Phase IIa/IIb monotherapy trial, having received 2 prior lines of conventional treatment, all achieved PR (tumor shrinkage 48%, 49%, 65%). Patient progression-free survival (PFS) is summarized in the Table. Safety in this small group with LUAD was consistent with observations in the overall trial populations. In patients who received brigimadlin 45 mg q3w in the Phase Ia/Ib monotherapy (n=140)/combination trials (n=74), the most common any-grade treatment-related adverse events (TRAEs) were nausea (67.9%/70.3%) and fatigue (53.6%/39.2%), respectively. The most common grade ≥3 TRAEs were neutropenia (25.0%/24.3%) and thrombocytopenia (22.9%/21.6%, respectively).

Conclusions: Brigimadlin treatment was associated with encouraging preliminary efficacy in patients with advanced MDM2-amplified LUAD and a manageable safety profile.

Keywords: brigimadlin, MDM2-amplification, advanced lung adenocarcinoma

Trial	Patient ID	Best response	PFS (days)	Number of prior systemic treatment lines	*MDM2* amplification status	Select genomic alterations
NCT03449381 Phase Ia/Ib monotherapy	1	SD	39	2	Pending	NA
	2	SD	177	4	*MDM2*-amp	NA
	3	SD	138	0*	*MDM2*-amp	NA
	4	SD	45+	1	*MDM2*-amp	NA
	5	NE	Too early to assess	4*	*MDM2*-amp	NA
	6	NE	Too early to assess	7	*MDM2*-amp	NA
	7	NE	Too early to assess	NA	*MDM2*-amp	NA
NCT05512377 Phase IIa/IIb monotherapy	8	PR	226+	2*	*MDM2*-amp (150 copies, NGS)	Variant: *EGFR, ROS1;* Amp: *CDK4, EGFR, ZNF217;* Rearrangement: *EGFRex20*
	9	PR	196+	2	*MDM2*-amp (12 copies, NGS)	*EGFRex20* insertion
	10	PR	115+	2	*MDM2*-amp (10 by FISH)	Short variant: *ALK*; Amp: *CDK4, ZNF217, ERBB3*
NCT03964233 Phase Ia/Ib combination	11	PR	296+	1	*MDM2*-amp (10 by FISH)	Variant: *ESR1, EGFR, PLCG2, AR;* Del: *FGFR3*
	12	SD	137	6	*MDM2*-amp	Variant: *SOX2, ARID1B, EGFR, NTRK3;* Amp: *AKT2, CCND1, EGFR;* Del: *JAK2*
	13	SD	86	3	*MDM2*-amp (10 by FISH)	NA
	14	PD	42	2	*MDM2*-amp (10.7 by FISH)	Variant: *TET1, CDK12, ZNF12;* Amp: *CHEK1;* Del: *FGF3, FGF9, FGF14, LAMP1*
	15	SD	219+	2*	*MDM2*-amp (10 by FISH)	Variant: *PIK3CA, SLIT2, SMO;* Amp: *CDK4*
	16	NE	Too early to assess	1	*MDM2*-amp	NA

*Patient received prior adjuvant chemotherapy. +, ongoing. Amp, amplified; Del, deletion; FISH, fluorescence in situ hybridization; NA, not available; NE, not evaluable; NGS, next-generation sequencing; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.

P3.12C.04 Seribantumab Results in Robust and Durable Responses in NRG1 Fusion-Positive Non-Small Cell Lung Cancer: A Multi-Center Case Series

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Introduction: NRG1 (neurgulin-1) gene fusions are implicated in oncogenesis in lung adenocarcinoma with an incidence of ~0.3%. More commonly seen in never-smokers with mucinous adenocarcinoma, NRG1 fusions produce chimeric proteins that promote constitutive activation of HER3 and HER4 via their heterodimerization with other ERBB kinases. NRG1 fusion-positive lung cancers are less likely to respond to standard-of-care therapies; for patients with metastatic disease enrolled in the global eNRGy1 registry, ORRs to chemotherapy (platinum doublet or taxane) and single-agent immunotherapy were <15% and 20%, respectively. Targeted agents, such as the pan-ERBB kinase inhibitor afatinib, fare slightly better, with an ORR in the eNRGy1 registry of 25%. Seribantumab, or MM-121, is a fully human monoclonal antibody targeting HER3 via blockade of heregulin-mediated signaling. Based on pre-clinical models demonstrating inhibition of NRG1-fusion mediated tumorigenesis, the phase II CRESTONE trial enrolled patients with locally advanced or metastatic solid tumors harboring NRG1 fusions, including patients with NSCLC. In data previously presented at AACR 2023, seribantumab produced a response rate of 39% in 18 NSCLC patients. Herein, we describe three NSCLC patients treated on that trial with deep and prolonged response.

Methods: The study was conducted retrospectively by reviewing medical records of patients treated with seribantumab at Northwestern Memorial Hospital, Atrium Health, and UCHealth between 1/1/2021 and 4/1/2024. All patients were enrolled on CRESTONE and completed at least one year of seribantumab as per trial protocol; responses were determined by RECIST 1.1 criteria.

Results: Patient one was a 43-year-old woman with advanced NSCLC, SLC3A2-NRG1 fusion. Following four cycles of neoadjuvant intent cisplatin/pemetrexed/durvalumab therapy, resection was aborted when pleural studding was noted intraoperatively, pathologically confirmed as adenocarcinoma. She initiated seribantumab with clinical benefit demonstrated by tumor reduction and partial response achieved at 21 months; at time of discontinuation of therapy at 35 months, response was sustained. She underwent pleurectomy and lobectomy with complete response noted in the pleura and no evidence of disease on subsequent imaging. Patient two was a 70-year-old man with bilateral metastatic NSCLC, CD74-NRG1 fusion. He was initially treated with dual immunotherapy (nivolumab/ipilimumab), then an investigational PGE2-receptor antagonist in combination with pembrolizumab. At time of progression he was initiated on seribantumab with partial response of 17 months duration. Patient three was a 59-year-old woman with bilateral metastatic recurrence of NSCLC, ITGB1-NRG1 fusion, previously treated with multiple resections, radiation, and systemic therapy including carboplatin/pemetrexed and nivolumab with progression. Seribantumab was subsequently initiated with a partial response on her first scans at 6 weeks deepening to a complete response after 6 months with a duration of response of 20 months. She continued on seribantumab through disease progression for a total of 32 months with clinical benefit.

Conclusions: NRG1 fusion-positive lung cancer remains a challenging clinical entity, with poor response to standard-of-care therapy in the advanced and metastatic setting. In patients with lung cancer positive for various NRG1-fusions with progression on prior lines of therapy, inhibition of HER3 with seribantumab has resulted in deep and prolonged responses, representing a promising treatment for this unique group of patients.

Keywords: NRG1 fusion, Lung adenocarcinoma, Seribantumab

P3.12C METASTATIC NON-SMALL CELL LUNG CANCER - TARGETED THERAPY - BRAF/ HER2 / MET / NOVEL TARGETS
MONDAY, SEPTEMBER 9, 2024 - 12:00 - 14:00

P3.12C.05 Thromboembolic Events in Patients with Oncogene-Addicted Advanced NSCLC

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Introduction: Thromboembolic events (TEs) in advanced non-small cell lung cancer (aNSCLC) increase morbidity, mortality, and healthcare costs with prevalence rising from 5-14% in the general NSCLC population to 30-48% in patients with oncogenic fusions. This study investigates TEs in molecular subsets of aNSCLC to identify high-risk patients.

Methods: This single-center, retrospective study includes patients with aNSCLC diagnosed after January 1, 2015, with comprehensive molecular profiling (OncoPanel, 447 genes) and ≥6 months follow-up. TEs—deep vein thrombosis, pulmonary embolism, and arterial thrombosis—were recorded throughout the cancer course or within six months before aNSCLC diagnosis. We assessed the prevalence, cumulative incidence of TEs (time 0=diagnosis of advanced disease) and median time to TE. Logistic regression evaluated factors independently predicting TE risk.

Results: Of 2,807 patients with aNSCLC, 59% were women, 43% were <65 years of age, 25% had no smoking history, and 74% had adenocarcinoma. The prevalence of venous TEs was 23%, including 44% in ROS1 (N=12/27), 40% in RET (N=12/30), 29% in MET exon 14 (N=13/45), 26% in EGFR (N=153/589), 23% in KRAS (N=127/563), 22% in BRAF (N=30/139), 20% in ALK (N=17/86), 20% in KRAS with STK11, KEAP1 or SMARCA4 (N=62/315), 17% in HER2 mutations (N=9/54) and 22% in other cases (N=208/959) (p=0.014). The prevalence of ischemic stroke was 2.2%, including 13% in RET, 3.7% in ROS1, 2.3% in ALK, 2.9% in KRAS with STK11, KEAP1 or SMARCA4, 2.3% in KRAS, 2.2% in MET exon 14, 2.2% in BRAF, 1.9% in EGFR, 1.9% in HER2, and 1.9% in other cases. The cumulative incidence of venous and arterial TEs is outlined in the Table. The median time to the first TE was 8.1 months for ROS1, 15 months for RET, 20.9 months for KRAS vs 14.1 months for KRAS with STK11, KEAP1 or SMARCA4 (p=0.0015), 21.4 months for HER2, 21.9 months for BRAF, 24.1 months for MET exon 14, 27.2 months for ALK, 27.3 months for EGFR and 16.4 months for other cases. Factors independently associated with venous TEs were ROS1 (OR = 3.09, p = 0.012) and for ischemic stroke, RET and age ≥65 (OR = 7.5, p = 0.02; OR = 1.94, p =0.024).

Conclusions: In aNSCLC, patients with RET and ROS1 fusions had the highest TE risk, with RET also predisposing to ischemic strokes. TEs occurred later with EGFR and ALK, while earlier with ROS1 or KRAS with STK11, KEAP1 or SMARCA4 co-mutations compared to those with KRAS mutations alone.

Keywords: thromboembolic event, ischemic stroke, oncogenic driver

%	0	6 weeks	6 months	1 year	2 years	3 years
Overall	2.8	6	11.7	15.8	21.5	26.2
ALK	5.3	10.7	12	14.8	14.8	17
BRAF	2.1	5.8	12.9	16.3	19.5	27.9
EGFR	2	5.8	10.2	14	17.9	23
HER2	0	3.5	7.2	9.2	19.5	23
KRAS	2.7	5.1	11.3	15.3	22.5	27.1
MET 14	6.8	11.3	21.2	21.2	23.9	27.7
RET	13.3	23.3	33.3	36.6	44.5	50.1
ROS1	12	20	34.2	34.2	45.1	53.3

P3.12C METASTATIC NON-SMALL CELL LUNG CANCER - TARGETED THERAPY - BRAF/ HER2 / MET / NOVEL TARGETS
MONDAY, SEPTEMBER 9, 2024 - 12:00 - 14:00

P3.12C.06 Clinical Characteristics and Outcomes in Patients with Leptomeningeal Disease (LMD) from Non-Small Cell Lung Cancer

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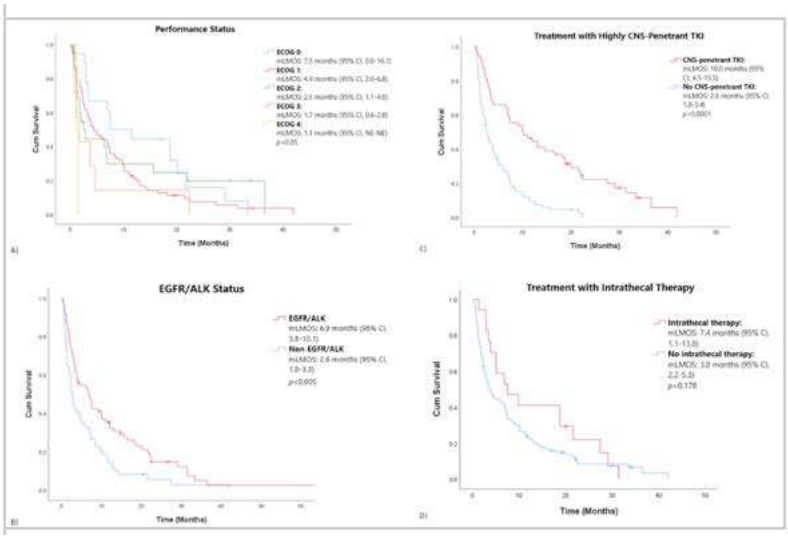
Introduction: Leptomeningeal disease (LMD) is a devastating complication occurring in 3-5% of patients with advanced-stage non-small cell lung cancer (NSCLC) that is associated with a dismal prognosis and remains a critical area of unmet need. Currently, there are very few prospective randomized clinical trials evaluating patients with LMD from NSCLC, and little is known about the impact of many novel targeted therapies, chemo/immunotherapy, intrathecal therapy, and intracranial radiation therapy on leptomeningeal survival.

Methods: We performed a single-center retrospective analysis using the Lung Cancer Moon Shot GEMINI database at the University of Texas MD Anderson Cancer Center, and identified a total of 124 individual patients in our institutional database from 2015 to 2023 with a diagnosis of NSCLC and radiographically or cytologically confirmed LMD. We collected data on their baseline demographic and clinical/ treatment history, and performed subgroup analyses to determine their association with leptomeningeal survival outcomes.

Results: Out of 124 individuals with a diagnosis of LMD from NSCLC, 53.7% of patients harbor an EGFR mutation, among which 45.5% are EGFR exon 19 deletions and 40.9%% EGFR exon 21 L858R. This is followed by 24.4% of patients without a driver mutation, 7.3% with KRAS, 5.7% with ALK, 4.1% with MET, and 1.6% each with RET, HER2, and ROS1-driven NSCLC. Most treatment-eligible patients (91.1%) were treated with a combination of systemic (71.0%), intrathecal (13.7%), and palliative CNS radiotherapy (64.5%) after establishing the diagnosis of LMD. The median overall survival from the diagnosis of LMD (LM-overall survival, LM-OS) was 4.3 months (95% CI 2.1-6.4 mo), with an overall survival (OS) of 30.5 months (95% CI 27.5- 33.6 mo) since NSCLC diagnosis. LM-OS was significantly improved among patients with better performance status (Fig 1A), alterations in EGFR and ALK (Fig 1B), as well as patients with oncogene-driven NSCLC who were treated with highly CNS-penetrant tyrosine kinase inhibitors (TKIs) (Fig 1C). CSF cytology result at diagnosis was not associated with significant differences in survival. Treatment of LMD with immunotherapy and palliative CNS radiation were not significantly associated with improved LM-OS, while treatment with intrathecal therapy trended towards improved LM-OS (Fig 1D).

Conclusions: Despite their overall poor prognosis, certain genomic features and treatment strategies of LMD in NSCLC are associated with improved survival. These factors may be considered in guiding treatment strategies and future clinical trial design for this population.

Keywords: Leptomeningeal Disease, Non-small cell lung cancer



P3.12C.07 Breaking New Ground: Selecting the Best Treatment for Non-Small Cell Lung Cancer According to Mutational Status

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Introduction: Precision Medicine was established as a new paradigm in cancer treatment, especially for Non-Small Cell Lung Cancer (NSCLC) where actionable mutations and individual characteristics might lead to better outcomes. Therefore, the need for comparison between multiple different clinical trials - with similar aspects, but different drugs being tested - has been made paramount to offer the best treatment option for NSCLC patients. This paper aims to elucidate the best treatment regimen for NSCLC based on STK11, KEAP1 and KRAS status.

Methods: Network meta-analysis (NMA) conducted for multicenter clinical trials that tested Immune Checkpoint inhibitors (ICI) for NSCLC over the last 15 years. Two independent researchers searched for and extracted data from articles in English on PUBMED/MEDLINE using MeSH terms and keywords related to NSCLC and ICI. Eligible studies were selected based on predefined criteria - if any discrepancies were found, a third researcher would resolve. All analyses were conducted with R®. The protocol was registered on PROSPERO (CRD42024525536).

Results: Of 463 articles found, 17 met inclusion criteria and were fully read, of which the following 6 trials were included: POSEIDON, CHECK-MATE 9LA, CHECK-MATE-227, KEYNOTE-042, KEYNOTE-189 and IMPOWER-150, comprehending a pool of 5069 eligible patients. For all mutations, ICI tended towards benefit as compared to chemotherapy, except for KRASm, which also showed the greatest heterogeneity between studies (I^2 = 61%). Of all, POSEIDON showed the lowest NNT consistently amongst all mutations and across time, as well as higher LYS except for KRASwt. In NMA, no trial was superior for any mutational status.

Conclusions: In this paper, we found that ICI was better than Chemotherapy overall and each mutation might benefit from different treatment combinations due to their intrinsic behavior.

Keywords: Non-Small Cell Lung Cancer, Immune Checkpoint inhibitors, Mutational Status

Mutation status	Study	HR	95% CI	
KRASm	POSEIDON vs CM-9LA	0.78	0.43	1.42
	POSEIDON vs KN-189	0.71	0.35	1.45
	POSEIDON vs KN-042	1.33	0.60	2.94
	POSEIDON vs IMP-150	1.12	0.62	2.01
	POSEIDON vs CM-227	0.80	0.43	1.47
	CM-9LA vs KN-189	0.91	0.46	1.82
	CM-9LA vs KN-042	1.71	0.80	3.69
	CM-9LA vs IMP-150	1.44	0.83	2.50
	CM-9LA vs CM-227	0.80	0.43	1.47
	KN-189 vs KN-042	1.88	0.80	4.44
	KN-189 vs IMP-150	1.58	0.81	3.10
	KN-189 vs CM-227	0.88	0.43	1.81
	KN-042 vs IMP-150	0.84	0.40	1.78
	KN-042 vs CM-227	0.47	0.21	1.03
	IMP-150 vs CM-227	0.56	0.31	1.00
	Overall Meta-analysis (IT Vs Chemo) - Q 2.68; p = 0.44; I^2 = 0%	0.61	0.49	0.76
KRASwt	POSEIDON vs CM-9LA	0.80	0.53	1.22
	POSEIDON vs KN-189	1.45	0.91	2.33
	POSEIDON vs KN-042	0.93	0.62	1.40
	POSEIDON vs IMP-150	0.82	0.59	1.14
	POSEIDON vs CM-227	1.23	0.76	2.00
	CM-9LA vs KN-189	1.82	1.09	3.03
	CM-9LA vs KN-042	1.16	0.74	1.83
	CM-9LA vs IMP-150	1.02	0.69	1.50
	CM-9LA vs CM-227	1.23	0.76	2.00
	KN-189 vs KN-042	0.64	0.39	1.06
	KN-189 vs IMP-150	0.56	0.36	0.87
	KN-189 vs CM-227	0.68	0.40	1.15
	KN-042 vs IMP-150	0.88	0.60	1.28
	KN-042 vs CM-227	1.06	0.66	1.70
	IMP-150 vs CM-227	1.21	0.81	1.82
	Overall Meta-analysis (IT Vs Chemo) - Q 7.63; p = 0.05; I^2 = 61%	0.87	0.68	1.10
STK11	POSEIDON vs Ipi+Nivo	0.71	0.32	1.56
	POSEIDON vs Pembro	0.75	0.29	1.90
	POSEIDON vs ABCP	0.82	0.38	1.77
	POSEIDON vs CM-227	0.88	0.38	2.02
	Ipi+Nivo vs KN-189	1.05	0.45	2.48
	Ipi+Nivo vs IMP-150	1.16	0.59	2.27
	Ipi+Nivo vs CM-227	1.23	0.58	2.61
	Pembro vs IMP-150	1.10	0.48	2.54
	Pembro vs CM-227	1.17	0.48	2.89
	IMP-150 vs CM-227	1.06	0.51	2.20
	Overall Meta-analysis (IT Vs Chemo) - Q 0.79; p = 0.85; I^2 = 0%	0.70	0.53	0.91
KEAP1	POSEIDON vs Ipi+Nivo	0.84	0.24	3.01
	POSEIDON vs Pembro	0.53	0.16	1.75
	POSEIDON vs ABCP	0.74	0.24	2.25
	POSEIDON vs CM-227	1.54	0.37	6.30
	Ipi+Nivo vs KN-189	0.63	0.24	1.66
	Ipi+Nivo vs IMP-150	0.88	0.37	2.08
	Ipi+Nivo vs CM-227	1.82	0.54	6.20
	Pembro vs IMP-150	1.40	0.67	2.93
	Pembro vs CM-227	2.89	0.92	9.07
	IMP-150 vs CM--227	2.07	0.72	5.94
	Overall Meta-analysis (IT Vs Chemo) - Q 1.54; p = 0.67; I^2 = 0%	0.60	0.44	0.81

Mutational Status	Study	NNT RAR 12m	NNT RAR 24m	NNT RAR 36m	NNT RMST	LYS	OS HR
KRASm	POSEIDON	6	4	5	2	0.75	0.56 (0.36 - 0.86)
	CHECK-MATE 9LA	13	15	15	5	0.39	0.72 (0.48 - 1.08)
	CHECK-MATE 227	NA	NA	NA	NA	NA	0.90 (0.57 - 1.42)
	KEYNOTE-189	7	Dominated	NA	7	0.20	0.79 (0.45 - 1.38)
	IMPOWER-150	5	4	5	2	0.80	0.50 (0.34 - 0.72)
KRASwt	POSEIDON	121	11	10	7	0.23	0.80 (0.62 - 1.04)
	CHECK-MATE 9LA	12	100	+INF	101	0.02	1.00 (0.72 - 1.39)
	CHECK-MATE 227	NA	NA	NA	NA	NA	0.81 (0.57 - 1.15)
	KEYNOTE-189	5	7	NA	3	0.44	0.55 (0.37 - 0.81)
	IMPOWER-150	34	42	Dominated	Dominated	Dominated	0.98 (0.80 - 1.21)
STK11	POSEIDON	8	4	NA	2	0.58	0.56 (0.30 - 1.03)
	CHECK-MATE 9LA	10	20	20	5	0.34	0.79 (0.48 - 1.28)
	CHECK-MATE 227	NA	NA	NA	NA	NA	0.64 (0.36 - 1.12)
	KEYNOTE-189	5	7	NA	4	0.31	0.75 (0.37 - 1.50)
	IMPOWER-150	6	11	NA	2	0.36	0.68 (0.43 - 1.07)
KEAP1	POSEIDON	6	3	NA	1	0.87	0.43 (0.16 - 1.25)
	CHECK-MATE 9LA	NA	NA	NA	NA	NA	0.51 (0.24 - 1.06)
	CHECK-MATE 227	NA	NA	NA	NA	NA	0.28 (0.11 - 0.76)
	KEYNOTE-189	7	286	NA	11	0.10	0.81 (0.44 - 1.49)
	IMPOWER-150	7	10	NA	1	0.47	0.58 (0.38 - 0.88)

P3.12C.08 Surufatinib Plus Docetaxel in Patients with Relapsed Advanced Driver-Negative Non-Squamous NSCLC: A Phase Ib/II Study

W. Jiang, J. He, R. Ning, Y. Zhao, S. Zhou, L. Xu, H. Wang, S. Chen, H. Gan, J. Lin, Q.T. Yu, Guangxi Medical University Cancer Hospital, Nan Ning/CN

Introduction: Recurrent advanced driver-negative non-squamous non-small cell lung cancer (nsq-NSCLC) has few treatment options. Docetaxel is recommended by NCCN guidelines (Version 3.2024) as the standard second-line therapy. Surufatinib (a small-molecule inhibitor of VEGFR1-3, FGFR1 and CSF-1R) has shown a synergistic effect with cell cycle-specific chemotherapy drugs in lung cancer cell lines (A549 cells and PC9 cells) and nude mice model. Here, we evaluated the efficacy and safety of surufatinib combined with docetaxel in advanced driver-negative nsq-NSCLC patients failed with first-line therapy.

Methods: This phase Ib/II, single-arm, open-label study included stage IIIb/IV nsq-NSCLC patients who progressed after first-line platinum-based treatments, allowing prior anti-PD-1 antibody/bevacizumab therapy. Patients received surufatinib (250mg, qd, po, q3w. Adjusted by DLTs at first cycle in 50mg dose units from 200mg to 300mg) plus docetaxel (60mg/m2, iv, d1, q3w). Treatment continued until disease progression, intolerable toxicity, or death. Primary endpoint was PFS. Secondary endpoints included DCR, ORR, OS, and safety.

Results: Up to Mar 20, 2024, 19 patients were enrolled. The median age was 56 years (range: 29-67 years) with male 52.63%, TNM stage IV 89.47%, ECOG PS 1 73.68%. Metastases occurred in 31.58% (bone), 15.79% (brain), and 10.53% (adrenal gland). Adenocarcinoma was confirmed in 84.21% of patients. Of the 16 patients assessable post-baseline, the ORR was 31.25% (5/16), DCR was 100 % (16/16). Based on best of response, 81.25% (13/16) patients had stable or shrinking tumors. Additionally, patients without extrapulmonary metastases had a notably higher ORR compared to those with such metastases (57.14% vs 11.11%, Table 1). Median PFS was 5.4 months (95% CI: 3.4, NA) with longer PFS (5.8 months) in patients with bone metastases. Median OS had not reached yet. All patients experienced at least 1 treatment emergent adverse events (TEAEs). The most common TEAEs included decreased white blood cell count (47.37%, 15.79% Grade ≥3), decreased neutrophil count (42.11%, 26.32%), and increased aspartate aminotransferase (36.84%, 5.26%).

Conclusions: Surufatinib combined with docetaxel demonstrated notable survival benefits and promising anti-tumor activity with manageable toxicity in the recurrent advanced driver-negative nsq-NSCLC, particularly effective in patients without extrapulmonary metastases. Surufatinib plus docetaxel warrant further investigation in a broader NSCLC patient group.

Keywords: Surufatinib, NSCLC, Driver-negative

Variables	Total N=16	Patients without extrapulmonary metastases N=7	Patients with extrapulmonary metastases N=9
Best objective response, n (%)			
Complete response	0	0	0
Partial response	5 (31.25)	4 (57.14)	1 (11.11)
Stable disease	11 (68.75)	3 (42.86)	9 (88.89)
Progressive disease	0	0	0
Objective response rate, n (%)	5 (31.25)	4 (57.14)	1 (11.11)
95% CI	(14.2, 55.6)	(25.0, 84.2)	(2.0, 43.5)
Disease control rate, n (%)	16 (100)	7 (100)	9 (100)
95% CI	(80.6, 100)	(64.6, 100)	(70.1, 100)
PFS, months, median (95% CI)	5.4 (3.4-NA)	/	/
OS, months, median (95% CI)	Not reached	/	/

P3.12D METASTATIC NON-SMALL CELL LUNG CANCER - TARGETED THERAPY - CLINICAL TRIALS IN PROGRESS
MONDAY, SEPTEMBER 9, 2024 - 12:00 - 14:00

P3.12D.01 A Phase Ib Study of Osimertinib and Tegavivint as First-Line Therapy in Patients with Metastatic EGFR-Mutant Non-Small Cell Lung Cancer (NSCLC)

R. Memmott[1], J. Gheeya[1], L. Wei[1], M. Phelps[1], W. Yang[1], D. Stenehjem[2], S. Horrigan[3], A. Duncan[3], D. Uribe[1], G. Amato[1], G. Otterson[1], J. Kaufman[1], A. Alahmadi[1], C. Presley[1], D. Owen[1], D. Carbone[1], [1]The Ohio State University Comprehensive Cancer Center--James, Columbus/OH/USA ,[2]University of Minnesota, Minneapolis/MN/USA ,[3]Iterion Therapeutics, Houston/TX/USA

Introduction: Drugs that inhibit the tyrosine kinase activity of EGFR, TKIs, improve clinical outcomes in patients with EGFR-mutant NSCLC. However, EGFR TKIs are not curative in the metastatic setting because of a nidus of drug-tolerant cells that persist due to transcriptional reprogramming. These cells eventually acquire genetic mutations that cause resistance and progression. Our preclinical studies showed that a subset of EGFR-mutant lung cancer cells enter a persistent state in response to TKIs due to increased transcriptional activity of β-catenin. Treatment of mice bearing EGFR-mutant NSCLC xenografts with the combination of an EGFR TKI and a β-catenin inhibitor caused a greater depth and duration of response than treatment with an EGFR TKI alone. Our studies also showed that patients who have the greatest increase in serum levels of the secreted β-catenin transcriptional target PAI-1 following treatment with a TKI have significantly worse progression free survival. These results provide rationale for a clinical trial evaluating the combination of an EGFR TKI with an inhibitor of β-catenin transcriptional activity as first-line therapy in patients with metastatic EGFR-mutant NSCLC.

Methods: NCT04780568 is a single-arm phase Ib trial investigating osimertinib (EGFR TKI) in combination with tegavivint, which inhibits β-catenin transcriptional activity by disrupting the interaction of β-catenin with TBL1. Patients with metastatic classical EGFR-mutant NSCLC who have not received prior treatment with an EGFR TKI are eligible. Patients receive osimertinib 80 mg by mouth daily (FDA approved dose). Tegavivint is administered intravenously weekly using a dose escalation schedule with four dose levels. Dose escalation is determined by Bayesian optimal interval design. The combination of osimertinib and tegavivint is given for four 28-day cycles, and then patients are switched to maintenance with osimertinib alone. The primary objectives are to assess safety and tolerability and to determine the recommended phase 2 dose (RP2D) of tegavivint in combination with osimertinib. Once the dose escalation phase of this trial is complete, the dose expansion phase will include a total of 12 patients at the RP2D to further assess clinical outcomes, including response rate, progression free survival, duration of response, and overall survival. Correlative studies include PK analysis, the evaluation of pharmacodynamic markers of β-catenin pathway activity, assessment of the clearance of EGFR-mutant ctDNA, and CT tumor volumetric studies.

Results: Eleven patients have been treated on study with three patients at each of the first three dose levels and two patients at the highest dose level of tegavivint (8 mg/kg). No dose limiting toxicities (DLTs), nor drug-related serious adverse events have occurred. Accrual is ongoing.

Conclusions: This phase Ib trial studies the safety and tolerability of an EGFR TKI, osimertinib, in combination with an inhibitor of β-catenin transcriptional activity, tegavivint, as first-line therapy in patients with metastatic EGFR-mutant NSCLC. NCT04780568 is currently enrolling at The Ohio State University, James Comprehensive Cancer Center

Keywords: EGFR-mutant NSCLC, Drug-tolerant persister cells, Beta-catenin

P3.12D METASTATIC NON-SMALL CELL LUNG CANCER - TARGETED THERAPY - CLINICAL TRIALS IN PROGRESS
MONDAY, SEPTEMBER 9, 2024 - 12:00 - 14:00

P3.12D.02 Phase 1/2 Clinical Trial of JIN-A02, a 4th Generation EGFR-TKI in EGFR Mutated Advanced/metastatic Non-Small Cell Lung Cancer (NSCLC)

S.M. Lim[1], B.C. Cho[2], J.Y. Han[3], S.W. Kim[4], K.H. Lee[5], M. Nagasaka[6], A. Jo[7], E. Seah[7], C. Kim[7], T. Reungwetwattana[8], [1]Yonsei Cancer Center, Seoul/KR ,[2]Division of Medical Oncology, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul/KR ,[3]Center for Lung Cancer, National Cancer Center - Graduate School of Cancer Science and Policy, Goyang/KR ,[4]Division of Medical Oncology, Asan Medical Center, University of Ulsan, Seoul/KR ,[5]Division of Medical Oncology, Chungbuk National University Hospital, Cheongju/KR ,[6]Department of Medicine, Chao Family Comprehensive Cancer Center, University of California Irvine Healthcare, California/CA/USA ,[7]J INTS BIO Inc., Seoul/KR ,[8]Division of Medical Oncology, Department of Medicine, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok/TH

Introduction: Epidermal growth factor receptor (EGFR) mutations are the predominant drivers of NSCLC. While EGFR tyrosine kinase inhibitors (TKIs) are the primary treatment for EGFR-mutant NSCLC patients, resistance inevitably develops, leading to disease progression. JIN-A02, a novel 4th generation EGFR-TKI intended for oral administration, selectively and reversibly binds to EGFR mutations, including the C797S and/or T790M mutation that causes resistance to 3rd generation of EGFR-TKIs. Pre-clinical studies with EGFR C797S and/or T790M mutated cell lines and C797S+ xenograft mice model showed that JIN-A02 inhibits cell and tumor growth in a dose dependent manner and exhibits high selectivity over wild-type EGFR. Moreover, JIN-A02 has been shown to penetrate the blood-brain barrier and exhibit anti-tumor activity in an intracranial tumor model. This phase 1/2 study is designed to evaluate the safety and anti-tumor activity of JIN-A02 in EGFR-mutant NSCLC patients.

Methods: JIN-A02 is under evaluation in Phase 1/2, multicenter, an open-label trial (NCT05394831) for subjects with advanced NSCLC harboring C797S and/or T790M mutation as a monotherapy. The primary object is to assess safety, tolerability, pharmacokinetics, and anti-tumor effect for determining the recommended phase 2 dose (RP2D) of JIN-A02. Inclusion criteria are that the subject (≥ 18 years) must have advanced or metastatic NSCLC showing progressive disease post-treatment with approved standard EGFR-TKI therapies and/or platinum-based anticancer chemotherapy, with ECOG status 0 or 1. EGFR mutation status is determined using either tumor tissue and/or plasma ctDNA prior to study enrollment. The study consists of three parts: dose escalation (Part A), dose exploration (Part B), and dose expansion (Part C). Part A comprises five cohorts ranging from a starting dose of 12.5 mg to a maximum dose of 150 mg orally once daily, with three subjects per cohort, conducted over 28-day cycles to evaluate the maximum tolerated dose. Dose-limiting toxicities (DLTs) are assessed over 21 days. Part B aims to further evaluate JIN-A02 safety and to determine the RP2D using two preliminary effective dose levels from Part A. In Part C, subjects are divided into five cohorts based on the EGFR mutation status (both or single positive for C797S and T790M), and the anti-tumor activity of JIN-A02 is evaluated according to RECIST v1.1 at the RP2D.

Results: As of March 27, 2024, Part A is still in progress at Cohort 4 of 100 mg daily. A total of 10 subjects were enrolled in the earlier three cohorts (12.5 mg, 25 mg, and 50 mg), and four subjects are still on therapy at 50 mg daily. No DLT has been reported in any of these three cohorts in Part A. Objective response evaluation showed that one subject achieved partial response (PR) and two subjects with stable disease (SD). There is a trend towards deepened response with increasing dose. Administration of JIN-A02 at a dose 50 mg once daily for 15 days resulted in approximately 3.6 to 4.8 fold accumulation, with Tmax observed at 3.8 h.

Conclusions: Further dose escalation is warranted to comprehensively assess both safety and anti-tumor efficacy of JIN-A02.

Keywords: NSCLC, EGFR-TKI, C797S

P3.12D METASTATIC NON-SMALL CELL LUNG CANCER - TARGETED THERAPY - CLINICAL TRIALS IN PROGRESS
MONDAY, SEPTEMBER 9, 2024 - 12:00 - 14:00

P3.12D.03 A Study to Investigate Safety, PK, And Anti-Tumor Activity of TRX-221 In EGFR Mutant NSCLC: TRX-221-001 In Progress

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Introduction: EGFR-TKIs are established as first-line therapy in NSCLC patients with known activating mutations in EGFR. Despite several therapeutic advances, resistance to EGFR-TKIs inevitably occurs, resulting in disease progression. C797X mutations have been considered one of the most frequent EGFR resistance mechanisms occurring upon progression after exposure to 3rd generation EGFR-TKIs, with different incidence. To date, the only approved second or further line therapy for patients experiencing disease progression following the use of 3rd generation EGFR-TKIs is platinum-based chemotherapy. TRX-221 is an investigational novel 4th generation EGFR-TKI designed to selectively target EGFR sensitizing mutations (exon19del and L858R), T790M as well as C797X. Preclinically, TRX-221 has shown robust anti-tumor activity in various osimertinib-resistant patient-derived xenograft (PDX) models harboring C797S mutation. First-in-human trial of TRX-221 (TRX-221-001; NCT06186076) is planned to investigate the safety, tolerability, pharmacokinetics, and anti-tumor activity of TRX-221 in the treatment of patients with EGFR mutant NSCLC, who progressed following prior EGFR-TKIs with activity against T790M (e.g., osimertinib).

Methods: Key eligibility criteria include adults with histologically or cytologically confirmed diagnosis of relapsed or refractory, locally unresectable advanced or metastatic NSCLC harboring activating EGFR mutations, Eastern Cooperative Oncology Group (ECOG) performance status 0-1, and previous treatment with at least 1 EGFR-targeted TKI. NSCLC with mixed cell histology or a tumor with histologic transformation of small cell elements and patients having tumor with any additional known driver of alteration are excluded. Primary endpoints are maximum tolerated dose (MTD), recommended phase 2 dose (RP2D) and safety in Phase 1; overall response rate (ORR) by RECIST 1.1 in Phase 2. Key secondary endpoints include ORR, pharmacokinetics in Phase 1; duration of response (DOR), progression-free survival (PFS), overall survival (OS), and safety in Phase 2. Phase 1 dose escalation will follow the Bayesian optimal interval design and RP2D will be decided after Part B dose exploration in at least 2 dose levels. In Phase 2, patients will receive TRX-221 at the RP2D in at least 2 groups based on EGFR mutational profile. All eligible patients will receive the study treatment at selected oral dose(s) once daily. Patients will be treated continuously until disease progression or any other pre-defined discontinuation criteria are met. Clinical Trial Information: NCT06186076

Keywords: 4th generation EGFR-TKI, Osimertinib resistance, C797X

P3.12D.04 Enhanced vs Standard Dermatologic Management with Amivantamab-Lazertinib in Advanced NSCLC: Phase 2 COCOON Study

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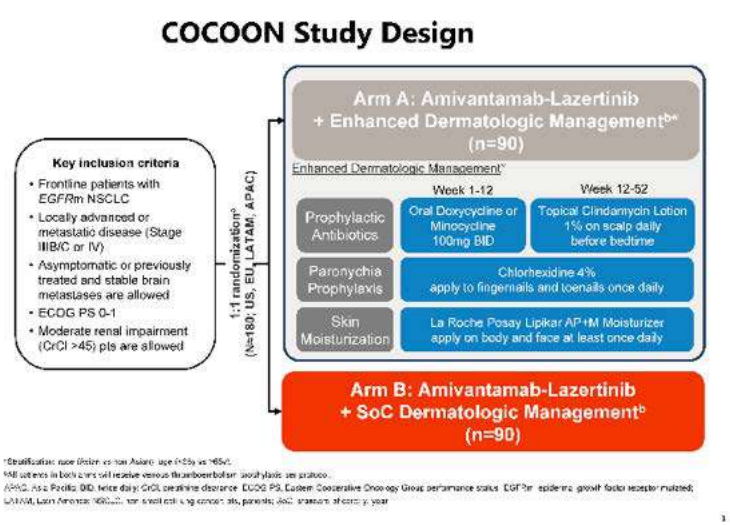
Introduction: Amivantamab is an EGFR-MET bispecific antibody with immune cell-directing activity. Lazertinib is a CNS-penetrant, third-generation EGFR tyrosine kinase inhibitor. Amivantamab-lazertinib significantly improved progression-free survival in patients with treatment-naïve, EGFR-mutated advanced non-small cell lung cancer (NSCLC; Cho Ann Oncol 2023;34:S1306). As EGFR-targeted therapies, amivantamab and lazertinib are independently associated with dermatologic adverse events (AEs). Dermatologic AEs are often treated reactively with topical/systemic corticosteroids and/or systemic antibiotics. Given that dermatologic AEs can impact patient quality of life (QoL) and treatment adherence, an enhanced prophylactic management strategy might improve clinical outcomes. Previous studies demonstrated that patients receiving EGFR inhibitors and prophylactic treatment with an oral tetracycline reported significantly fewer grade ≥2 dermatologic AEs (Petrelli Br J Dermatol 2016;175:1135-1136). COCOON aims to evaluate the impact of enhanced versus standard management on dermatologic AEs among patients treated with first-line amivantamab-lazertinib.

Methods: The open-label, global, phase 2, randomized COCOON study (NCT06120140) is currently enrolling patients with treatment-naïve, locally advanced or metastatic NSCLC harboring EGFR Ex19del and L858R substitutions. As background anticancer therapy, all patients will receive intravenous amivantamab (1050 mg or 1400 mg if ≥80 kg) weekly for the first 4 weeks, then every 2 weeks thereafter, plus oral lazertinib (240 mg daily). Prophylactic anticoagulation is mandatory for the first 4 months of treatment.

Eligible patients will be randomized 1:1 to receive enhanced dermatologic management (arm A) starting on the first day of anticancer treatment or standard-of-care (SoC) management without restrictions (arm B) per local institutional guidelines. Enhanced dermatologic management includes four components (Figure 1) and a digital health tool to increase treatment adherence and monitor compliance (arm A only). All patients in both arms will receive general recommendations for skincare and will be eligible to receive additional dermatologic measures as per physician discretion.

The primary objective is to evaluate the incidence of grade ≥2 dermatologic AEs of interest by week 12 with enhanced versus SoC dermatologic management. Secondary objectives include characterizing dermatologic toxicities and their impact on patients' QoL, incidence of venous thromboembolic events, and efficacy of antitumor treatment. Planned enrollment is 180 patients, which is estimated to provide a power of 90% with a 2-sided alpha of 0.05 to detect a treatment difference between arms A and B in the incidence of grade ≥2 dermatologic AEs. Safety will be assessed throughout the study by AE frequency and severity.

Keywords: Amivantamab, lazertinib, dermatologic management



P3.12D METASTATIC NON-SMALL CELL LUNG CANCER - TARGETED THERAPY - CLINICAL TRIALS IN PROGRESS
MONDAY, SEPTEMBER 9, 2024 - 12:00 - 14:00

P3.12D.05 Furmonertinib Plus Icotinib as First-Line Treatment in EGFR-Mutated NSCLC: Updated Results in L858R and CNS Metastases Groups

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Introduction: Third-generation EGFR-TKI is the preferred first-line treatment for EGFR-mutated non-small cell lung cancer (NSCLC), but for patients with L858R mutation and central nervous system (CNS) metastases, the efficacy and prognosis still remains clinically challenging. Furmonertinib, a highly brain-penetrant, selective EGFR-TKI with activity against EGFR classical, T790M resistant and Ex20ins mutations, plus Icotinib, a first-generation EGFR-TKI, have demonstrated an encouraging ORR of 88.9% (n=18) with acceptable safety in high proportion of CNS metastases patients (15/18,83.3%) (Chen et al., ELCC 2023). Here we present updated results in L858R and CNS metastases groups.

Methods: This ongoing phase II study enrolled untreated advanced NSCLC patients with Ex19Del/L858R/Ex20ins mutation. Patients with stable CNS metastases were allowed to enroll. The regimen consisted of furmonertinib (80 mg p.o, qd) and icotinib (125 mg p.o, tid). The primary endpoint was PFS. Secondary endpoints were ORR, DCR, OS, and safety.

Results: As of the data cutoff date of Feb 29, 2024, 45 patients received study treatment, 22 (48.9%) patients with L858R mutation and 30 (66.7%) patients with CNS metastases. Treatment is ongoing in 32 patients. The baseline characteristics were as follows: the median age 61.8 years (range 42-82), female 55.6%, ECOG PS 0/1/2 15.6%/80.0%/4.4%, never smokers 65.6%. Median follow-up was 14.7 months. In the L858R group, the ORR was 95.5%, DCR was 100%, PFS was 17.6 months (95%CI:14.1-22.5). In the CNS metastasis group, the ORR was 90%, DCR was 100%, CNS ORR was 94.1%, CNS DCR was 100%, PFS was 21.1 months (95%CI:20.4-NR). All treated patients (100%) experienced TEAEs, of whom 6 (13.3%) experienced grade 3 TEAEs, and no grade 4 or 5 TEAEs were observed. The most common TEAEs (≥25%) included rash (44.4%), diarrhea (44.4%), dry skin (31.1%), elevated aspartate aminotransferase (26.7%). Dose interruptions due to TEAEs were reported in 6 (13.3%) patients. There was no incidence of dose reduction, treatment discontinuation or deaths due to TEAEs.

Conclusions: Furmonertinib plus Icotinib as first-line treatment in L858R mutation and CNS metastases groups had an encouraging efficacy and the manageable safety. This study is still ongoing and further analyses will be conducted to evalute longer-term outcomes, which may help define the role of dual EGFR TKI therapy in first-line setting in L858R mutation and CNS metastases.

Keywords: EGFR L858R, CNS metastases, Furmonertinib

P3.12D METASTATIC NON-SMALL CELL LUNG CANCER - TARGETED THERAPY - CLINICAL TRIALS IN PROGRESS
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P3.12D.06 Beamion LUNG-1 And LUNG-2: The Zongertinib Clinical Program in Patients with Non-Small Cell Lung Cancer and HER2 Mutations

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Introduction: HER2 mutation-positive (HER2m+) non-small cell lung cancer (NSCLC) is relatively insensitive to chemotherapy; thus, there is a substantial unmet need for targeted treatments. Zongertinib (BI 1810631), an oral HER2-selective tyrosine kinase inhibitor, binds to wild-type and mutated HER2, including mutations associated with exon 20 insertions, sparing EGFR. The Beamion LUNG-1 (NCT04886804) phase 1a dose-escalation trial (starting at 15 mg twice daily or 60 mg once daily [QD] and increasing to 150 mg twice daily or 360 mg QD, respectively) enrolled patients with HER2 aberration-positive advanced, unresectable, or metastatic solid tumors refractory to/unsuitable for conventional treatment, or who exhausted treatment options. As of September 29, 2023, zongertinib conferred objective response/disease control rates of 49/91% in patients with pretreated HER2 aberration-positive solid tumors, and 58/97% in patients with HER2m+ NSCLC, with manageable safety and limited EGFR-associated adverse events (AEs). Here we present the study design and other parameters of the ongoing zongertinib clinical development program, including the Beamion LUNG-1 (phase 1b) and Beamion LUNG-2 (phase 3; NCT06151574) trials in patients with HER2m+ NSCLC.

Previously presented at WCLC 2022 (Beamion LUNG-1) and ELCC 2024 (Beamion LUNG-2).

Methods: Beamion LUNG-1 (phase 1b) is a dose-expansion study evaluating early efficacy of zongertinib in patients with NSCLC with or without prior treatment. This study initially enrolled patients with HER2 tyrosine kinase domain (TKD) mutation-positive, pretreated NSCLC (cohort 1, n~70). It was then expanded to include patients with treatment-naïve NSCLC with HER2 TKD mutations (2, n~70), NSCLC with non-TKD HER2 mutations (3, n~30), NSCLC with HER2 TKD mutations and active brain metastases (4, n~30), and NSCLC with HER2 TKD mutations and prior treatment with a HER2-directed antibody-drug conjugate (5, n~30). Beamion LUNG-2 is a phase 3 study that will compare the efficacy/safety of zongertinib with the standard of care in patients with histologically or cytologically diagnosed advanced and/or metastatic nonsquamous NSCLC with TKD HER2 mutation and no prior systemic treatment in the locally advanced or metastatic setting. Key exclusion criteria: tumors that have alterations with available therapy, and radiotherapy/major surgery ≤4 weeks before randomization. Target enrollment, randomization, dosing, and endpoints for both trials are outlined in the Table.

Keywords: Advanced non-small cell lung cancer, HER2, Targeted treatment

	Beamion LUNG-1 (Phase 1b)	**Beamion LUNG-2**
Target enrollment	~230 patients from ~86 sites/18 countries	~270 patients from ~160 sites/30 countries
Randomization and dosing	Single arm • Oral zongertinib 120 mg QD	Randomized 1:1* • Experimental arm: oral zongertinib 120 mg QD (21-day cycles) • Comparator arm: intravenous pemetrexed 500 mg/m^2 chemotherapy plus either cisplatin 75 mg/m^2 or carboplatin AUC 5, plus pembrolizumab 200 mg on day 1 every 3 weeks (q3w) for 4 cycles, followed by pemetrexed 500 mg/m^2 plus pembrolizumab 200 mg q3w for ≤35 cycles
Primary endpoint	Objective response	Progression-free survival
Secondary endpoints	• Number of patients with dose-limiting toxicities throughout the entire treatment period • Pharmacokinetic parameters • Duration of response • Disease control • Duration of disease control • Progression-free survival	• Overall response (defined as best overall response of complete or partial response) • Patient-reported outcomes (changes from baseline to week 25) • Overall survival • AEs during the on-treatment period
*In both arms, treatment will continue until progressive disease (RECIST 1.1), undue toxicity, or other criteria are met		

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P3.12D.07 Divarasib Versus Adagrasib or Sotorasib in Pretreated KRAS G12C+ Advanced or Metastatic Non-Small Cell Lung Cancer (NSCLC)

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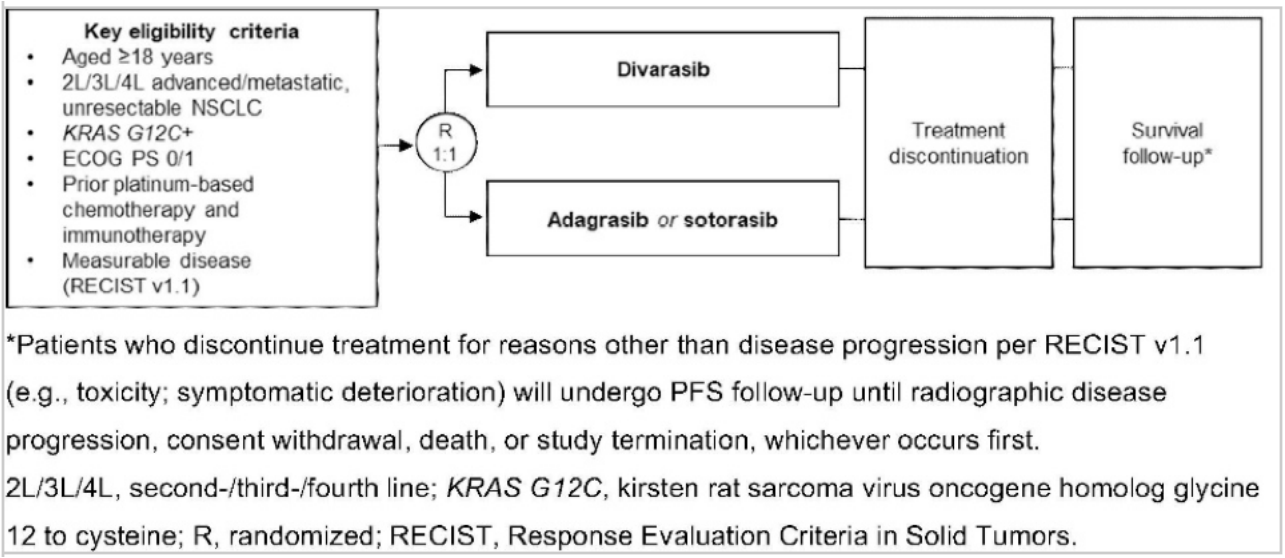
Introduction: KRAS G12C mutations occur in approximately 12% of patients with NSCLC. Patients with advanced/metastatic KRAS G12C+ NSCLC who have previously received standard-of-care therapies (platinum-based chemotherapy, immunotherapy, or a combination of both) have a poor prognosis. Adagrasib and sotorasib are oral, selective KRAS G12C inhibitors with accelerated FDA and conditional EMA approvals for the treatment of patients with previously treated advanced/metastatic KRAS G12C+ NSCLC. However, an unmet need remains for more effective treatments with acceptable safety and tolerability profiles to improve patient outcomes. Divarasib is an oral, selective, KRAS G12C inhibitor previously shown to be 5-20 times as potent and ≤50 times as selective for KRAS G12C in vitro as adagrasib and sotorasib. Divarasib monotherapy (≤400mg once daily [QD]) previously demonstrated encouraging antitumor activity and an acceptable safety profile in patients with advanced/metastatic KRAS G12C+ solid tumors, including NSCLC (confirmed objective response rate [ORR]: 56.4%, 95% CI 39.6-72.2; progression-free survival [PFS]: 13.7 months, 95% CI 8.1-not estimable, in patients with NSCLC; 400mg dose). The observed adverse events were mostly low grade, manageable, and reversible. The phase 3 trial presented here will evaluate the efficacy and safety of divarasib versus adagrasib or sotorasib in patients with previously treated KRAS G12C+ advanced/metastatic NSCLC.

Methods: This phase 3, randomized, active control, open-label multicenter study (EudraCT: 2024-510908-37-00) will enroll patients aged ≥18 years with histologically/cytologically confirmed, unresectable, advanced/metastatic (stage IIIC or IV) NSCLC harboring a KRAS G12C mutation (Figure). Patients must have experienced disease progression on ≥1 prior systemic therapy in the metastatic setting, have measurable disease per RECIST v1.1, and Eastern Cooperative Oncology Group performance status (ECOG PS) 0/1. Prior KRAS inhibitor therapy is not permitted. Patients will be randomized 1:1 to receive divarasib or either adagrasib or sotorasib (based on local approval status and investigator's choice) until disease progression, intolerable adverse events, consent withdrawal, death, or study termination. Tumor assessments will occur at screening, every six weeks for the initial 48 weeks, and every nine weeks thereafter. The primary endpoint is PFS per RECIST v1.1. Secondary endpoints include: overall survival; patient-reported outcomes (time to confirmed deterioration of cough [EORTC QLQ-LC13], dyspnea, or physical functioning [both EORTC QLQ-C30]); ORR and duration of response per RECIST v1.1; and safety.

Keywords: Advanced NSCLC, Divarasib, KRAS G12C+ NSCLC



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P3.12D.08 DCC-3116 In Combination with Sotorasib in Advanced or Metastatic KRASG12C-Mutant Cancers: First-in-human Phase 1/2 Study

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Introduction: The inhibition of the RAS/MAPK pathway activates autophagy, a cellular stress response that recycles nutrients, to promote cancer cell survival. Unc-51-like autophagy activating kinases 1 and 2 (ULK1/2) are critical regulators of autophagy and are tonically inhibited by signaling through the RAS/MAPK pathway; inhibitors of this pathway, such as those that target KRAS, have consequently been shown to release ULK to mediate an autophagy pro-survival resistance response. Therefore, ULK1/2 inhibition represents a potential targeted approach to selectively inhibit autophagy and is an attractive strategy for combination with RAS/MAPK pathway inhibitors. Additive or synergistic anticancer effects were observed with combination RAS/MAPK pathway and ULK1/2 inhibition in mouse xenograft models. Sotorasib is a KRASG12C inhibitor approved for the treatment of adult patients with KRASG12C-mutant locally advanced or metastatic non-small cell lung cancer (NSCLC) who have received ≥1 prior systemic therapy. DCC-3116 is an investigational, selective, potent, switch-control kinase inhibitor of ULK1/2 in clinical development for combination with targeted therapies that activate autophagy, such as sotorasib. Here, we describe a first-in-human, phase 1/2, multicenter, open-label study of DCC-3116 in combination with sotorasib in patients with advanced or metastatic solid tumors harboring KRASG12C mutations (NCT04892017).

Methods: This study includes a dose escalation (part 1) and a dose expansion (part 2) phase. In the ongoing part 1, eligible patients ≥18 years must have a pathologically confirmed diagnosis of an advanced or metastatic solid tumor with a documented KRASG12C mutation of any histology. Daily oral DCC-3116 is administered in 28-day cycles in combination with sotorasib, using a modified 3+3 design, to patients with advanced KRASG12C-mutant solid cancers, irrespective of prior KRASG12C inhibitor treatment. Patients with previous sotorasib treatment resulting in therapy discontinuation due to a drug-related adverse event are excluded. In the planned part 2 expansion, patients ≥18 years with pathologically confirmed NSCLC with a documented KRASG12C mutation will be enrolled. Patients must have received at least 1 prior line, but no more than 3 prior lines, of systemic therapy in the advanced or metastatic setting and must have not previously received sotorasib or other KRASG12C inhibitors. Exclusion criteria for both parts include use of other anticancer treatments, any investigational therapies, or strong or moderate inhibitors or inducers of cytochrome P450 3A4 or P-glycoprotein within 14 days of the first dose. Proton pump inhibitors and H2 receptor antagonists must be discontinued at least 3 days prior to study drug. Additional exclusion criteria include the presence or history of central nervous system metastases or leptomeningeal disease. Safety is the primary endpoint in part 1. Objective response rate by local read using Response Evaluation Criteria in Solid Tumors version 1.1 in patients with KRASG12C-mutant NSCLC is the primary endpoint in the planned part 2 global expansion. Secondary endpoints for both parts include progression-free survival, duration of response, and pharmacokinetics; exploratory endpoints include pharmacodynamics. Part 1 of this study is currently enrolling patients.

Keywords: DCC-3116, Sotorasib, Advanced or metastatic KRASG12C-mutant Cancers

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P3.12D.09 Trial in Progress: A Phase Ib Study of HMBD-001, An Anti-HER3 Antibody, in Advanced Squamous Non-Small Cell Lung Cancer

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Introduction: Squamous non-small cell lung cancer (sqNSCLC) accounts for approximately 30% of lung cancers, with poorer prognosis compared to other subtypes of NSCLC. There is a significant unmet need for effective treatments following combined or sequential use of immune checkpoint inhibitors (ICIs) and platinum-based chemotherapy. Squamous cell carcinomas (SCCs) exhibit common genetic alterations such as Chr 3q amplification and Chr 3p loss, which increase signaling through human epidermal growth factor receptor (HER) 3 and epidermal growth factor receptor (EGFR) during early oncogenesis. Despite the high expression of EGFR in sqNSCLC, combinations of EGFR-targeting agents and chemotherapy have shown limited clinical activity. Upregulation of HER3 activity has been implicated in resistance to EGFR inhibitors such as cetuximab. Inhibition of HER3 signaling, alone or in combination with EGFR inhibitors, may confer therapeutic benefit in sqNSCLC. HMBD-001 is a humanized IgG1 monoclonal antibody that specifically targets the dimerization interface of HER3, thereby inhibiting both ligand-dependent and -independent HER3 activation. Initial data from the first-in-human dose escalation study supports a highly tolerable safety profile for HMBD-001, suggesting that HMBD-001 can be combined with other targeted agents and/or standard of care chemotherapy.

Methods: HMBD-001 is being evaluated in a multicenter, open label, Phase Ib trial in advanced sqNSCLC. The study evaluates two treatment regimens (Arm A: HMBD-001 + docetaxel; Arm B: HMBD-001 + cetuximab + docetaxel) in patients with advanced or metastatic sqNSCLC following progression on platinum-based chemotherapy and ICIs. A Simon 2-stage optimal design with an initial safety lead-in using a 3+3 design is employed for each treatment arm. The primary objectives are to determine the safety and tolerability of both treatment regimens and to assess their preliminary anti-tumor activity in terms of objective response rate (ORR) by RECIST v1.1. Secondary endpoints include duration of response (DOR), disease control rate (DCR), progression free survival (PFS) and overall survival (OS), as well as characterization of the pharmacokinetic (PK) and immunogenicity profile. Exploratory analysis of genomic alterations in the MAPK and PI3K pathways will be performed and correlated with ORR. Enrollment of patients into the first stage of the study is currently ongoing.

Keywords: HMBD-001, squamous NSCLC, HER3

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P3.12D.10 Phase 1b Study of AMG 193, An MTA-Cooperative PRMT5i, Alone and in Combination with Other Therapies in MTAP-deleted NSCLC

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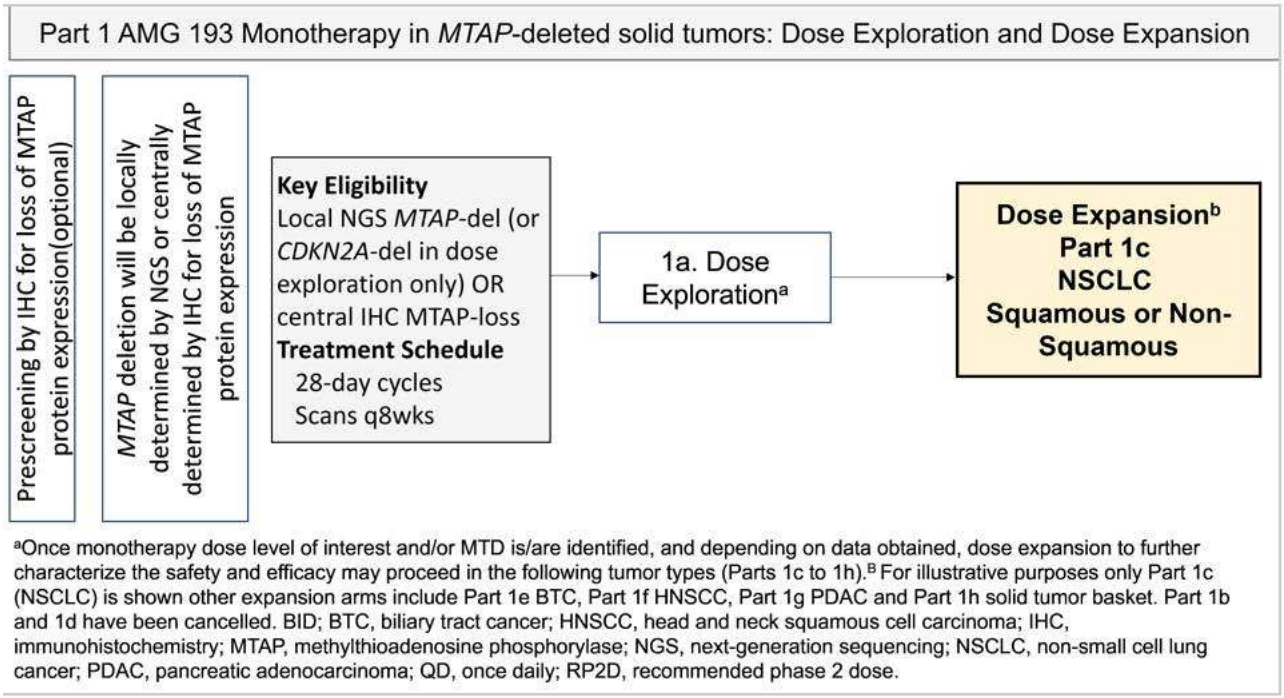
Introduction: AMG 193 is an oral S-methyl-5'-thioadenosine (MTA)-cooperative protein arginine methyltransferase 5 (PRMT5) inhibitor designed to induce synthetic lethality in cancers harboring deletion of methylthioadenosine phosphorylase (MTAP). MTAP is deleted in many solid tumors (squamous NSCLC [16-20%]; non-squamous NSCLC [12-16%]), often with CDKN2A, and leads to the accumulation of MTA, which binds to and inhibits PRMT5, an enzyme responsible for methylation and gene silencing of proteins commonly dysregulated in cancer. Thus, MTAP-deleted cancers have reduced PRMT5 activity, and as a result, they are susceptible to further inhibition of PRMT5 activity. AMG 193 preferentially targets and inhibits the MTA-bound state of PRMT5 which is enriched in MTAP-deleted tumor cells. In preclinical models, AMG 193 demonstrated selective antitumor activity in MTAP-deleted versus wild type NSCLC with in vitro cell line assays and NSCLC cell line-derived xenograft mouse models (Belmontes, 2023 AACR-NCI-EORTC). Furthermore, combining AMG 193 with cytotoxic chemotherapy and/or checkpoint inhibitors, as well as the KRAS G12C inhibitor sotorasib, may significantly augment antitumor activity. AMG 193 also demonstrated CNS penetrance with PK models in vivo. In the first-in-human dose escalation study, AMG 193 demonstrated antitumor activity with objective responses observed in multiple tumor types with no evidence of clinically significant myelosuppression, confirming a differentiated benefit-risk profile from first-generation PRMT5 inhibitors. (Rodon, 2023 AACR-NCI-EORTC). This promising therapeutic profile of AMG 193 is being further evaluated in combination with other therapies in patients with MTAP-deleted advanced thoracic tumors, including NSCLC.

Methods: This is a master protocol (subprotocol A-C), phase 1, open-label study of AMG 193, alone or in combination with other therapies, in patients with MTAP-deleted advanced thoracic tumors. Subprotocol A-C will enroll patients with MTAP-deleted NSCLC. Central pre-screening NGS testing will be offered to all participating sites. Subprotocol A (N ~ 312) will evaluate AMG 193 in combination with pembrolizumab with (arm A and B) or without (arm C) platinum-based doublet chemotherapy in NSCLC. Subprotocol B (N ~ 94) will evaluate AMG 193 plus sotorasib in MTAP-deleted and KRAS G12C-mutated NSCLC. Subprotocol C (N ~ 94) will evaluate AMG 193 alone in MTAP-deleted NSCLC with active brain metastases. Primary objectives are identification of the maximum tolerated dose and safety of AMG 193. Secondary objectives include antitumor activity by investigator-assessed RECIST and pharmacokinetics of AMG 193. Key eligibility criteria include adult patients (> 18 years of age) with MTAP-deleted NSCLC. Patients will be required to have PD-L1-positive tumors in subprotocol A arm C, KRAS G12C-mutated tumors in subprotocol B, and active brain metastasis in subprotocol C. AMG 193 will be administered daily continuously. The study is expected to start recruitment in April 2024.

Keywords: AMG 193, MTA-cooperative PRMT5 inhibitor, MTAP-deleted NSCLC



[a]Once monotherapy dose level of interest and/or MTD is/are identified, and depending on data obtained, dose expansion to further characterize the safety and efficacy may proceed in the following tumor types (Parts 1c to 1h).[B] For illustrative purposes only Part 1c (NSCLC) is shown other expansion arms include Part 1e BTC, Part 1f HNSCC, Part 1g PDAC and Part 1h solid tumor basket. Part 1b and 1d have been cancelled. BID; BTC, biliary tract cancer; HNSCC, head and neck squamous cell carcinoma; IHC, immunohistochemistry; MTAP, methylthioadenosine phosphorylase; NGS, next-generation sequencing; NSCLC, non-small cell lung cancer; PDAC, pancreatic adenocarcinoma; QD, once daily; RP2D, recommended phase 2 dose.

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P3.12D.11 Phase 1/2, Dose-expansion Study of AMG 193, an MTA-cooperative PRMT5 Inhibitor, In MTAP-deleted NSCLC

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Introduction: AMG 193 is an oral S-methyl-5'-thioadenosine (MTA)-cooperative protein arginine methyltransferase 5 (PRMT5) inhibitor being evaluated for the treatment of methylthioadenosine phosphorylase (MTAP)-deleted cancers. MTAP deletion occurs in 16-20% of squamous and 12-16% of non-squamous non-small cell lung cancer (NSCLC). Deletion of MTAP leads to the accumulation of MTA, which binds to and inhibits PRMT5, an enzyme responsible for methylation and gene silencing of cell-essential proteins. Thus, in the context of MTAP-deleted cancers, MTA accumulation creates an additional vulnerability to further inhibit PRMT5 activity. AMG 193 preferentially targets and inhibits the MTA-bound state of PRMT5. In preclinical models, AMG 193 demonstrated selective antitumor activity in in vitro and in vivo MTAP-deleted compared to MTAP-wild type NSCLC cell line assays and NSCLC cell line-derived xenograft mouse models (Belmontes, 2023 AACR-NCI-EORTC). AMG 193 also demonstrated central nervous system penetrance with pharmacokinetic models. In the ongoing first-in-human (FIH) study with AMG 193 monotherapy, RECIST responses have been observed in a variety of MTAP-deleted tumors without dose-limiting myelosuppression and a favorable safety profile (Rodon, 2023 AACR-NCI-EORTC), demonstrating differentiated safety from the first generation indiscriminate PRMT5 inhibitors. This study will enroll up to 40 previously treated NSCLC patients in dose expansion (Part 1c), currently open for enrolment.

Methods: This is a FIH, open-label, phase 1/2, dose escalation and expansion study of AMG 193 administered continuously in 28-day cycles in patients with advanced MTAP-deleted tumors (FIGURE). Up to 40 previously treated patients with NSCLC (squamous and non-squamous histology) will be enrolled in Part 1c. Central prescreening NGS will be offered to all participating sites. One interim futility will be conducted by using Simon's minimax two-stage design. The primary objectives are safety and tolerability; secondary objectives include antitumor activity by investigator-assessed RECIST, pharmacokinetics, and pharmacodynamics. Key eligibility criteria for patients with NSCLC (Part 1c) include adult patients (≥ 18 years of age) with MTAP-deleted advanced tumors (determined by NGS or evidence of MTAP depletion determined by IHC); treatment with 1-3 prior lines of systemic therapy in the advanced/metastatic setting including platinum-based chemotherapy. Additionally, patients without actionable mutations must have received treatment with a PD(L)-1 inhibitor (unless contraindicated or PD-L1 < 1%), and patients whose tumors harbor actionable genomic aberrations (i.e. EGFR, ALK, MET, RET, ROS1, KRASG12C) should have disease progression on approved systemic therapies for these aberrations.

Keywords: AMG 193, MTA-cooperative PRMT5 inhibitor, MTAP-deleted NSCLC

P3.12E METASTATIC NON-SMALL CELL LUNG CANCER - TARGETED THERAPY - KRAS
MONDAY, SEPTEMBER 9, 2024 - 12:00 - 14:00

P3.12E.02 MEK Inhibitor Combined with RTK Inhibitor (Trametinib Plus Anlotinib) In Non-g12c KRAS-Mutant Non-Small Cell Lung Cancer: A New Strategy

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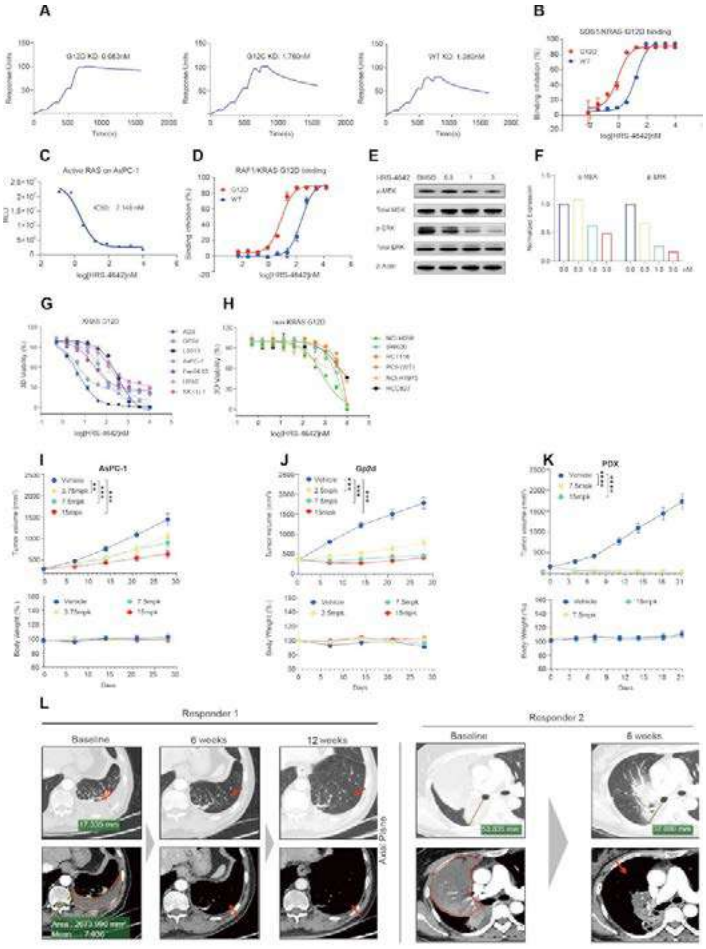
Introduction: It remains as a big challenge to provide therapeutic regime for the non-G12C KRAS-mutant non-small cell lung cancer (NSCLC) patients. The strategy of co-inhibition of MEK/RTKs pathways via trametinib and anlotinib showed preliminary activity in non-G12C KRAS-mutant NSCLC. However, whether the strategy is effective in clinic remains elusive.

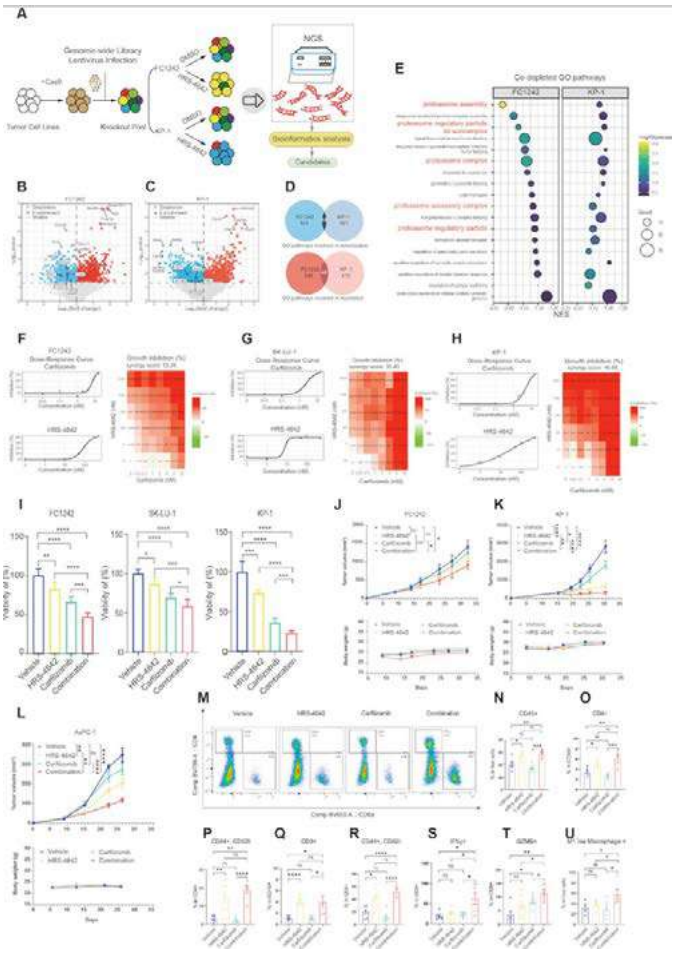
Methods: To determine whether trametinib in combination with anlotinib will be effectiveness and safety in patients with advanced non-G12C KRAS-mutant NSCLC patients. This phase I clinical trial enrolled patients with advanced non-G12C KRAS-mutant NSCLC patients from April 13, 2021, to May 13, 2023. The trial was divided into 2 parts including phase Ia and phase Ib. Phase Ia involved dose escalation, while phase Ib consisted of expansion cohorts. The data cutoff date for this analysis was March 26, 2024. Trametinib and anlotinib were administered orally once daily, with anlotinib being used for every two weeks followed by a one-week discontinuation cycle. The primary endpoint of phase Ia was to evaluate the determine the recommended phase 2 dose (RP2D), and the primary endpoint of phase Ib was to evaluate the objective response rate (ORR). The secondary endpoints were progression-free survival (PFS), disease control rate (DCR) and safety.

Results: The phase Ia containing 13 patients showed that the RP2D is trametinib (2 mg) plus anlotinib (8 mg), the ORR is 69.2%, the PFS is 6.9 months, DCR is 92% and the rate of adverse events (AEs) ≥ grade 3 is 23%. The phase Ib containing 20 patients showed high efficacy of this combinational therapy (trametinib (2 mg) plus anlotinib (8 mg)), with the ORR at 65%, the PFS is 11.5 months, the DCR at 100%, and the rate of AEs ≥ grade 3 at 35%. An integrative analysis for the phase Ia plus phase Ib (33 patients) indicated that the ORR is 66.7%, the PFS is 10.3 months, the DCR is 97% and the rate of adverse events (AEs) ≥ grade 3 is 30%.

Conclusions: This study provides a potential combinational therapeutic strategy for those non-G12C KRAS-mutant lung cancer patients via oral administration of trametinib and anlotinib.

Keywords: KRAS-mutant NSCLC, Targeted therapy, Trametinib plus anlotinib





P3.12E METASTATIC NON-SMALL CELL LUNG CANCER - TARGETED THERAPY - KRAS
MONDAY, SEPTEMBER 9, 2024 - 12:00 - 14:00

P3.12E.03 Anti-Tumor Efficacy of HRS-4642 and its Potential Combination with Proteasome Inhibition in KRAS G12D-Mutant Cancer

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Introduction: KRAS G12D is the most prevalent KRAS mutation subtype in solid tumors. Currently, this subtype lacks effective targeted treatment strategies.

Methods: In this study, we conducted the following explorations: (1) Confirmation of the efficacy and selectivity of HRS-4642 in multiple preclinical in vitro models; (2) Assessment of the efficacy, safety, pharmacokinetics, and pharmacodynamics of HRS-4642 in various preclinical in vivo models; (3) Exploration of the efficacy and safety of HRS-4642 in treating patients with solid tumors harboring KRAS G12D mutations in clinical trials; (4) Generation of a comprehensive CRISPR-based map depicting the synergistic sensitization/resistance profile of HRS-4642 across the entire genome, facilitating the identification of potential targets; (5) Validation of candidate target (proteasome inhibitor) in multiple in vitro and in vivo models to assess their anti-tumor effects when combined with HRS-4642; (6) Investigation of the potential impact of HRS-4642 as a monotherapy or in combination with proteasome inhibitor on the tumor immune microenvironment.

Results: We revealed that: (1) HRS-4642 exhibits high selectivity in inhibiting the viability of KRAS G12D mutant cell lines. (2) HRS-4642 demonstrates significant anti-tumor efficacy in vivo. (3) HRS-4642 exhibits significant anti-tumor activity in two NSCLC patients. (4) Whole-genome CRISPR screening identifies proteasome inhibitor as potential agent for synergistic sensitization with HRS-4642. (5) In vitro and in vivo experiments confirm the synergistic killing of KRAS G12D-mutant cells by HRS-4642 and the proteasome inhibitor (carfilzomib). (6) Flow cytometry and immunohistochemical analysis reveal that HRS-4642 as a monotherapy or in combination with carfilzomib significantly increases the infiltration of CD4+ and CD8+ T cells in tumors.

Conclusions: (1) HRS-4642 exhibits high selectivity for KRAS G12D. (2) HRS-4642 synergizes with proteasome inhibitor carfilzomib again KRAS G12D-mutant tumors. (3) HRS-4642, or in combination with carfilzomib, has the potential to reshape the tumor immune microenvironment.

Keywords: KRAS G12D, HRS-4642, Carfilzomib

P3.12E METASTATIC NON-SMALL CELL LUNG CANCER - TARGETED THERAPY - KRAS
MONDAY, SEPTEMBER 9, 2024 - 12:00 - 14:00

P3.12E.04 Long-Term Outcomes with Sotorasib in KRAS G12c-Mutated Advanced NSCLC from the Global Expanded Access Program (EAP) Study-436

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Introduction: Sotorasib, a first-in-class KRASG12C inhibitor, was available under an EAP to treat KRAS G12C-mutated advanced non-small cell lung cancer (NSCLC), which included a global study protocol (Study-436). We previously reported outcomes from this study including real-world progression-free survival (rwPFS) and overall survival (OS) after 1 year of follow-up. Here, we describe outcomes with approximately 2 years of follow-up from Study-436.

Methods: Starting January 29, 2021, patients with KRAS G12C-mutated advanced NSCLC and ECOG PS ≤ 2, who had exhausted standard of care treatments, enrolled across 50 centers in 6 countries (USA, ARG, BRA, ISR, SAU, TWN) and received oral sotorasib 960 mg once daily. Patients could be included if they had asymptomatic CNS metastases. Safety was the primary endpoint. OS and duration of treatment were key secondary endpoints. rwPFS was evaluated as an ad hoc endpoint.

Results: At the primary analysis, 150 patients (median age, 66 years; 52.7% female) received sotorasib. At baseline, 38 (25.3%) patients had ECOG PS 2 and 50 (33.3%) had a history of CNS metastases. Median prior lines of anticancer therapy was 2 (range, 0-8). Consistent with previously reported outcomes, and with median study follow-up of 23.8 (95% CI, 19.5-27.1) months, median OS and rwPFS were 9.5 (95% CI, 8.6-12.0) months and 6.3 (95% CI, 5.0-7.3) months, respectively. Kaplan-Meier (KM) estimated OS at 2 years was 27.0% (95% CI, 19.5-35.1). Median duration of treatment, which considers end of treatment for any reason, was 5.2 (95% CI, 4.3-6.9) months with a range of 0.3 to 27.3 months. Efficacy was also observed in subgroups with historically poorer outcomes including those with CNS metastases, where median OS in patients with and without CNS metastases was 9.4 (95% CI, 7.2-12.7) and 10.3 (95% CI, 8.4-13.9) months, respectively (Table 1). KM estimated OS at 2 years was similar to the overall population in patients with (27.8%) and without (26.2%) CNS metastases. Safety was consistent with previously reported data. Treatment-related adverse events (TRAEs) were reported in 97 (64.7%) patients with Grade ≥ 3 TRAEs occurring in 32 (21.3%). Discontinuation due to TRAEs occurred in 10 (6.7%) patients.

Conclusions: In this long-term follow-up of 150 patients from a global EAP, real-world outcomes were consistent with the sotorasib CodeBreaK clinical trials. Approximately a quarter of patients were still alive after 2 years. Efficacy was demonstrated across subgroups including those with poorer prognostic indicators such as CNS metastases.

Keywords: Sotorasib, Non-small cell lung cancer, KRAS G12C

	Patients, n	Median OS, months (95% CI)	Median rwPFS*, months (95% CI)
Overall	150	9.5 (8.6-12.0)	6.3 (5.0-7.3)
Age			
< 65	64	6.7 (5.1-8.9)	3.9 (3.0-5.8)
≥ 65	86	12.7 (10.3-23.2)	9.0 (6.5-11.8)
Baseline ECOG PS			
0	25	13.6 (9.4-NE)	9.4 (5.3-15.4)
1	87	9.0 (7.2-12.5)	6.2 (3.9-7.4)
2	38	7.9 (5.8-11.8)	5.6 (3.7-8.1)
Prior lines of anticancer therapy			
0	1	-	-
1	58	10.5 (8.4-16.1)	6.9 (3.9-9.7)
2	50	8.9 (7.9-11.6)	6.3 (4.3-7.6)
≥ 3	41	9.0 (5.8-18.0)	6.3 (3.9-9.0)
Prior anti PD-(L)1 therapy			
Yes	134	9.3 (8.4-12.0)	6.3 (4.7-7.3)
No	16	14.8 (4.0-NE)	6.8 (2.7-14.8)
History of CNS metastases			
Yes	50	9.4 (7.2-12.7)	5.7 (4.3-8.1)
No	100	10.3 (8.4-13.9)	6.5 (4.4-8.6)
History of liver metastases			
Yes	21	8.1 (4.0-24.4)	6.3 (3.1-9.1)
No	129	9.7 (8.6-12.5)	6.4 (4.6-7.6)
PD-L1 expression			
< 1%	49	9.7 (7.9-14.0)	7.1 (5.2-9.7)
≥ 1% and < 50%	56	10.3 (8.1-16.1)	7.0 (4.3-9.0)
≥ 50%	35	8.4 (6.0-12.7)	5.0 (3.4-6.5)
Unknown/missing	10	11.8 (0.8-NE)	3.6 (0.8-24.3)

*rwPFS was estimated based on time from start of sotorasib to end of protocol due to disease progression or death, any death before new anticancer therapy, or end of commercial sotorasib, whichever occurred earlier. CI, confidence interval; CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group Performance Status; PD-L1, programmed death-ligand 1.

P3.12E METASTATIC NON-SMALL CELL LUNG CANCER - TARGETED THERAPY - KRAS
MONDAY, SEPTEMBER 9, 2024 - 12:00 - 14:00

P3.12E.05 Real-World Comparative Effectiveness of Sotorasib vs Docetaxel as 2L/2L+ Treatment of KRAS G12c-Mutated Advanced NSCLC

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Introduction: Sotorasib, a KRASG12C inhibitor, is approved to treat patients with previously treated KRAS G12C-mutated advanced non-small cell lung cancer (NSCLC). While the phase 3 CodeBreaK 200 trial of sotorasib vs docetaxel was not powered to demonstrate an overall survival (OS) benefit, post-marketing real-world data provide an opportunity to further evaluate sotorasib's clinical benefit. We evaluated the comparative effectiveness of sotorasib monotherapy vs docetaxel as monotherapy or in combination for patients with pretreated KRAS G12C-mutated advanced NSCLC in the real-world setting.

Methods: This was a retrospective, active comparator study conducted within the US-based Flatiron Health electronic health record-derived de-identified database. Patients with pretreated KRAS G12C-mutated advanced NSCLC who initiated sotorasib between May 28, 2021 (date of US FDA approval) and September 30, 2022, or docetaxel between January 01, 2019 and September 30, 2022, were included. A longer window for docetaxel was warranted to enhance the sample size in this population. A minimum 12-month opportunity for follow-up was required. Treatment groups were balanced via overlap weighting propensity score methods. Median OS with corresponding 95% confidence intervals (CIs) in the second-line (2L) and 2L+ settings were calculated using Kaplan-Meier estimates. Hazard ratios (HR) were estimated via weighted Cox proportional hazard regression models.

Results: After propensity score weighting, clinical characteristics in sotorasib and docetaxel cohorts were mostly balanced (Table 1). At baseline, most patients were >65 years of age, had ECOG PS of 0-1, were from the community practice setting, had advanced stage at initial diagnosis, and had prior anti-PD-(L)1 treatment and/or platinum-based chemotherapy. In the 2L setting, the weighted median OS (95% CI) for sotorasib (N=102) vs docetaxel (N=59) was 10.2 (7.6-16.3) vs 6.0 (4.2-11.0) months, with a corresponding HR (95% CI) of 0.61 (0.41-0.92). In the 2L+ setting, the weighted median OS (95% CI) for sotorasib (N=164) vs docetaxel (N=118) was 10.2 (8.0-14.6) vs 7.1 (5.0-10.6) months, with a corresponding HR (95% CI) of 0.64 (0.48-0.86). Due to the small sample size, some residual imbalance remained in patients with prior anti-PD-(L)1 treatment and platinum-based chemotherapy. This was further evaluated with sensitivity analysis, and results were consistent with the primary analysis favoring sotorasib.

Conclusions: In this real-world comparative analysis of a US-based population of patients with pretreated KRAS G12C-mutated advanced NSCLC, sotorasib demonstrated a longer median OS vs docetaxel which further supports sotorasib as an important treatment option in this setting.

Keywords: Comparative effectiveness, Sotorasib, Docetaxel

	2L			2L+		
	Sotorasib	Docetaxel	SMD[a]	Sotorasib	Docetaxel	SMD[a]
	N=102	N=59		N=164	N=118	
Mean age, years (SD)	68 (8.46)	68 (8.08)	<0.01	69 (8.12)	69 (8.06)	<0.01
Age in years, n (%)			0.1			0.24
< 65	31 (30%)	19 (32%)		56 (34%)	35 (30%)	
65-74	48 (47%)	25 (42%)		67 (41%)	55 (47%)	
75-84	23 (23%)	15 (26%)		41 (25%)	26 (21%)	
≥ 85	0 (0%)	0 (0%)		0 (0%)	2 (2%)	
Gender, n (%)			<0.01			<0.01
Female	58 (57%)	34 (57%)		90 (55%)	65 (55%)	
Male	44 (43%)	25 (43%)		74 (45%)	53 (45%)	
Race, n (%)			<0.01			<0.01
White	73 (71%)	42 (71%)		115 (70%)	83 (70%)	
Black or African American	11 (11%)	6 (11%)		18 (11%)	13 (11%)	
Other race or not available	18 (18%)	11 (18%)		31 (19%)	22 (19%)	
Smoking history, n (%)			0.29			0.1
History of smoking	95 (93%)	58 (99%)		157 (96%)	116 (98%)	
No history of smoking	7 (7%)	1 (1%)		7 (4%)	2 (2%)	
Practice type, n (%)			<0.01			<0.01
Academic	19 (19%)	11 (19%)		34 (21%)	25 (21%)	
Community only	83 (81%)	48 (81%)		130 (79%)	93 (79%)	
Stage at initial diagnosis, n (%)			<0.01			<0.01
Advanced stage (or not reported)[b]	83 (81%)	48 (81%)		133 (81%)	96 (81%)	
Early stage	19 (19%)	11 (19%)		31 (19%)	22 (19%)	
ECOG PS at index, n (%)			<0.01			<0.01
0	16 (16%)	9 (16%)		22 (13%)	16 (13%)	

1	44 (43%)	25 (43%)		72 (44%)	52 (44%)	
2	15 (15%)	9 (15%)		25 (15%)	18 (15%)	
≥ 3	6 (6%)	4 (6%)		7 (4%)	5 (4%)	
Not available	20 (20%)	12 (20%)		38 (23%)	27 (23%)	
Histology, n (%)			0.29			0.25
Non-squamous cell carcinoma	100 (98%)	55 (93%)		157 (96%)	113 (96%)	
Squamous cell carcinoma	2 (2%)	3 (5%)		2 (1%)	4 (3%)	
NSCLC histology NOS	0 (0%)	1 (2%)		5 (3%)	1 (1%)	
Most recent PD-L1 expression at baseline (tumor cell staining), n (%)			<0.01			<0.01
< 1	33 (32%)	19 (32%)		43 (26%)	31 (26%)	
1-49	27 (26%)	15 (26%)		44 (27%)	32 (27%)	
≥ 50	18 (18%)	11 (18%)		38 (23%)	27 (23%)	
No valid test	24 (24%)	14 (24%)		39 (24%)	28 (24%)	
Presence of actionable gene alterations (e.g., *ALK*, *EGFR*, *ROS1*, and *BRAF*), n (%)	0 (0%)	0 (0%)	0.21	3 (2%)	4 (3%)	0.05
Prior lines of treatment, n (%)			-			<0.01
1	-	-		93 (57%)	67 (57%)	
2	-	-		43 (26%)	31 (26%)	
≥ 3	-	-		28 (17%)	20 (17%)	
Prior treatment, n (%)						
Anti PD-(L)1	79 (77%)	58 (98%)	0.64	134 (82%)	114 (97%)	0.5
Chemotherapy	84 (83%)	50 (85%)	0.07	139 (85%)	109 (92%)	0.22
Platinum-based chemo and anti PD-(L)1 combo	63 (62%)	49 (83%)	0.47	85 (52%)	73 (62%)	0.56

[a]SMDs <0.1 indicate good balance, SMDs 0.1-0.2 indicate moderate balance, and SMDs >0.2 indicate inadequate balance; [b]Stage was not reported in 1 patient each for sotorasib and docetaxel in the 2L cohort, and in 6 sotorasib-treated patients vs 2 docetaxel-treated patients in the 2L+ cohort. Chemo, chemotherapy; ECOG PS, Eastern Cooperative Oncology Group performance status; NOS, not otherwise specified; NSCLC, non-small cell lung cancer; PD-L1, programmed cell death ligand 1; SD, standard deviation; SMD, standardized mean difference.

P3.13C SMALL CELL LUNG CANCER AND NEUROENDOCRINE TUMORS - BIOMARKERS AND DISEASE MONITORING
MONDAY, SEPTEMBER 9, 2024 - 12:00 - 14:00

P3.13C.02 A Plasma Proteomics-Based Model for Clinical Benefit Prediction in Small Cell Lung Cancer Patients Receiving Immunotherapy

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Introduction: Small cell lung cancer (SCLC) is an aggressive disease with limited treatment options. Immune checkpoint inhibitor (ICI) therapy with concurrent chemotherapy is the preferred first-line treatment for patients with extensive-stage SCLC. However, the addition of ICIs to chemotherapy only modestly improves clinical outcomes while posing a risk of ICI-related toxicities. Thus, identifying patients likely to benefit from ICIs is critical for optimizing treatment decisions. Here, we describe a test derived from a novel computational model that analyzes pretreatment plasma proteomic profiles to predict clinical outcomes in patients with SCLC receiving ICI-based therapies.

Methods: An observational study collected pretreatment plasma samples from 79 patients with extensive-stage SCLC treated with ICI-based therapy (NCT04056247). Proteomic profiling of plasma samples was performed using aptamer-based technology, measuring approximately 7000 proteins per sample. A machine learning model was developed to predict the clinical benefit (CB) from ICI-based therapy, where CB was defined as 6-month progression-free survival. Given the limited cohort size, CB prediction was achieved by integrating two computational models. Model 1, based on 146 plasma proteomic biomarkers, was developed from the SCLC dataset using cross-validation. Model 2, based on a 4-protein signature, was developed from a previously reported NSCLC dataset (Christopoulos et al. JCO prec. onc. 2024). The hybrid model stratified patients into two groups (i.e., 'positive' or 'negative') based on a pre-defined CB probability threshold. Bioinformatic analysis of the SCLC-specific proteomic biomarkers was performed to gain insight into the potential mechanisms driving ICI therapeutic benefit and resistance in SCLC.

Results: The model displayed a robust predictive capability, as demonstrated by the area under the curve (AUC) of the receiver operating characteristic (ROC) plot of 0.63 (p-value = 0.02) and a high correlation between the predicted CB (i.e., model output) and the observed CB rate (R2 = 0.93). Furthermore, overall survival (OS) was significantly longer in patients stratified to the positive group compared to those in the negative group. Median OS was 14 months versus 8.8 months in positive versus negative patient groups (Hazard ratio = 0.47, 95% Confidence interval: 0.25-0.90, p-value = 0.02). Bioinformatic analysis of model proteins revealed significant enrichment of lung tumor-associated proteins, poor prognostic factors in lung cancer, extracellular matrix-related proteins, intermediate filaments, and replicative immortality (Fisher exact test; FDR<0.1). Multiple model proteins are also known to be involved in fibroblast growth factor signaling and glutathione metabolism. Given their association with different treatment resistance mechanisms, such proteins represent potential targets for intervention.

Conclusions: We describe preliminary results from a novel pretreatment plasma proteomics-based predictive model that can potentially inform treatment decisions for patients with SCLC. Bioinformatic analysis demonstrates that the model is based on a composite of biologically and clinically relevant biomarkers. The potential clinical utility of this model is being investigated in a large prospective clinical trial.

Keywords: SCLC, Biomarker, Immunotherapy

P3.13C.03 Basal Circulating Leukocyte-Platelet Complexes and PD-L1 Expression on Circulating Cells in Patients with Advanced SCLC

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Introduction: Prognosis of patients with extensive disease small-cell lung cancer (ED-SCLC) is poor even when treated with first-line anti-PD(L)-1 in combination with platinum and etoposide. Determination of PD-L1 expression in the tumor by IHC does not fully discriminate patients who benefit the most from this treatment. There are factors that could be limiting the efficacy of this treatment, i.e. the expression of PD-L1 in the surface of circulating cells or the anti-inflammatory role of circulating leukocyte-platelet aggregates. Our objectives were to determine basal circulating levels of leukocyte-platelet complexes, levels of PD-L1 on circulating cells, levels of activated platelets and the absolute number of free platelets in ED-SCLC patients before starting treatment with first-line durvalumab-platinum-etoposide, and to compare them to the levels and numbers in healthy donors.

Methods: Patient (p) data and blood samples from 41 consecutive p enrolled in NCT04712903 Trial (EudraCT: 2020-002328-35) were assessed. Blood samples were collected at baseline, lymphocytes were gated according to size and complexity. Samples were analyzed by flow cytometry. We determined circulating levels of leukocyte-platelet complexes, circulating PD-L1+ leukocytes and platelets, activated platelets and the absolute number of free platelets in ED-SCLC patients and compared them with those from healthy donors (HD) (N=22). Descriptive statistics were used to report baseline characteristics. Kaplan-Meier was used to estimate survivals. Comparisons between groups were analyzed with t-test. All p-values are based on a two-sided hypothesis and those under 0.05 are considered statistically significant.

Results: The median age was 64 years (48-84), 27p (65.9%) were male, 11p (26.8%) had an ECOG PS of 0 and 30p (73.2%) had an ECOG PS of 1. 13p (31.7%) had liver metastases and 4p (9.8%) had CNS metastases.

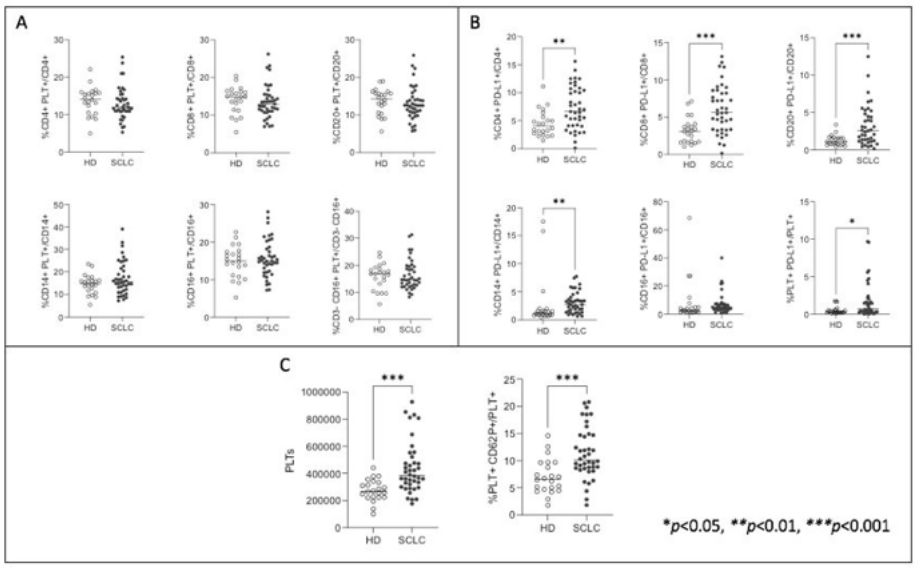
Flow cytometry results are represented in Figure 1: higher percentages of PDL1+ CD4+ T lymphocytes (p<0.01), PDL1+ CD8+ T lymphocytes (p<0.001), PDL1+ CD20+ T lymphocytes (p<0.001), PDL1+ monocytes (CD14+) (p<0.001) and PDL1+ platelets (p<0.05), were observed in ED-SCLC p compared to HD. Levels of activated platelets (CD62P+) also showed higher percentages in ED-SCLC p (p<0.001), as well as the absolute number of free platelets (p<0.001).

No statistically significant differences were observed in the percentages of circulating leukocyte-platelet (PLT) complexes, nor in PDL1+ neutrophils (CD16+) in ED-SCLC p compared to healthy donors.

Conclusions: Our results suggest that the percentages of circulating PD-L1+ leukocytes, PDL1+ platelets and activated platelets were significantly higher in ED-SCLC patients compared to healthy donors before starting first-line durvalumab-platinum-etoposide.

Keywords: Small-cell lung cancer, Leukocyte-platelet complexes, PD-L1 expression on circulating cells

Figure 1. Percentage of circulating leukocyte-platelet (PLT) complexes (A), circulating PD-L1+ cells (B), absolute number of platelets and levels of activated platelets (C) in ES-SCLC patients (N=41) (SCLC) compared to healthy donors (N=22) (HD) obtained by flow cytometry, represented by dot plots.



P3.13C SMALL CELL LUNG CANCER AND NEUROENDOCRINE TUMORS - BIOMARKERS AND DISEASE MONITORING
MONDAY, SEPTEMBER 9, 2024 - 12:00 - 14:00

P3.13C.04 Assessing ctDNA using a Methylation-informed Molecular Response Algorithm in Extensive-Stage Small Cell Lung Cancer Patients

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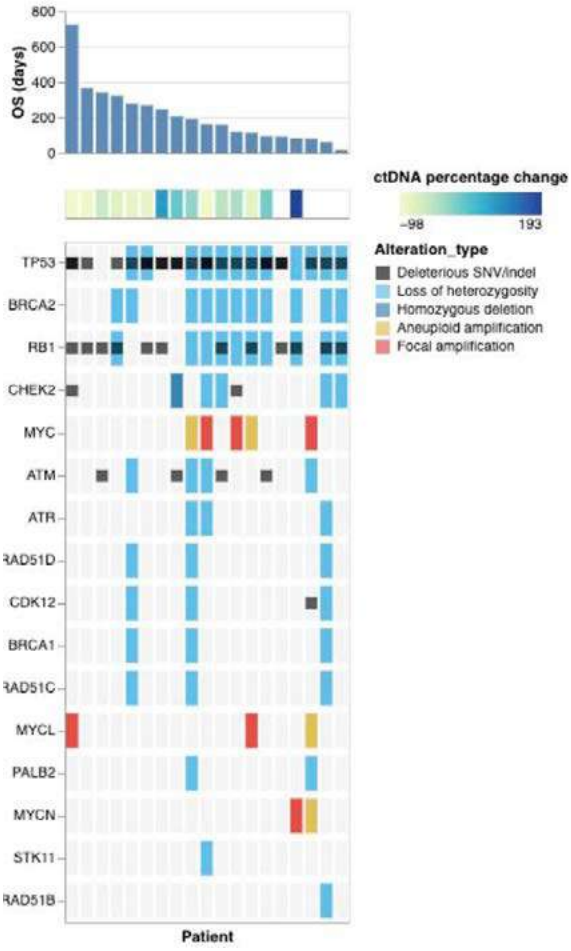
Introduction: Noninvasive liquid biopsies could be used to assess evolving treatment responses and overall survival (OS) in patients with advanced cancers. We previously reported that an early decrease in ctDNA from the baseline (BL) in ES-SCLC patients treated with nivolumab and temozolomide (N+T) was associated with improved PFS (NCT03728361). Here, we evaluate treatment response and OS via a methylation-based molecular response (MR) algorithm.

Methods: ES-SCLC patients who have progressed on chemoimmunotherapy were treated with N+T. Plasma was collected at BL, cycle 2 day 1 (C2D1), and C5D1 and analyzed using the Guardant360 Infinity assay, which includes genotyping >750 genes and methylation-informed tumor fraction (methyl TF). Molecular treatment response was assessed using the Guardant methylation-informed MR algorithms, where a >50% decrease in ctDNA was defined as achieving MR. Survival curves were compared using the log-rank test.

Results: 36 samples from 20 ES-SCLC patients were analyzed. 34 samples had methylation-based ctDNA successfully profiled, of which 33 (97%) had ctDNA detected. BL methyl TF was available for 18 patients, of which 50% were classified as high methyl-TF (threshold 10.3%). There were no differences in OS based on BL methyl-TF (p=0.32). BL and C2D1 ctDNA samples were available for 15 patients. Genomic and methylation MRs correlated positively (Pearson R=0.957, p <0.01). One patient had discordant results, with genomic non-MR (-33%) but methylation MR (-98%); notably, this patient experienced >700-day OS, suggesting methylation MR may be a good surrogate marker of response. While highly correlated in the 15-patient cohort, methylation MR is more closely associated with OS (p=0.07) compared to genomic MR (p=0.67). TP53, BRCA2, and RB1 were the most common BL genomic alterations (figure 1). Of 12 patients with BL TF > 0.2%, 8 had concurrent TP53/RB1 loss of heterozygosity (LoH) with a median OS of 114 days, while 4 patients without TP53/RB1 LoH had a median OS of 272 days (log-rank p = 0.03).

Conclusions: In this MR analysis of ES-SCLC patients treated with N+T, genomic variance allelic frequency and methyl TF dynamics were associated with OS, though methyl TF was a more robust indicator of OS. BL TP53/RB1 LoH was associated with shorter OS. These data suggest the potential utility of BL and early on-treatment assessment of ctDNA and methyl-TF in predicting treatment response. additional trials should continue to explore these patterns, which can provide valuable insights into the clinical utility of these assays.

Keywords: SCLC, ctDNA, methylation-informed tumor fraction



P3.13C SMALL CELL LUNG CANCER AND NEUROENDOCRINE TUMORS - BIOMARKERS AND DISEASE MONITORING
MONDAY, SEPTEMBER 9, 2024 - 12:00 - 14:00

P3.13C.05 Relationship Between Tumor Volume and Clinical Outcomes in Relapsed SCLC

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Introduction: For stage IA-IIIC SCLC, tumor burden is a predictor of clinical outcomes, but there is no data exploring whether tumor burden is a predictor of clinical outcomes in relapsed SCLC.

Methods: In this correlative study analyzing a Vanderbilt University Medical Center cohort of 93 patients with relapsed SCLC (49% Men, 90% White, 80% ≥ 65 years old, 69% initially ES-SCLC), total body tumor volume (TV), progression free survival (PFS) and overall survival (OS) were calculated and a Cox Proportional Hazards Model was used to evaluate the relationship between TV and PFS/OS.

Results: Our analysis revealed that TV was significantly associated with OS in a non-linear fashion (p 0.0059). Up to a tumor burden of 500cc, there was a nearly linear relationship between tumor burden and overall survival. As tumor burden reached levels higher than 500cc, this relationship plateaued. There was also a significant association between Eastern Cooperative Oncology Group Performance Status (ECOG PS) and overall survival (p=0.0003). When compared, ECOG PS was more strongly associated with OS than TV. When controlling for ECOG PS, the significant association between TV and OS persisted (p = 0.0064). In this cohort, there was no statistically significant association between TV and PFS or ECOG PS and PFS.

Conclusions: We observed that TV is a potential predictor of OS in patients with relapsed SCLC, though not as strong of a predictor as PFS. Further studies are needed to evaluate whether initiation of standard systemic therapy at lower TV is able to consistently improve PFS and OS.

Keywords: Relapse, SCLC, Tumor Burden

P3.13C SMALL CELL LUNG CANCER AND NEUROENDOCRINE TUMORS - BIOMARKERS AND DISEASE MONITORING
MONDAY, SEPTEMBER 9, 2024 - 12:00 - 14:00

P3.13C.06 Artificial Intelligence Meets SCLC - Integrating Clinicopathological and Whole-Slide Image Data for Prognostic Prediction in SCLC.

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Introduction: Small-cell lung cancer (SCLC) represents a unique clinical challenge characterized by its aggressive nature, poor prognosis, and limited therapeutic options. Upfront prediction of overall survival (OS) and progression-free survival (PFS) in this disease could impact patient care by refining risk stratification and personalize treatment strategies. Here, we investigate the utility of a deep learning (DL) model using digital pathology to enhance the outcomes prediction of patients diagnosed with SCLC.

Methods: Data from 307 SCLC patients with comprehensive clinical and follow up information, including age, clinical stage, treatment type, and performance status, progression free survival (PFS) and overall survival (OS) and corresponding Whole Slide Images (WSI) at diagnosis were collected. The cohort was divided into a training set (n=263) consisting of patients treated at Hospital del Mar, Barcelona, Spain, and a validation set (n=44) comprising patients included in the CANTABRICO phase IIIB clinical trial (NCT04712903). LT_OS (Long-Term Overall Survival) was defined as OS exceeding 12 months for metastatic patients and 25 months for non-metastatic patients. For LT_PFS (Long-Term Progression Free Survival) prediction PFS was defined as longer than 5 or 14.3 months for extensive-stage-SCLC and limited-stage-SCLC patients, respectively. We built a random forest (RF) model using clinical data and a DL based model using WSI as inputs. Model performance was assessed using the area under the receiver operating characteristic curve (AUC) with 5-fold cross-validation to minimize bias and variance of the performance. We report the mean and 95% confidence interval of the AUC values across the folds.

Results: In the training set, the RF model achieved an AUC of 0.728 (95% CI: 0.662-0.792) for LT_OS prediction, while the combined RF and DL model achieved an AUC of 0.744 (95% CI: 0.680-0.807). For LT_PFS prediction, the RF model achieved an AUC of 0.689 (95% CI: 0.625-0.753), whereas the combined model achieved an AUC of 0.704 (95% CI: 0.640-0.767). Application of the combined RF and DL model to the validation cohort yielded an AUC for LT_OS of 0.604 (95% CI: 0.582-0.626) and an AUC for LT_PFS 0.690 (95% CI: 0.643-0.738), indicating potential clinical applicability.

Conclusions: Our results showcase the feasibility of integrating clinicopathological data with whole slide imaging (WSI) from digital pathology through a deep learning model to enhance prediction outcomes in patients with SCLC. Inclusion of additional biomarkers (i.e. immunohistochemical markers, genomic alterations) might further increase the potential of prediction using deep learning models. This approach holds promise in helping physicians in personalize treatment strategies that better suit individual patient needs.

Keywords: Small-cell lung cancer, Deep-learning model, Digital pathology

P3.13C SMALL CELL LUNG CANCER AND NEUROENDOCRINE TUMORS - BIOMARKERS AND DISEASE MONITORING
MONDAY, SEPTEMBER 9, 2024 - 12:00 - 14:00

P3.13C.07 Novel Nomogram Integrating Clinial, Radiomics and Genomics for Prediction of Radiation Pneumonitis in Limited-Stage Small Cell Lung Cancer

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Introduction: Definitive chemoradiotherapy (dCRT) is the standard treatment for limited-stage small cell lung cancer (SCLC), but varying degrees of radiation pneumonitis (RP) occur in some patients. This study aimed to construct a nomogram combining radiomic, genomic, and clinical factors for the prediction of RP after dCRT in individual patients with limited-stage SCLC.

Methods: Totally 150 limited-stage SCLC patients treated with dCRT were divided into training (n=103) and validation (n=45) cohorts. All tumor tissue samples were subjected to gene sequencing, and 851 radiomics features of lung excluding the hilum, atelectasis and tumor were extracted from initial computed tomography images. The least absolute shrinkage and selection operator (LASSO) method was applied to select features and build a radiomic score (Radscore). Combining radiomics, genomics and clinical factors, a nomogram was established by univariate and multivariate analyses. The predictive ability and application value were evaluated based on the area under the receiver operating characteristic curve (AUC), calibration curve, and decision curve.

Results: The Radscore constructed from six selected features was significantly associated with grade ≥2 RP (P<0.01). Multivariate analysis identified NQO1(rs1131341) allele mutation, Radscore, and mean lung dose as independent risk factors for RP. Compared with the individual clinical (AUC=0.717 and 0.641), radiomic (AUC=0.703 and 0.635) or genomic (AUC=0.581 and 0.571) models, the nomogram had the highest AUC values of 0.857 and 0.688 in the training and validation groups, respectively. The calibration curves indicated good agreement between the predictions and actual observations. Moreover, decision curves showed the nomogram had high clinical practicability.

Conclusions: Radiomic and genomic features have potential to assist with prediction of RP. The developed nomogram incorporating radiomic, genomic, and clinical factors provides robust personalized prediction of RP.

Keywords: small cell lung cancer, radiation pneumonitis, radiogenomics

P3.13C.08 Optimal Treatment Strategies for Older Adults with Clinical Stage IA Small Cell Lung Cancer

M. Yang, A. Potter, D. Srinivasan, D. Wang, M. McCarthy, J. Sands, D. Kozono, C-F.J. Yang, Massachusetts General Hospital, Boston/MA/USA

Introduction: Data on treatment strategies for early-stage small cell lung cancer (SCLC) in patients aged 80 and older are limited. The objectives of this study are to (1) assess treatment patterns over time and (2) evaluate survival outcomes of different treatment modalities in this patient population.

Methods: Patients aged 80-89 diagnosed with clinical stage IA SCLC from 2004-2021 in the National Cancer Database were identified for analysis. Treatment patterns from 2004-2021 were examined. Overall survival stratified by treatment type was assessed using Kaplan-Meier analysis and multivariable Cox proportional hazard analysis. A subgroup analysis was performed on surgery and SBRT groups.

Results: A total of 553 patients met inclusion criteria. Median follow up was 18.2 months (IQR, 8.7 to 39.9). From 2004 to 2021, the proportion of patients undergoing chemotherapy alone or no treatment decreased, while numbers receiving SBRT increased (Figure 1). The majority (37.3%) of patients underwent chemotherapy alone, 20.3% underwent SBRT, 13.0% underwent surgery, and 10.0% underwent non-SBRT radiation. 11.4% underwent unknown/other treatment, while 8.1% underwent no treatment. Overall survival by treatment type is shown in Table 1. In unadjusted and multivariable-adjusted analysis, SBRT was associated with similar overall survival compared to surgery; chemotherapy alone, non-SBRT radiation, no treatment, and other/unknown treatment were associated with significantly worse overall survival. In a subgroup analysis of patients who underwent surgery or SBRT (n=189), surgery alone, surgery with chemotherapy, SBRT alone, and SBRT with chemotherapy were associated with similar overall survival.

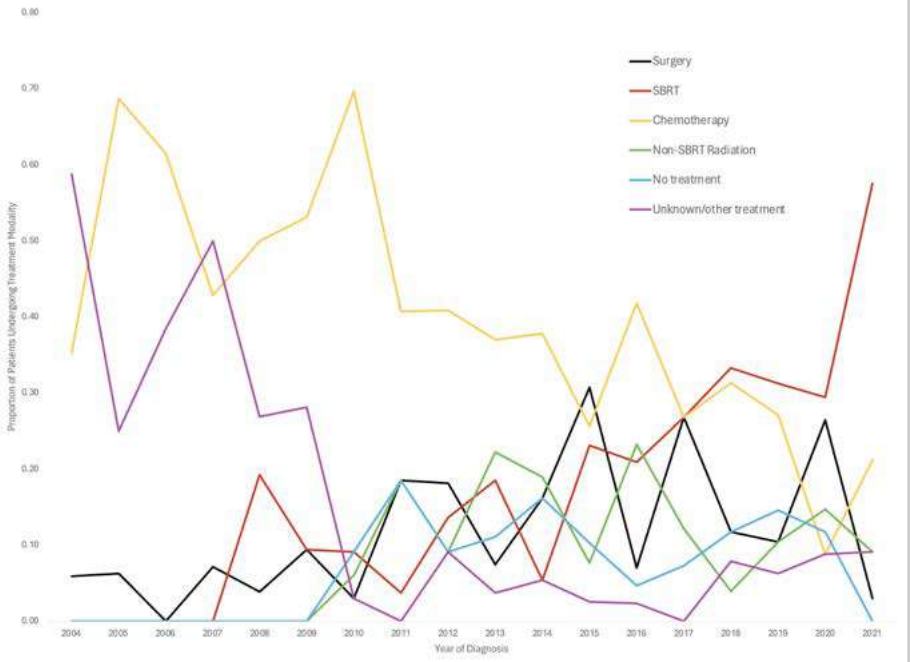
Conclusions: In this national analysis, the use of SBRT for patients aged over 80 years diagnosed with clinical stage IA SCLC has increased over the last two decades and was the most common treatment for this patient population in 2021. SBRT was associated with similar overall survival when compared to surgery; both were associated with better survival than other treatment modalities.

Keywords: Small Cell Lung Cancer, Treatment

Table 1. Unadjusted and Multivariable-adjusted Analyses

All Treatment Groups					
Unadjusted Analysis			**Multivariable Cox Model**		
Treatment	***5-year survival (95% CI)***	***P value***	***Treatment v Surgery (ref) Hazard Ratio***	***95% CI***	***P value***
Surgery	33.6% (21.7%-45.9%)	<0.001	N/A		
SBRT	21.0% (11.9%-31.9%)		1.36	0.90, 2.03	0.14
Chemotherapy	19.7% (14.3%-25.8%)		1.54	1.08, 2.20	0.02
Radiation (non-SBRT)	5.8% (1.2%-16.3%)		1.84	1.19, 2.85	0.006
No treatment	8.4% (1.9%-21.2%)		3.02	1.90, 4.80	<0.001
Unknown/other treatment	7.6% (2.5%-16.5%)		2.19	1.41, 3.40	0.001
Subgroup Analysis: Surgery with or without chemotherapy, SBRT with or without chemotherapy					
Unadjusted Analysis			**Multivariable Cox Model**		
Treatment	***5-year survival (95% CI)***	***P value***	***Treatment v Surgery (ref) Hazard Ratio***	***95% CI***	***P value***
Surgery alone	33.4% (19.3%-48.1%)	0.52	N/A		
Surgery with chemotherapy	31.5% (12.9%-52.2%)		1.58	0.80, 3.14	0.19
SBRT	19.2% (9.6%-31.2%)		1.52	0.88, 2.63	0.13
SBRT with chemotherapy	24.3% (7.2%-46.8%)		1.18	0.56, 2.48	0.67

Figure 1. Use of Treatment Modalities in Patients Aged 80-89 With Small Cell Lung Cancer Between 2004-2021



P3.13C.09 First-Line Treatments for Advanced Pure Large Cell Neuroendocrine Tumors (LCNEC):Insights from a Global Clinico-Genomic Study

A.H. Nassar[1], K. Matteson[1], T. Adeyelu[2], A. Ocejo[3], F. Ardeshir[4], T. Leal[4], S. Ramalingam[4], J.E. Gray[5], K. Hicks[5], D. Kaldas[5], J. Baena[6], M. Zurera Berjaga[6], D.J. Kwiatkowski[7], F. Aboubakar Nana[8], C. Grohe[9], H. Leuders[9], F. Citarella[10], A. Cortellini[10], E.C. Mingo[10], D. Pancirer[11], M. Das[11], T. John Ellis-Caleo[11], J.M. Cheung[12], J.J. Lin[12], A. Watson[13], R. Camidge[13], A. Sridhar[14], K. Parikh[14], F. Crowley[15], T. Marron[15], V. Aggarwal[16], A. Murtaza[17], K. Sankar[17], H. Kawtharany[18], J. Zhang[18], D. Owen[19], M. Li[19], M. Nagasaka[20], D. Pinato[21], K. Alhamad[22], S. Puri[22], N. Awosika[21], U. Zaman[23], M. Evans[24], A. Vanderwalde[24], G. Lopez[3], h. borghaei[25], C. Kim[26], A.R. Naqash[23], A. Chiang[1], [1]Yale Cancer Center, New Haven/CT/USA ,[2]CARIS, Irving/TX/USA ,[3]Jackson Memorial Hospital, Miami/FL/USA ,[4]Emory Winship, Atlanta/GA/USA ,[5]Moffitt Cancer Center, Tampa/FL/USA ,[6]Hospital [12] de Octubre, Madrid/ES ,[7]Brigham and Women's Hospital, Boston/MA/USA ,[8]UC Louvain, Louvain-la-Neuve/BE ,[9]Klinik für Pneumologie-Evangelische Lungenklinik, Berlin Buch, Berlin/DE ,[10]Università Campus Bio-Medico di Roma, Roma/IT ,[11]Stanford, California/CA/USA ,[12]MGH, Boston/MA/USA ,[13]University of Colorado Cancer Center, Denver/CO/USA ,[14]Mayo Clinic, Rochester/MN/USA ,[15]Mount Sinai Icahn School of Medicine, New York/NY/USA ,[16]Georgetown, Washington/DE/USA ,[17]Cedars Sinai Medical Center, Los Angeles/CA/USA ,[18]University of Kansas Medical Center, Andover/KS/USA ,[19]The Ohio State University Comprehensive Cancer Center, Ohio/OH/USA ,[20]UC Irvine, Irvine/CA/USA ,[21]Imperial College, London/GB ,[22]Huntsman Cancer Institute, Utah/UT/USA ,[23]Stephensen Cancer Center, Oklahoma City/OK/USA ,[24]Caris Life Sciences, Irving/TX/USA ,[25]Fox Chase Cancer Center, Philadelphia/PA/USA ,[26]MedStar Georgetown Cancer Institute, Washington/DC/USA

Introduction: Therapeutic strategies for LCNEC are not standardized and are derived from protocols for SCLC and NSCLC, which might not be entirely appropriate due to the unique biology of LCNEC.

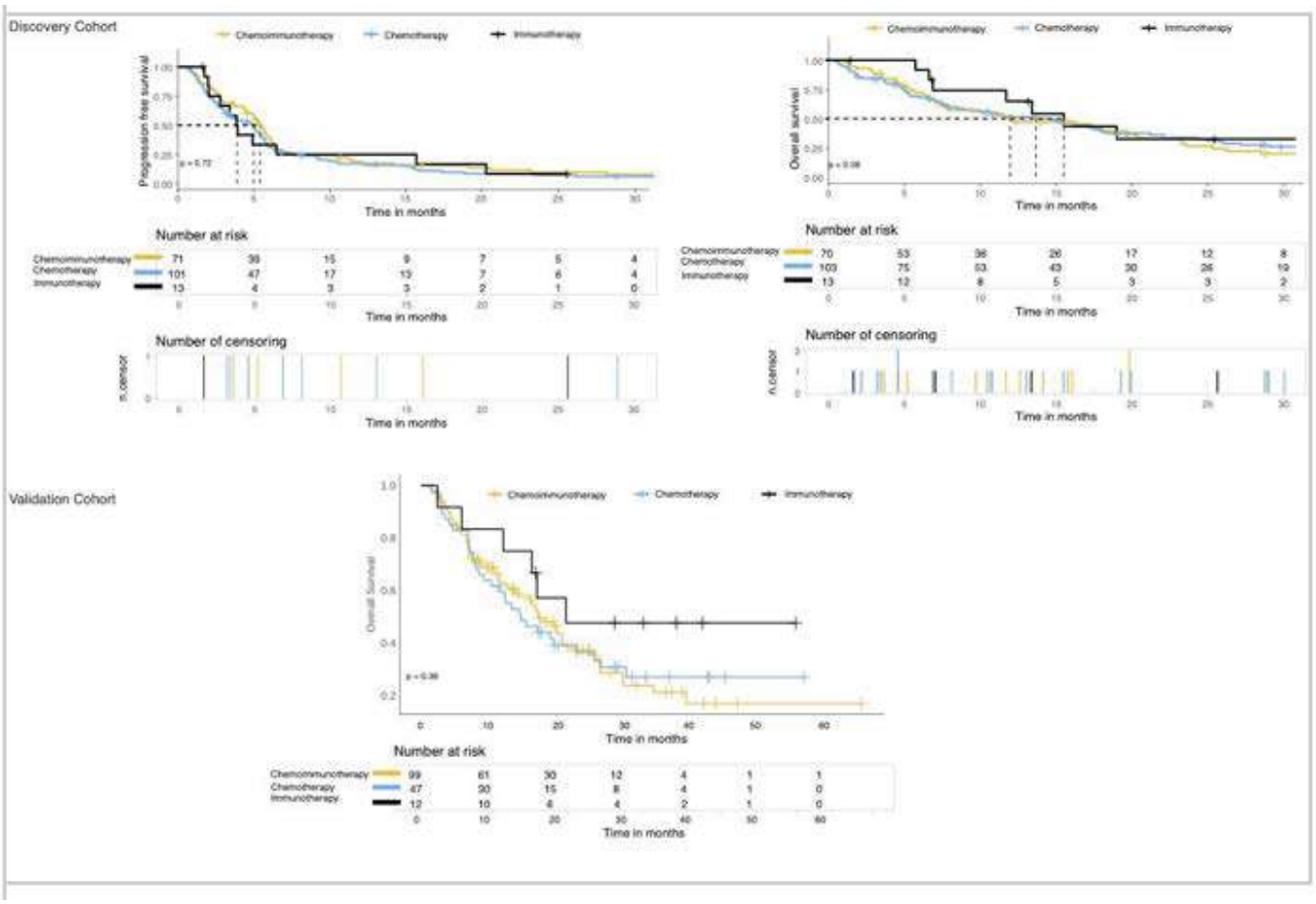
Methods: For discovery, we leveraged a multi-institutional retrospective cohort from 23 centers of metastatic pure LCNEC (diagnosed locally). For validation, clinical and molecular profiles of patients with pure LCNEC were obtained from Caris Life Sciences. Patients received 1st-line systemic therapy between 2015-2023 and were either treated with chemotherapy(chemo), immunotherapy(IO), or a combination(chemoIO). Clinical outcomes included progression-free survival(PFS), overall survival(OS), and treatment-related adverse events(trAE). Survival comparisons were made by genomic alteration (TP53/RB1/STK11/KEAP1/KRAS).

Results: The discovery cohort had 190 patients with median age at 1st-line systemic therapy of 66 years; 55% (n=105) were males. First-line treatments were chemoIO(n=72), chemo(n=105), or IO(n=13). Median follow-up time was 54 months(mo), 45 mo, and 26 mo for the chemo, IO, and chemoIO groups, respectively. Of 116 patients with available PD-L1, 74(64%) were negative and 42(36%) were ≥1%. The most common chemo regimen was platinum-etoposide (n=83,72%). The most common chemoIO regimen was carboplatin/etoposide/atezolizumab (n=30,43%). In the IO group, one patient received dual IO. For the validation cohort(n=158), 47, 99, and 12 received chemo, chemoIO, and IO, respectively.

In the discovery cohort, there was no significant difference in PFS across the groups (Figure, top left) on multivariable analysis adjusting for ECOG and "M" stage (p=0.09 and 0.54 for chemo vs. chemoIO; chemo vs. IO comparisons, respectively). Similarly, there was no difference in OS (p=0.77 and 0.23 for chemo vs. chemoIO and chemo vs. IO comparisons, respectively, Figure, top right). In the validation cohort, median OS was not significantly different across treatment groups(p=0.38, Figure bottom). In the discovery cohort with available genomic data (n=129), those harboring TP53 mutations in LCNEC exhibited significantly inferior OS and PFS when treated with chemo (Median OS TP53-mutant:11mo vs. 24.5mo for TP53-WT, p=0.04; median PFS TP53-mutant 10.4 vs.19.2mo for WT, respectively, p=0.008) but not chemoIO. Any grade trAE occurred in 56(54%), 41(57%), and 6(46%) patients treated with chemo, chemoIO, and IO, respectively. There were significantly less grade ≥3 trAEs in the IO-treated group vs. chemo and chemoIO (22% vs. 24% vs. 0%, respectively, p=0.04).

Conclusions: As first-line therapy for mLCNEC, chemo, chemoIO, and IO show comparable survival outcomes with significantly less toxicities in the IO-treated group. The findings underscore the opportunity for further innovation in treatment strategies, prompting the need for future clinical trials.

Keywords: Large cell neuroendocrine carcinoma, Genomics, Systemic therapy


Discovery Cohort
Chemoimmunotherapy
Chemotherapy
Immunotherapy
Progression free survival
Time in months
Number at risk
Number of censoring
Overall survival
Validation Cohort
Overall Survival

P3.13D SMALL CELL LUNG CANCER AND NEUROENDOCRINE TUMORS - MOLECULAR PROFILING AND MOLECULAR TARGETS
MONDAY, SEPTEMBER 9, 2024 - 12:00 - 14:00

P3.13D.01 Proteomic Characterization of Antibody Drug Conjugate Target Expression Profiles in Small Cell Lung Cancer (SCLC)

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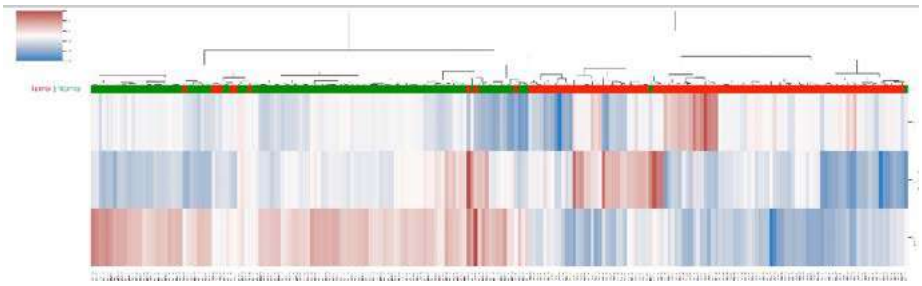
Introduction: Despite advancements in diagnosis and therapy, outcomes for small cell lung cancer (SCLC) remain suboptimal. Recent studies exploring antibody drug conjugates (ADCs) have demonstrated promising preliminary results. However, further characterization of target expression profiles is needed for optimal patient selection. Here, we aim to utilize mass spectrometry to characterize the proteomic patterns of ADC targets within SCLC.

Methods: We analyzed the expression of ADC targets including DLL3 (DLL3), B7H3 (CD276), Trop2 (TACSTD2), and SEZ6 (SEZ6) in patients with treatment-naïve SCLC (n=112) from Clinical Proteomic Tumor Analysis Consortium (CPTAC) database. Isobaric tandem mass tag labeled mass spectrometry (TMT-11 plex) data from SCLC tumor tissue and normal adjacent lung tissue was obtained. Differential protein expression between tumors and normal adjacent tissue was assessed with a threshold Log2 fold change >1 and Benjamini-Hochberg adjusted P-value <0.01. Hierarchical clustering was used to identify transcriptomic and proteomic patterns of ADC target expressions.

Results: A total of 214 samples from 107 patients which passed quality control were used for downstream analyses. Differential protein expression analysis showed significantly increased DLL3 (Log2FC=2.9, P=4.7E-4), decreased Trop2 (Log2FC=-1.9, P=2E-19), and no difference in B7H3 (P=0.50, Log2FC=-0.05) in SCLC tumors compared to normal adjacent lung tissue. SEZ6 expression was missing for over 50% of samples, precluding further analysis. By hierarchical clustering, normal lung tissue could be distinguished from tumor tissue based on high Trop2 expression. Tumor subsets formed clusters based on either increased expression of DLL3 (22.4%) or B7H3 (24%). Interestingly, DLL3 and B7H3 displayed a nearly mutually exclusive pattern of overexpression.

Conclusions: In SCLC, overexpression of DLL3 and B7H3 is seen in approximately one quarter of tumors with these targets being mutually exclusive. Meanwhile, Trop2 was significantly overexpressed in normal tissues. Further prospective research utilizing proteomics-based approach may enable optimal utilization of ADCs in patients with SCLC.

Keywords: small cell lung cancer, proteomics, bispecific antibodies



P3.13D.02 DLL3 Expression in Early-Stage SCLC: Comparative Analysis of IHC and mRNA ISH in Tumor and Lymph Nodes

M-L. Meyer[1], H. Yu[2], F. Hirsch[3], [1]Mount Sinai, NEW YORK/NY/USA ,[2]University of Colorado Anschutz Campus, Aurora/CO/USA ,[3]Mount Sinai Hospital, NEW YORK/NY/USA

Introduction: Small cell lung cancer (SCLC) is highly lethal. Delta Like Canonical Notch Ligand 3 (DLL3) is commonly overexpressed in SCLC and is a target for new therapies. 80%-93% of advanced SCLC cases are DLL3 positive, but its expression in early-stage SCLC lacks documentation, and especially the correlation with metastatic lymph node expression. This study aimed to assess DLL3 expression in early-stage SCLC tumors using immunohistochemistry (IHC) and mRNA in situ hybridization (ISH), correlate these assays with matched metastatic lymph nodes, and correlate DLL3 expression with outcomes and characteristics.

Methods: This single-center retrospective study evaluated 248 resected samples from patients with early-stage SCLC between 1978 and 2013. IHC staining was performed using the Ventana Benchmark XT autostainer and SP347 Antibody Assay. For mRNA ISH, the Leica Bond RX autostainer was utilized. IHC positivity was defined as an H-score of ≥1 (ranging from 0 to 300), and mRNA ISH positivity was defined as a score of ≥1 using the ACD-approved method (ranging from 0 to 3). A linear correlation between IHC and mRNA ISH scores was calculated. Univariable and multivariable Cox regression analyses were conducted using the PASW Statistics 22.0 package and R versions 3.5.2 and 4.3.1.

Results: 248 patients with histologically confirmed early-stage SCLC were included, with 32 matched lymph nodes metastasis. Among the tumor samples, 233 were evaluable using IHC, with 58% testing positive. For mRNA ISH, 235 samples were evaluable, with 87% showing positivity. DLL3 positivity in lymph nodes was 69% with IHC and 100% with mRNA ISH. Correlation between IHC and mRNA ISH was significant (Spearman's rank, p<0.001). Additionally, DLL3 positivity was significantly correlated between tumor and lymph nodes metastasis for both IHC (p=0.024) and mRNA ISH (p=0.047). DLL3 positivity in the tumor was not correlated with patients' clinical characteristics. A non-significant trend towards better median overall survival (mOS) was observed for patients with a tumor IHC score <1, showing a mOS of 27.1 months (95% CI: 12.5-59.0) versus 21.0 months (95% CI: 18.2-30.4), p=0.893. A similar trend was observed with an mRNA ISH score <1: mOS of 38.9 months (95% CI: 26.6-NA) versus 18.9 months (95% CI: 14.9-28.8), p=0.221.

Conclusions: In this study of 248 early-stage resected SCLC, DLL3 positivity was 58% with IHC and 87% with mRNA ISH. Both IHC and mRNA ISH showed significant correlation in tumors and lymph node metastasis. An observed trend suggested improved survival in patients with no DLL3 expression.

Keywords: Delta Like Canonical Notch Ligand 3 (DLL3), immunohistochemistry (IHC), mRNA in situ hybridization

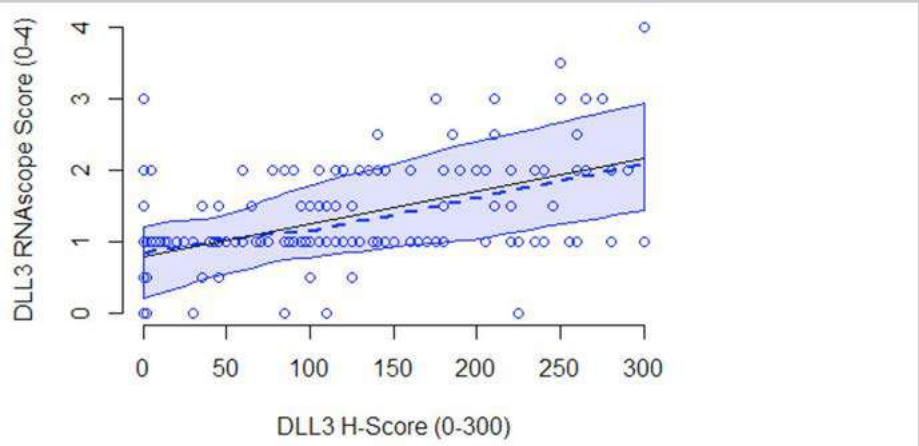


Figure 1. Comparison of DLL3 expression. Linear regression fitted line (black), Loess smoothing line (dashed blue), 95% confidence bands (solid blue). Spearman's rank correlation rho=0.557, p<0.001.

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P3.13D.03 Inhibition of LSD1 Prevented Tumor Progression and Recurrence to Radioimmunotherapy in Small Cell Lung Cancer

F. Na, H. Wang, X. Pan, K. Kang, Z. Yao, Y. Zheng, G. Lin, Y. Wu, R. Luo, X. Zhang, R. Tong, C. Chen, Y. Lu, West China Hospital of Sichuan University, Chengdu/CN

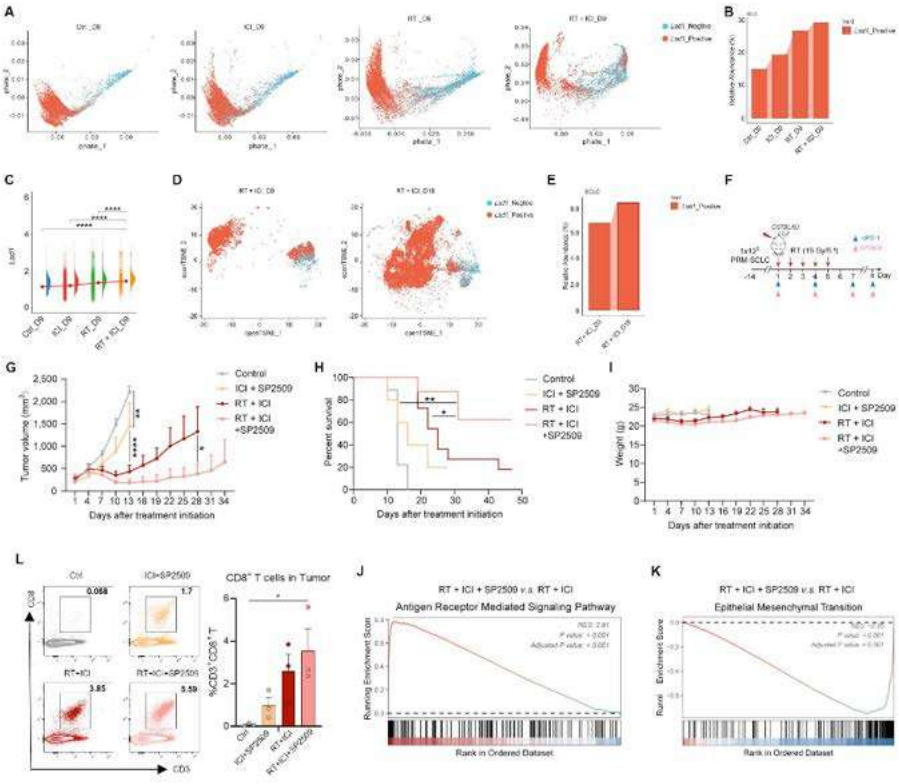
Introduction: Small cell lung cancer (SCLC) remains a highly metastatic neuroendocrine cancer with high lethality. Intratumor heterogeneity and genomic instability are additional features of SCLC. Previous studies revealed radiotherapy (RT) combined with immune checkpoint inhibitors (ICIs) had synergistic anti-tumor effect in SCLC, but tumor recurrence still occurred in the late stage of treatment. Therefore, it's necessary to elucidate the mechanism of recurrence and progression of SCLC in this new combination therapy and explore new therapeutic targets.

Methods: We constructed murine SCLC model and used multi-omics methods to analyze the dynamic changes of SCLC from sensitivity to recurrence after radioimmunotherapy treatment, especially the role and molecular mechanism of lysine-specific demethylase 1 (LSD1) in the process of recurrence. We further evaluate the anti-tumor effect of the triple therapy of RT + ICI + LSD1 inhibitor (SP2509) on SCLC.

Results: Single-cell RNA-Seq (scRNA-Seq) data revealed that according to the expression of Lsd1, the tumor cells from four groups in the murine SCLC model were divided into two clusters: Lsd1 positive and Lsd1 negative. It was observed that despite the synergistic anti-tumor effect of RT + ICI, the proportion of Lsd1 positive tumor cells also increased on Day 9 in the RT + ICI group. Subsequent analysis of tumor tissues in recurrence stage of RT + ICI treatment (Day 18) showed the proportion of Lsd1 positive tumor cells further increased compared to Day 9, indicating these Lsd1 positive tumor cells may be not sensitive to RT + ICI treatment and associated with tumor recurrence and progression in the late stage of treatment. Furthermore, the addition of LSD1 inhibitor (SP2509) into RT + ICI treatment had a superior anti-tumor effect and prolonged the survival of mice. The complete response rate of tumors tripled to 60% with the triple therapy regimen, which was well tolerated with no weight loss observed in mice throughout the experiment. Flow cytometry analysis demonstrate the triple therapy resulted in the most T cell infiltration in tumor. Bulk RNA-Seq data demonstrated that the triple therapy regimen upregulated the antigen presentation pathway and downregulated the epithelial-mesenchymal transition (EMT) pathway.

Conclusions: In our murine SCLC model, Lsd1 positive tumor cells were enriched in the recurrence stage of RT+ ICI treatment. Triple therapy of RT+ ICI + LSD1 inhibitor could delay the tumor progression and recurrence to radioimmunotherapy through upregulating the antigen presentation pathway, downregulating the EMT pathway.

Keywords: Small cell lung cancer, radioimmunotherapy, LSD1



P3.13D.04 Extrachromosomal MYC-Paralogs Amplification Defines Immunosuppressive Microenvironment with Metastatic Potential in Small Cell Lung Cancer

J. Zhang[1], J. Deng[1], Y. Jin[2], H. Lin[2], K. Dai[1], X. Hu[2], K. Sun[1], E. Yang[2], X. Li[1], [1]Peking University People's Hospital, Beijing/CN ,[2]Peking University Health Science Center, Beijing/CN

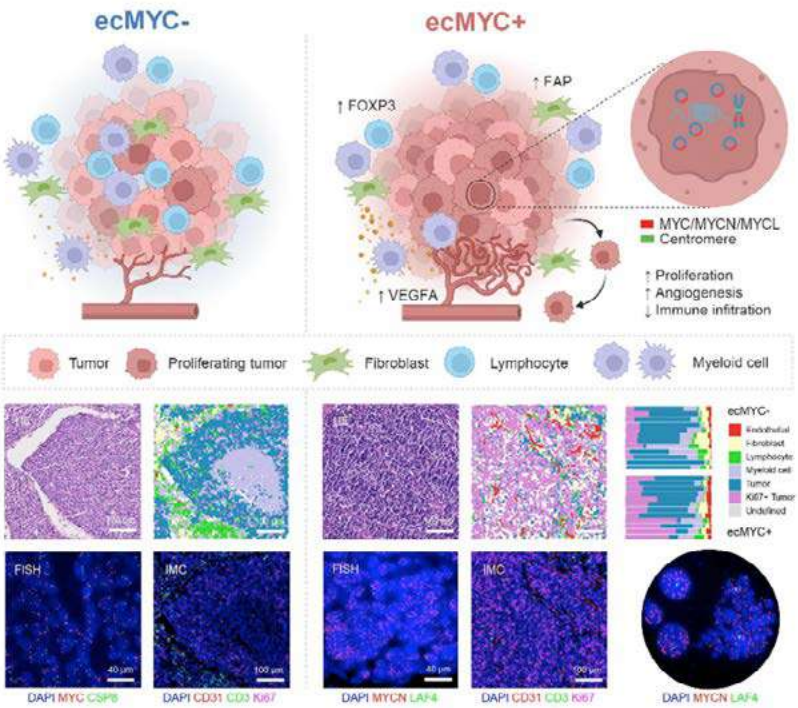
Introduction: Although immunotherapy has demonstrated promise in small cell lung cancer (SCLC), a certain number of patients encounter limited benefits, underlining the necessity for identifying molecular biomarkers of immunosuppressive characteristics. Extrachromosomal circular DNA (ecDNA) promotes amplification of MYC-paralogs (MYC, MYCN and MYCL), which are recognized as recurrent drivers of cross-resistance in SCLC. Nevertheless, it remains unclear whether ecDNA-mediated MYC-paralogs amplification (ecMYC+) denotes immunosuppressive traits in SCLC.

Methods: Whole-genome sequencing (WGS) and bulk RNA sequencing (RNA-seq) data were retrieved from the Cancer Cell Line Encyclopedia (CCLE) database (n = 329), the Cancer Genome Atlas (TCGA) database (n = 1857) and European Genome-phenome Archive (EGAS00001000925, n = 87). The overexpression and amplification of MYC-paralogs were identified by immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH) in SCLC clinical samples (n = 42). Imaging mass cytometry (IMC) with 40-plex antibody panel was used to characterize the subpopulation frequency and spatial distribution of SCLC tumor microenvironment. The relative copy number of MYC-paralogs was investigated by real-time polymerase chain reaction (qPCR). RNA-sequencing and flow cytometry were performed in controlled and drug-treated SCLC cell lines.

Results: The mean copy number of ecDNAs were higher in SCLC than the other lineages (15.3 vs 8.4), as well as the frequency of ecMYC+ cell lines (SCLC 22/47 vs others 15/282, p = 3.9×10-12). Highly amplified MYC-paralogs (> 20-fold) were detected in resectable SCLC samples, including treatment-naïve T1 stage patient, indicating early relapse and poor prognosis. With 102,008 cells resolved from 24 pathological regions, we identified higher expression of MKI67, VEGFA, FAP and FOXP3 in ecMYC+ samples, and found reduced T cell infiltration along with higher frequencies of endothelial and CD163+ macrophages. Furthermore, ecMYC+ samples exhibited elevated cellular neighborhood dominated by Ki-67+ tumors, with reduced spatial interaction with immune and stroma cells. Various immune-related pathways were downregulated and nucleotide metabolism processes were upregulated in ecMYC+ SCLC, and inhibition of nucleotide metabolism induced by hydroxyurea and gemcitabine led to diminishment of ecMYC, accompanied with activation of antigen presenting pathway. In pan-cancer lineages, ecMYC+ cell lines also exhibited multiple down-regulated immune pathways, higher frequency of metastatic collection sites (p = 1.2 × 10-3) and suspension growth (p = 4.3× 10-4) independent of MYC-paralogs overexpression.

Conclusions: Our findings underscore the significance of extrachromosomal MYC-paralog amplification in shaping the immunosuppressive tumor microenvironment and potentially contributing to metastasis, indicating potential targets for improving immunotherapy outcomes in SCLC.

Keywords: small cell lung cancer, extrachromosomal MYC-paralogs amplification, tumor microenvironment



Schematic model illustrating the proposed role of extrachromosomal MYC-paralogs amplification (ecMYC+) in SCLC (top) and pathological samples images (bottom). The images include hematoxylin-eosin staining (HE), fluorescence in situ hybridization (FISH), imaging mass cytometry (IMC), and cell neighborhood analysis (CN) results for both ecMYC- and ecMYC+ SCLC samples. The bottom right part exhibited the landscape of various subpopulations proportions from 24 SCLC regions of interests (ROIs), while the lower 12 ROIs were from ecMYC+ samples. The circular image demonstrates MYCN (red) amplified outside the metaphase chromosome (in blue) in metaphase cells.

P3.13D.05 Genomics and Immune Infiltration Biomarkers for Short-term and Long-Term ES-SCLC Survivors with First-Line Chemoimmunotherapy

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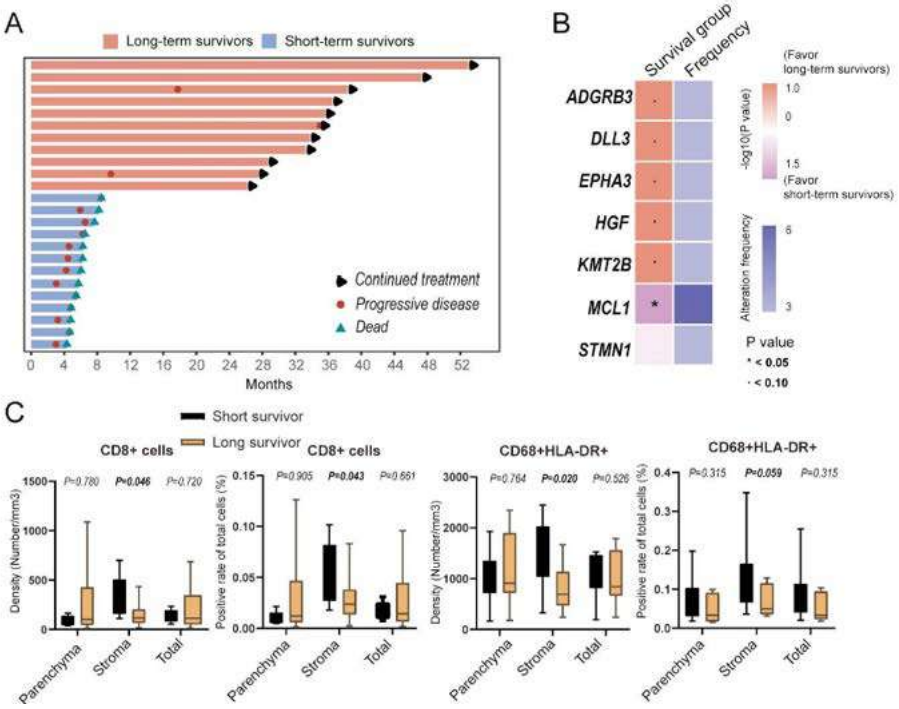
Introduction: First-line chemoimmunotherapy has largely enhanced survival in patients with unselected extensive-stage small cell lung cancer (ES-SCLC). Nevertheless, only a minor subset of ES-SCLC patients are bestowed with prolonged survival, which warrants robust biomarkers. As such, we aim to explore the differences in genomics and spatial distribution of immune cells between long-term and short-term ES-SCLC survivors.

Methods: We retrospectively recruited 11 long-term (>2 years) and 13 short-term (<9 months) ES-SCLC survivors treated with first-line chemoimmunotherapy. Samples were processed using targeted next-generation sequencing (tNGS), programmed death ligand-1 (PD-L1) staining, multiple immunohistochemical staining of immune cells (mIHC) (CD8A, CD68, HLA-DR, CD56, panCK, DAPI), tumor mutational load (TMB) and chromosomal instability (CIN) score testings.

Results: Genomically, a higher proportion of the smoking mutational signature and a heavier TMB suggested better prognoses. The single gene and pathway level's analysis indicated that the amplification of MCL1 and STMN1, as well as apoptotic pathway's alterations accumulated more frequently in short-term survivors, whereas DLL3, KMT2B, HGF, EPHA, and ADGRB3 alterations, and the alterations of the corresponding lysine deprivation and HGF-cMET pathways were commonly detected in long-term survivors. The spatial distribution of immune cells illustrated that long-term survivors showed higher infiltration of parenchymal and stromal M1-like macrophages yet lower levels of CD8+T in the stromal areas. Furthermore, using the public bulk and single-cell transcriptomic databases, we managed to find that high levels of STMN1 and DLL3 typified immunosuppressive phenotypes, whereas HGF, MCL1, and EPHA3 characterized immune-responsive phenotypes. The SCLC-N subtype possessed a higher expression of STMN1 compared to the rest of the subtypes.

Conclusions: The present study revealed that the infiltration of stromal CD8+ T cells and M1-like macrophages in any location differed between long-term and short-term ES-SCLC survivors. Genomic features including alterations of MCL1, STMN1, KMT2B, EPHA3, HGF, DLL3 and ADGRB3, as well as the proportion of smoking mutational signature were proven to be prognosis-related. This may steer us through the maze of selecting suitable ES-SCLC patients benefiting from first-line chemoimmunotherapy and expedite the exploitation of therapeutic targets.

Keywords: immunotherapy, genomics, immune microenvironment



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P3.13D.06 Distinct Single-Cell Transcriptomic Characteristics and Responses to the Front-Line Therapy in Patients with Central or Peripheral ES-SCLC

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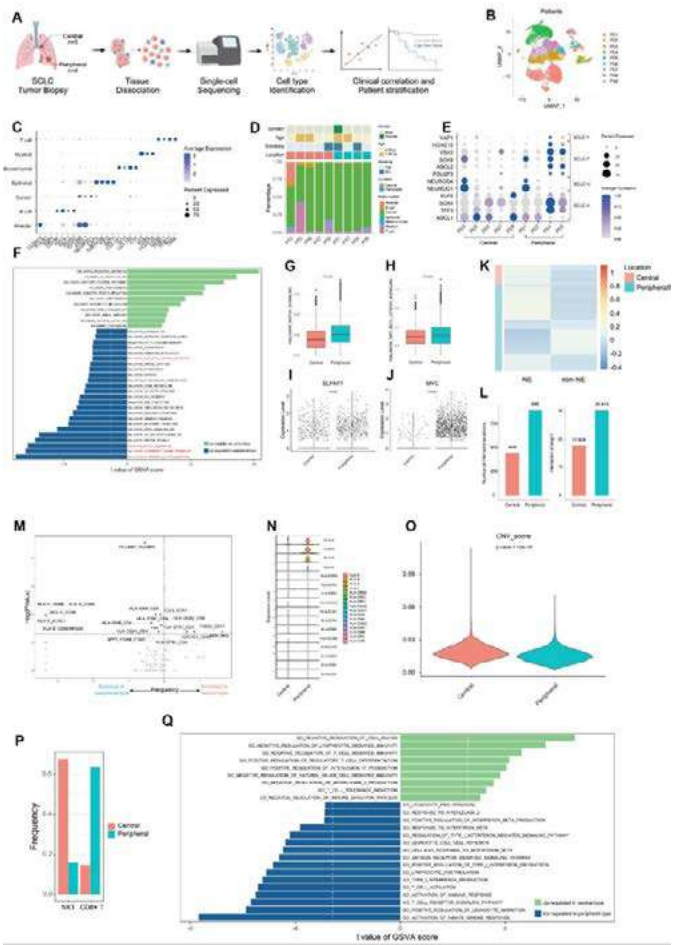
Introduction: Extensive-stage small-cell lung cancer (ES-SCLC) remains a big challenge and in-depth understanding of its biology is urgently needed.

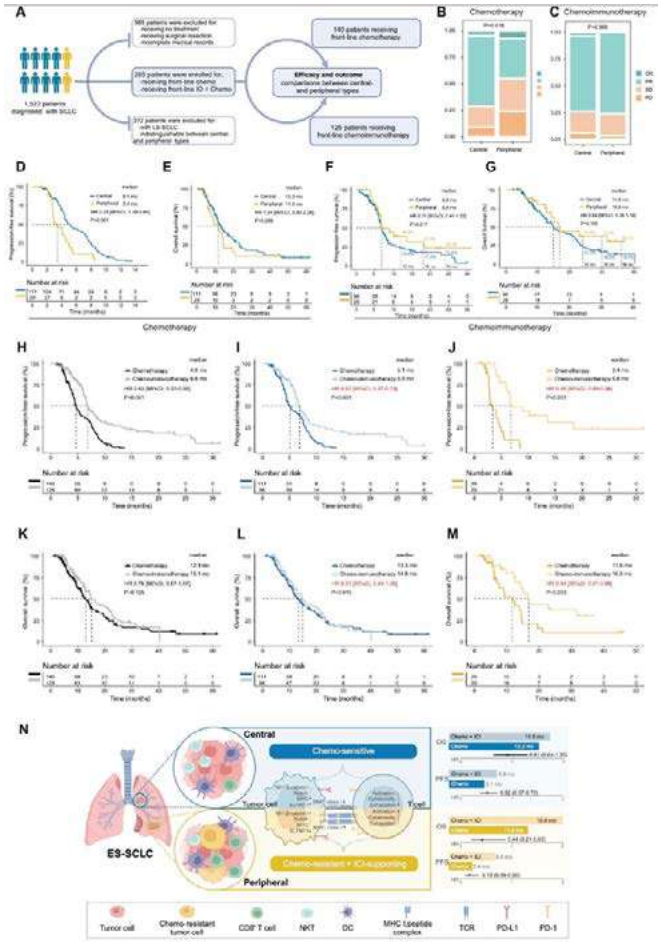
Methods: n this study, we performed scRNA-seq on 9 treatment-naïve samples to investigate the potential prediction for clinical outcomes of front-line therapy, and collected a cohort of 265 ES-SCLC patients for verification.

Results: The scRNA-seq included 12,897 cells. Prominent interindividual heterogeneity was observed in cell-type composition and small-cell lung cancer subtype-specific transcription factor expression, especially between patients with peripheral- and central-type ES-SCLC. The peripheral-type was associated with lower SLFN11 expression, higher MYC expression, activated NOTCH and WNT signaling, non-neuroendocrine components, fewer copy number alterations, higher MHC class I gene expression, and more CD8+ T cell presence. In patients receiving chemotherapy, peripheral-type had lower ORR (44.8% vs. 71.2%, P=0.008), shorter PFS (median 3.4 vs. 5.1 months, P=0.001) and OS (median 11.6 vs. 13.3 months, P=0.268) than central-type. Nevertheless, when comparing chemo-immunotherapy with chemotherapy, peripheral-type subgroup showed the potential to reduce progression (HR, 0.18 and 0.52 respectively) and death (HR, 0.44 and 0.91 respectively) risks than central-type.

Conclusions: The scRNA-seq of ES-SCLC demonstrated that primary location was associated with distinct tumoral and microenvironmental traits, which might associate with distinct responses to the front-line treatment.

Keywords: scRNA-seq, ES-SCLC, Chemo-immunotherapy





P3.13D.07 Longitudinal Tumor Microenvironment Analysis in Extensive Stage SCLC Patients Treated with Dual Checkpoint Inhibitor Blockade

A. Chiang[1], R. Matera[1], K. Ashley[2], B.K. Rajendran[2], K.A. Schalper[2], [1]Yale University School of Medicine, New Haven/CT/USA ,[2]Yale University, New Haven/CT/USA

Introduction: In patients with advanced small cell lung cancer (SCLC), the impact of immunotherapy on the tumor microenvironment and clinical implications of these alterations are very poorly understood with no clear predictive biomarkers to guide patient selection.

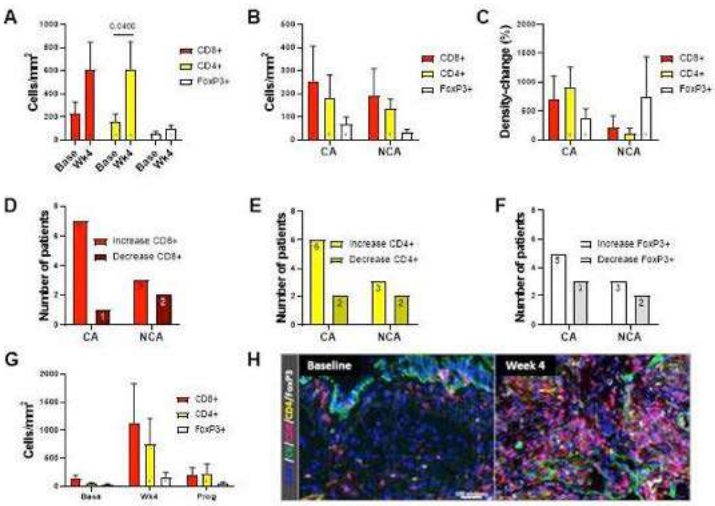
Methods: We collected paired baseline (pre-treatment), on-treatment (week 4), and progression biopsies from patients with relapsed extensive-stage SCLC treated with combination nivolumab (nivo) and ipilimumab (ipi) in a single-arm, phase 2 clinical trial (NCT03670056). Nivo 1 mg/kg and ipi 3 mg/kg were administered every 3 weeks for 4 cycles, followed by nivo maintenance until progressive disease (PD) by RECIST 1.1 or treatment-limiting toxicity. Paired pre/on-treatment samples were available from 13/22 patients, as well as 4 biopsies at progression. The tumor samples were studied using multiplexed quantitative immunofluorescence (mQIF) in addition to whole exome DNA sequencing (including germline DNA) and RNA-sequencing.

Results: 9/17 evaluable patients had PD; 8 patients showed clinical activity of treatment (2 with partial response). Among the 9 evaluable subjects that were previously treated with immunotherapy, there was 1 PR and 2 SD (DCR 33%). Median PFS was 1.7 months (95% CI: 1.1 - 5.8) and median OS of 7.3 months (95% CI: 4.9 - 10.1). mQIF analysis showed an increase in both CD8+ effector T cells and CD4+ helper T cells at week 4 compared to baseline samples without significant change in FoxP3+ regulatory T cells. CD4+ helper T cells exhibited the greatest expansion among patients with clinical activity, whereas FoxP3+ regulatory T cells were increased among those with no clinical activity. Tumors at progression showed a notable reduction of TILs, comparable to baseline levels. C to A mutation rate was significantly elevated in patients with clinical benefit. Week 4 tumors showed multiple novel DNA mutations and changes in transcriptional regulation.

Conclusions: Dual checkpoint blockade using ipilimumab and nivolumab has clinical activity in patients with relapsed SCLC, even those previously treated with immunotherapy. Immunotherapy induced changes in TIL number and composition are associated with clinical activity. We identified multiple novel genetic and transcriptional changes in week 4 and progression samples which may be implicated in immunotherapy resistance.

Keywords: SCLC, Tumor Microenvironment, immunotherapy

Figure 1. Longitudinal analysis of tumor microenvironment changes correlated with clinical activity of ipilimumab and nivolumab in extensive stage SCLC patients. A) T cell counts in baseline and on treatment week 4 biopsies and at progression (G). B) T cell counts in patients with clinical activity (CA) vs no clinical activity (NCA). C) Change in T cell density from pre-treatment to week 4 correlated with clinical activity. D-F) Patients with increase in T cells correlated with activity. H) Quantitative immunofluorescence of T cells shows overall increase in T cells at week 4.



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P3.13D.08 MYCNOS Epigenetically Regulated by Super-Enhancer is a Potential Predictor to NOTCH Inhibitor in Chemoresistance SCLC

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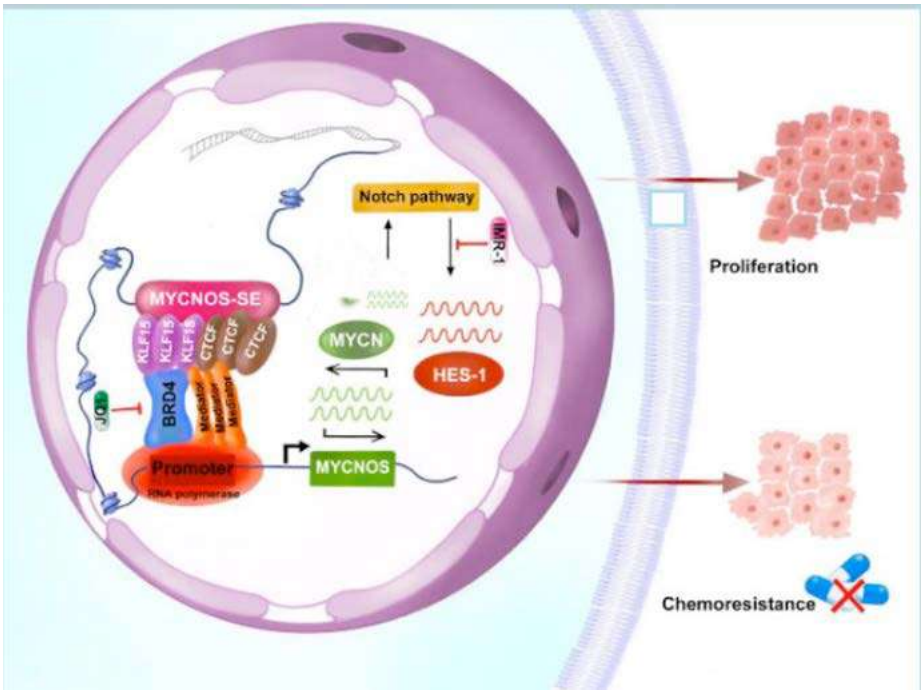
Introduction: SCLC is an aggressive form of lung cancer that frequently develops resistance to chemotherapy, leading to tumor recurrence and metastasis. A comprehensive understanding the molecular mechanisms of chemoresistance is crucial for identifying effective therapeutic targets. In this study, we aim to investigate the mechanisms underlying super-enhancer-mediated drug resistance for advancing clinical management in small cell lung cancer (SCLC).

Methods: In this study, we employed RNA-Seq to identify highly expressed molecules associated with chemoresistance. To further investigated the potential regulatory mechanism governing the expression of these molecules, we conducted H3K27Ac and ATAC-Seq binding analyses to identify super-enhancers involved and their corresponding transcription factors. Subsequent in vivo and in vitro experiments were performed to assess the impace of these molecules. Clinical samples were also collected to establish the prognostic value for patients. Additionally, we explored the efficacy of NOTCH pathway inhibitors in multiple PDX models and searched for molecular markers that could predict treatment response.

Results: Our findings revealed elevated expression of MYCNOS, demonstrating its chemoresistant properties in both in vitro and in vivo models of SCLC. Furthermore, we identified MYCNOS-SE can directly regulate MYCNOS expression through two key transcription factors, including CTCF and KLF15. Specifically, MYCNOS-SE-E5 was proven to be the most significant constituent of MYCNOS-SE in mediating chemoresistance. Additionally, we showed that MYCNOS binds to MYCN, enhancing its expression to influence chemotherapy sensitivity via the NOTCH pathway. Moreover, we demonstrated NOTCH inhibitors enhance chemotherapy sensitivity both in vitro and in vivo, while MYCNOS emerging as a protein-level predictor of the effectiveness of NOTCH inhibitors in SCLC.

Conclusions: This study highlights the significance of super-enhancer-regulated target genes as distinctive markers for chemoresistance in SCLC. Furthermore, it suggests that MYCNOS as a potential predictor to identify patients who may benefit from NOTCH inhibitors. These findings provide valuable insights for future studies developing therapeutic strategies targeting the identified pathways.

Keywords: Small cell lung cancer(SCLC), Super-enhancer, Chemoresistance



P3.13D.09 Prevalence and Prognostic Impact of SEZ6 Expression in a Real-World Cohort of Patients with Small-Cell Lung Cancer

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Introduction: ABBV-706, an antibody-drug conjugate (ADC) comprising an anti-seizure related 6 homolog (SEZ6) antibody conjugated to a topoisomerase 1 inhibitor payload, is being clinically evaluated in a phase 1 study (NCT05599984) of patients with advanced solid tumors, including small cell lung cancer (SCLC). While recent research has identified SEZ6 overexpression in SCLC and other tumor types with a high unmet need, additional characterization of the prevalence of SEZ6 expression in SCLC, its association with different molecular subtypes of SCLC, and its prognostic value is needed. Herein, we present data from a real-world cohort of patients from the City of Hope (COH) National Medical Center.

Methods: Tissue samples and clinical data pertaining to treatment and outcomes of patients with extensive-stage SCLC were obtained from COH. Tissue samples underwent immunohistochemistry (IHC) testing using an analytically validated clinical trial assay, as well as whole-transcriptome RNA sequencing and whole-exome DNA sequencing analysis. Molecular subtypes were determined on the basis of transcriptional profiles using a proprietary algorithm. Relative timing of tissue acquisition to the line of treatment (LOT) was determined to enable longitudinal biomarker expression analysis along different LOT. Standard-of-care (SOC) treatment consisted of first-line platinum-based chemotherapy with or without immune checkpoint inhibitors and second-line topotecan/irinotecan or lurbinectedin. The abundance of immune cell infiltrates was determined in each sample.

Results: Tissue samples and clinical data were available for 112 patients. The IHC prevalence of SEZ6 using a validated cutoff of ≥25% tumor cells with 1+ staining was 63%; with a cutoff of ≥50%, the prevalence rate was 44%. SEZ6 IHC score distributions of patients' biopsies collected prior to first LOT and in between first and second LOT were similar, indicating the front-line SOC treatment did not alter SEZ6 expression significantly. SEZ6 was enriched in SCLC-A (ASCL1) and SCLC-N (NEUROD1) subtypes; prevalence rates of SCLC-A and SCLC-N subtypes in this real-world cohort were 50% and 24%, respectively. Immune cells were significantly higher in the SCLC-I (inflamed) subtype. In patients with high versus low SEZ6 expression and clinical response status reported, best response rate to first line SOC treatment was 57% and 50%, and clinical benefit rate (CBR) was 100% and 85%, respectively. Hazard ratio for progression-free survival (PFS) was 0.9 (95% confidence interval, 0.44 - 2.00; P=0.872).

Conclusions: In this real-world cohort of patients with SCLC, SEZ6 was a prevalent biomarker, overexpressed in 44 - 63% of patients depending on the selected cutoff, and showed stability across LOT and enrichment in SCLC-A and -N molecular subtypes. Clinical outcomes, including PFS, response rate, and CBR were not significantly impacted by SEZ6 expression levels and thus, SEZ6 is not a prognostic biomarker. Although the sample size was small and the study was limited to a single site, these data support SEZ6 as a potential ADC-targetable biomarker in SCLC. This real-world SCLC cohort could also be used as a borrowed control for the phase 1 single-arm study being conducted in patients with SCLC treated with ABBV-706 to help identify novel predictive biomarkers and interpret the outcomes from the study.

Keywords: SCLC, SEZ6, antibody-drug conjugate

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P3.13D.10 Clinical Outcomes of Transformed Small-Cell Lung Cancer Versus Extensive Primary Small-Cell Lung Cancer

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Introduction: The treatments and clinical outcomes of transformed small-cell lung cancer (T-SCLC) were previously considered to be comparable to those of primary SCLC (P-SCLC). Yet, a comprehensive evaluation of prognosis correlating with treatments and biomarkers between the two cohorts remains lacking in the era of chemoimmunotherapy.

Methods: A total of 211 patients diagnosed with T-SCLC (n = 46) and extensive P-SCLC (n = 165) in our hospital from March-2018 to March-2023 were retrospectively enrolled. Patients with T-SCLC had received at least one line of standard treatment with EGFR-TKIs before pathological transformation. In the P-SCLC cohort, 105 were treated with immunotherapy (P-I/O subgroup), while the other 60 with chemotherapy (P-chemo subgroup). In the T-SCLC cohort, 23 with immunotherapy (T-I/O subgroup), and the remaining 23 with chemotherapy (T-chemo subgroup). Clinicopathological data, blood tumor markers and survival outcomes were collected and analyzed. The overall survival (OS) of T-SCLC was calculated since the start of first-line treatment after transformation.

Results: There was no significant difference in median OS (mOS) between the T-SCLC and P-SCLC cohorts (11.7m vs. 12.9m, P=0.0656). In the chemotherapy group, the mOS of T-chemo subgroup was significantly shorter than that of P-chemo subgroup (8.5m vs. 11.0m, P=0.0427). In the immunotherapy group, the mOS of T-I/O subgroup and P-I/O subgroup did not show significant difference (16.5m vs. 13.9m, P=0.6495). Additionally, in the T-SCLC cohort, the mOS of the T-I/O subgroup was significantly longer than that of T-chemo subgroup (16.5m vs. 8.5m, P<0.001). Similarly, in the real-world P-SCLC cohort, the mOS of the P-I/O subgroup was significantly longer than that of P-chemo subgroup (13.9m vs. 11.0m, P=0.0126). Moreover, the optimal cutoff value of baseline neuron-specific enolase (NSE) levels in predicting prognosis differed between T-SCLC (30.8 ng/ml) and P-SCLC (74.8 ng/ml). Higher baseline NSE levels correlated with poorer mOS in both T-SCLC (8.40 m vs. 15.90 m, P<0.0001) and P-SCLC (10.40 m vs. 16.30 m, P=0.0002).

Conclusions: Overall, the prognosis of T-SCLC and P-SCLC was similar. However, chemotherapy yielded significantly poor outcomes with T-SCLC compared to P-SCLC, indicating only chemotherapy could be inappropriate for T-SCLC. Further analysis demonstrated T-SCLC could benefit more from immunotherapy. The baseline NSE levels could be a biomarker in predicting prognosis in both P-SCLC and T-SCLC.

Keywords: Small-cell lung cancer, Immunotherapy, Outcomes

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P3.13D.11 SEZ6 Expression in Neuroendocrine Tumors

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Introduction: Novel treatment options for SCLC and extrapulmonary neuroendocrine (NE) cancers remain an unmet need. Seizure-related homolog 6 (SEZ6) is a cell surface protein with a likely neurosecretory role in SCLC. SEZ6 represents a target for novel SEZ6-targeting antibody-drug conjugates, but SEZ6 expression patterns in SCLC and extrapulmonary NE cancers are poorly understood.

Methods: RNA sequencing (whole transcriptome) was performed for 1312 SCLC and 2231 extrapulmonary NE cancer samples submitted to Caris Life Sciences. Within each of the cancer types, samples were stratified by SEZ6 RNA expression quartile (Q1: low, Q4: high). Samples were additionally classified as SCLC-A, SCLC-N, SCLC-P, SCLC-Y, TF-neg, or Mixed groups based on the expression of ASCL1, NEUROD1, POU2F3, and YAP1. Significance was tested using the Mann-Whitney U test. Real-world overall survival was obtained from insurance claims data and calculated from collection date to time of last contact; associated p-values were calculated using the log-rank test.

Results: SEZ6 expression in SCLC tumors was higher than extrapulmonary NE tumors (1.92-fold, $p < 0.0001$). Comparing primary tumor sites, median SEZ6 expression in SCLC, at 39.9 transcripts per million (TPM) was higher than NE tumors of the bladder (33.6 TPM, $p = 0.0236$), cervix (28.5 TPM, $p = 0.0004$), pancreas (22.6 TPM, $p < 0.0001$), ileum (20.0 TPM, $p < 0.0001$), colon (17.7 TPM, $p < 0.0001$), and adrenal gland (1.2 TPM, $p < 0.0001$) but lower than those of the prostate (52 TPM, $p = 0.0013$) and not significantly different to NE tumors of the rectum (33.6 TPM, $p = 0.465$). Within SCLC tumors, SEZ6 expression was correlated with the expression of ASCL1 (0.43, $p < 0.0001$), NEUROD1 (0.17, $p < 0.0001$), and YAP1 (0.16, $p < 0.0001$), but not POU2F3 (-0.04, $p = 0.1386$). Accordingly, comparing each subtype vs all others, median SEZ6 was greatest in the Mixed group (53.3 TPM, $p < 0.0001$), followed by SCLC-A (48.1 TPM, $p < 0.0001$), SCLC-N (33.5 TPM, $p = 0.4159$), SCLC-Y (32.0 TPM, $p = 0.0002$), TF-neg (25.1 TPM, $p < 0.0001$), and SCLC-P (4.8 TPM, $p < 0.0001$). Among patients with SCLC, median survival was longest for SEZ6-Q2 (13.1 mos.) followed by SEZ6-Q1 (11.0 mos.), SEZ6-Q3 (10.7 mos.) and SEZ6-Q4 (10.1 mos., $p = 0.0327$). Among patients with extrapulmonary NE cancers, median survival was also longest for SEZ6-Q2 (34.2 mos.), followed by SEZ6-Q3 (23.6 mos.), SEZ6-Q1 (21.8 mos.), and SEZ6-Q4 (18.4 mos., $p < 0.0001$).

Conclusions: SEZ6 expression is higher in SCLC than in extrapulmonary NE tumors but there is notable heterogeneity by transcriptional subtype, with the highest expression in the SCLC-A and Mixed groups and lowest expression in SCLC-P. Among extrapulmonary NE tumors, SEZ6 expression varies by site of origin and is highest in prostate neuroendocrine tumors. These data support further exploration of SEZ6- directed therapy in other neuroendocrine tumors.

Keywords: Small Cell Lung Cancer, SEZ6, Neuroendocrine

P3.13E SMALL CELL LUNG CANCER AND NEUROENDOCRINE TUMOURS - NEUROENDOCRINE TUMOURS: LCNEC, CARCINOID, TRANSFORMED SCLC
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P3.13E.01 Is Systematic Lymphadenectomy Pivotal for Bronchial Carcinoid Surgical Treatment? A TNM 9th Classification Validation Pilot Study

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Introduction: This study aims to compare systematic nodal dissection, with or without bench dissection of the lymph nodes present along the segmental bronchial branches of the surgical specimen, with nodal sampling according the 9th pTNM lung cancer staging proposal.

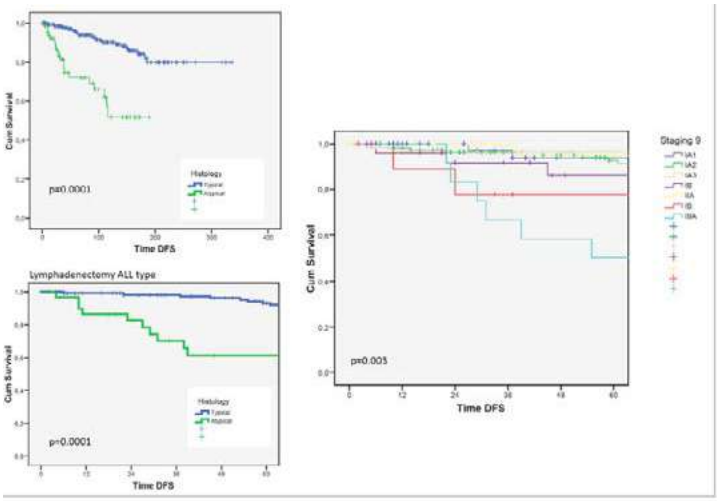
Methods: A retrospective study prospectively collected data from two institutional databases were considered. The χ2 test or Fisher's test and the Mann-Whitney test were used to analyze categorical and continuous variables, respectively. Survival analysis was performed using the Kaplan-Meier (KM) method and the Log-rank test. Cancer-specific and disease-free survival analyses were carried out. P-value <0.05 was considered statistically significant.

Results: Between 14/2/1983 and 17/11/2023, 367 patients(297TC and 70AC) were included in the study. FIGURE 1 describes the demographic and results. Sixteen patients(5.38%) with TC and 11 patients(15.71%) with AC had metastatic nodal disease on the pathology report. Overall, KM progression-free survival was achieved at five years with adequate survival in TC compared to AC(p =0.0001) [FIGURE 2].

Conclusions: Performing a systematic lymphadenectomy during surgery for a NET lung tumor is crucial, even if the TC or AC histotype has not been identified before. This helps prevent the risk of recurrence and avoids understaging the disease, which could otherwise delay adjuvant therapy if necessary.

Keywords: carcinoid, lymph node, 9th TNM Classification

		297 Typical Lung Carcinoids	70 Atypical Lung Carcinoids	p-value
Male / Female		107 / 90	30 / 40	
Age (years)		59 (15-81)	60 (17-82)	
Smoking history		131	35	
Charlson Comorbidity Index		1.99 (0-10)	2.17 (0-6)	
SURGERY				
Bronchoplasty		16	2	
wedge		35	4	
Segmentectomy		8	2	
Lobectomy		205	47	
Sleeve Lobectomy		25	11	
Pneumonectomy		8	4	
Lymphnodal dissection and multifocal pulmonary neuroendocrine proliferation (MNEP)				
# No Lymphadenectomy		28	12	
# Sampling		133	27	
# Systematic Lymphadenectomy		85	22	
# Systematic Lymphadenectomy + Benchmark lymphnodal lung dissection		51	9	
Multifocal pulmonary neuroendocrine proliferation (MNEP)		49 (16.4%)	10 (14.28%)	
PATHOLOGY				
pT mean (mm) mean / range		20.25 (3-70)	25.44 (7-80)	0.003
pNx		28	12	
pN0		238	46	
pNpositive		19	12	
	pN1	13	6	
	pN2a	1	2	
	pN2b	5	4	
Correlation of type of lymphnodal dissection and pathology report				
% N+ with Sampling		3.75% (5/133)	14.8% (4/27)	
% N+ with Systematic Lymphadenectomy		9.4% (8/85)	27.2% (6/22)	
% N+ with Systematic Lymphadenectomy + Benchmark lymph nodal dissection on surgical specimens		7% (4/51)	11% (1/9)	



P3.13E SMALL CELL LUNG CANCER AND NEUROENDOCRINE TUMOURS - NEUROENDOCRINE TUMOURS: LCNEC, CARCINOID, TRANSFORMED SCLC
MONDAY, SEPTEMBER 9, 2024 - 12:00 - 14:00

P3.13E.02 Adjuvant Chemotherapy in cT1N0M0 Large-Cell Neuroendocrine Cancer with or without Pathological Upstaging

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Introduction: Large-cell neuroendocrine cancer (LCNEC) is a rare histology associated with poor prognosis. The effectiveness of adjuvant chemotherapy in early-stage LCNEC has been debated but has yet to be concluded. This study aims to analyze the outcomes of clinical T1N0M0 LCNEC (≤ 3 cm) with a focus on their upstaging and adjuvant chemotherapy.

Methods: We performed a single-institution, retrospective study on patients who underwent lobectomy or therapeutic sublobar resection for clinical T1N0M0 LCNEC and its mixed pathology, from January 1, 2002, to December 31, 2022. The patients with pathological upstaging were classified into T-upstage and N-upstage groups. The prognostic value of adjuvant chemotherapy was analyzed for each group.

Results: During the study period, 62 lobectomies and 34 sublobar resections (20 segmentectomies and 14 wedge resections) were performed for clinical T1N0M0 LCNEC. Occult lymph node metastasis was detected in 11 patients (11.5%; N-upstage), and another 24 patients experienced upstage due to T factor (25.0%; T-upstage), leaving 61 patients as pathological Stage IA without upstage (63.5%; No-upstage). The N-upstage group had significantly shorter recurrence-free survival (RFS) compared with the T-upstage and No-upstage groups (RFS; median: 11.4 vs 50.9 vs 40.3 months; p=0.004; Figure 1). Adjuvant chemotherapy was delivered to 35 patients (36.5%) and was associated with significantly better RFS (median: 64.1 vs 19.4 months; p=0.020; Figure 2A). This tendency was seen across the groups (Figure 2B-D) while statistically not significant in the T-upstage group. Of note, even in the No-upstage group (pathological T1N0M0), 11 patients (18%) with adjuvant chemotherapy had significantly longer RFS than those without adjuvant chemotherapy (median: 107.2 vs 18.5 months; p=0.015; Figure 2B).

Conclusions: Upstaging was relatively common in clinical T1N0M0 LCNEC, and a poor prognostic effect of occult node metastasis was noted. Adjuvant chemotherapy was associated with better survival and may be considered even in pathological T1N0M0.

Keywords: Large-cell endocrine cancer, Adjuvant chemotherapy, Occult node disease

Figure 1. Recurrence-free Survival by Upstage Group

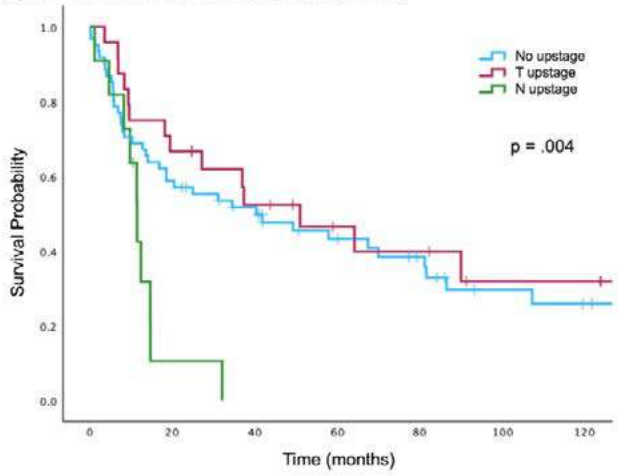
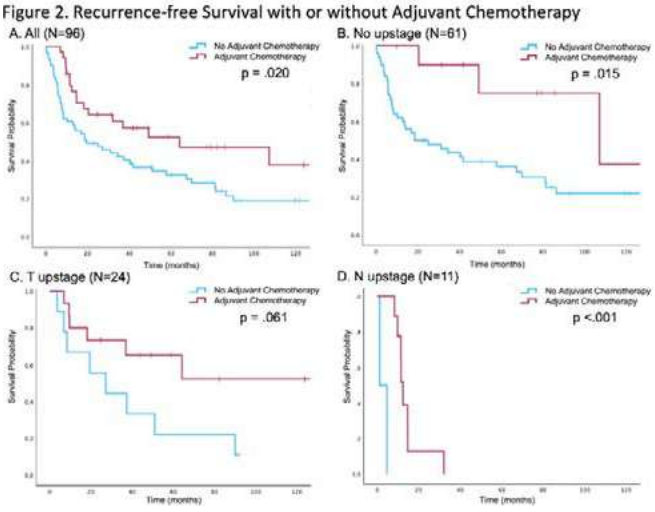


Figure 2. Recurrence-free Survival with or without Adjuvant Chemotherapy



P4.04C SCREENING AND EARLY DETECTION - INNOVATIVE SCREENING TECHNOLOGY
MONDAY, SEPTEMBER 9, 2024 - 18:30 - 20:00

P4.04C.01 Incidental Pulmonary Nodule Management Using Computer Assisted Detection and Patient Tracking: PINPOINT Project, Pilot Data

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Introduction: Early detection of lung cancer has a pivotal role in improving lung cancer survival. Incidental pulmonary nodule (IPN) detection can identify patients with early-stage lung cancer, potentially leading to a stage shift in lung cancer diagnosis. Implementing Computer Assisted Detection (CAD) in routine clinical practice has the potential to increase IPN detection rate. Adequate management following detection is equally important and could be achieved through implementation of a virtual nodule clinic (VNC) that allows monitoring of referrals and follow-up. It has been shown that implementation of a VNC can substantially reduce loss-to-follow-up of actionable IPN. In PINPOINT, CAD combined with a VNC is implemented in European medical centers to evaluate its clinical value. This pilot study is performed to assess the impact of the program on clinical workflow.

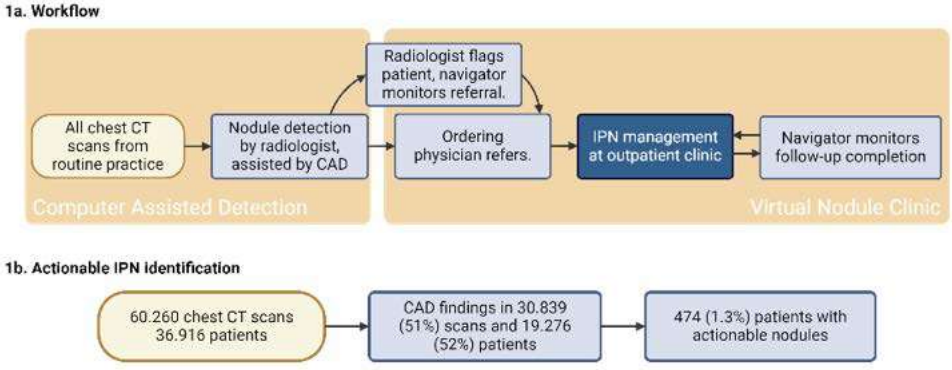
Methods: CAD software was implemented in 4 medical centers. All consecutive chest CT scans from routine practice were analyzed by CAD-software. No patients were excluded. Radiologists flagged patients with IPN requiring follow-up as "actionable" in the local VNC. (Figure 1a) In each center, a navigator was appointed to supervise referral and management of actionable patients through the VNC. Nodule management was in accordance with the British Thoracic Society (BTS) Guidelines. The impact of the program on clinical workflow was evaluated by collecting aggregated data from the VNC including IPN incidence, referral trends and initial management. In one center, we additionally assessed flagging accuracy and the number of interventions by the navigator.

Results: From July 2022 until January 2024, a total of 60.260 chest CT scans from 36.916 patients were analyzed. The CAD-software detected nodules in 30.839 (51%) scans and in 19.276 (52%) patients. 474 (1.3%) patients had nodules flagged as actionable by radiologists and are being monitored in the VNC.(Figure 1b) Thus far, 4 (0.6%) patients with actionable nodules were diagnosed with clinical stage IA lung cancer. In the center where this data was collected, intervention by the navigator was required for the referral of 5 out of 64 (7.8%) patients with actionable nodules.

Conclusions: IPN detection and adequate management can be optimized by CAD and a VNC in routine clinical practice. Further evaluation of early-stage lung cancer detection and cost-effectiveness of the program are subject of current research.

Keywords: Early detection of lung cancer, Computer Assisted Detection, Incidental Pulmonary Nodules

Figure 1: IPN detection and management through CAD and a VNC, workflow and first results.



Abbreviations: CAD = Computer Assisted Detection; IPN = Incidental Pulmonary Nodule; VNC = Virtual Nodule Clinic

P4.04C SCREENING AND EARLY DETECTION - INNOVATIVE SCREENING TECHNOLOGY
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P4.04C.02 Discrimination of Lung Cancer and Benign Lung Diseases Using BALF Exosomal DNA Methylation Profile

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Introduction: The early detection of lung cancer utilizing low-dose computed tomography (LDCT) screening holds promise for enhancing treatment outcomes. However, while LDCT effectively identifies lung nodules, its capacity to differentiate malignant potential often leads to unnecessary invasive interventions for benign lesions. This study endeavors to address this diagnostic challenge by leveraging epigenetic insights from DNA methylation patterns in bronchoalveolar lavage fluid (BALF) samples obtained from individuals suspected of having lung malignancies.

Methods: In this retrospective marker screening study, DNAs isolated from 138 exosome isolates purified from clinical BALF specimens of patients suspected of lung cancer via LDCT underwent real-time PCR assays targeting differential methylation regions (DMRs) on approximately 80 tumor suppressor genes linked to early lung cancer development. Seven DMRs exhibiting the highest discrimination rate, with an area under the curve (AUC) of ≥ 0.79 between lung cancer and benign conditions, were selected and a lung cancer prediction model was constructed utilizing logistic regression. The validity of the model was independently verified using 100 BALF exosome DNA collected from 65 patients with lung cancer and 35 patients with benign diseases.

Results: In the screening phase, the combination of the seven epigenetic biomarkers which were identified to be specifically methylated in lung cancer BALF samples demonstrated an AUC of 0.97, with 88.24% sensitivity and 97.14% specificity for discriminating lung cancer and benign conditions . Each individual biomarker exhibited statistically significant and higher Mean Methylation Levels (MML) in both non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) specimens compared to non-cancer groups, with fold-changes ranging from 1.7 to 13.36. MMLs of these biomarkers were found to be moderately elevated with increasing patient age and smoking history, irrespective of patient sex. Additionally, a higher correlation was observed between MML and NSCLC stage progression, with detection sensitivities of 79% for early-stage (stage I, II) NSCLC and 92% for advanced-stage (stage III, IV) NSCLC. In the validation cohort, testing an additional 100 BALF exosome DNA samples using seven-methylation biomarker model yielded an AUC of 0.95, with clinical sensitivity and specificity rates at 94% each. Furthermore, the sensitivity to discriminate NSCLC early stage (I) patients was increased from 88.00% to 92.00% when evaluating the smoking history as an additional risk factor with the combination of the seven epigenetic biomarkers.

Conclusions: This study highlights the potential of BALF exosomal DNA methylation biomarkers to address the limitations of LDCT screening, facilitating the differentiation between lung nodules and cancer. By exploiting the epigenetic landscape, this innovative approach offers a promising avenue for refining diagnostic precision and advancing personalized treatment strategies. Our findings suggest that BALF exosomes harbor cancer-specific biomolecules and may serve as a potent biomaterial for cancer detection, particularly at early stages. Comprehensive validation and further clinical investigations are imperative to fully establish the clinical utility of this pioneering methodology in managing lung nodules.

Keywords: LDCT screening, DNA methylation, BALF

P4.04C SCREENING AND EARLY DETECTION - INNOVATIVE SCREENING TECHNOLOGY
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P4.04C.03 Nodule Type Classification for Lung Cancer Screening with CT

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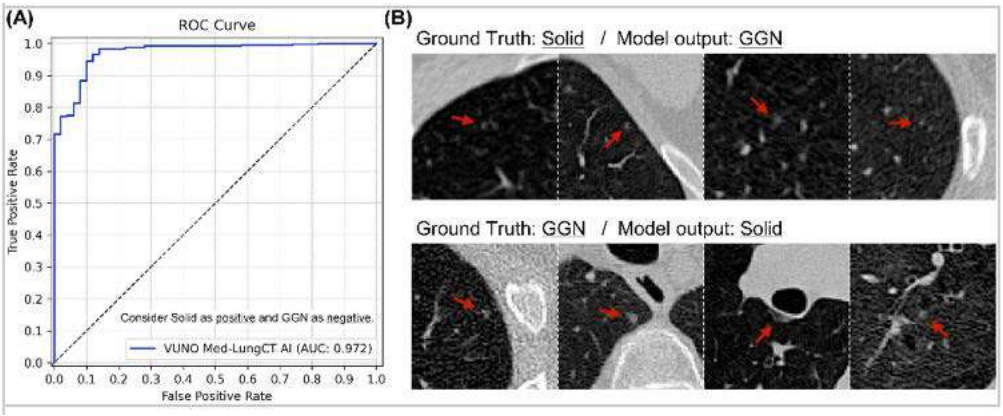
Introduction: The American College of Radiology has periodically updated its lung cancer screening guidelines, known as the Lung Imaging Reporting and Data System (Lung-RADS). Despite these updates, distinguishing nodule types—solid, part-solid, and ground-glass nodules (GGN)—remains clinically important. For instance, patient management guideline varies depending on nodule type, even when nodules have the same size. Therefore, precise classification of lung nodule types lays the groundwork for nodule management. Typically, radiologists assess by comparing adjacent pulmonary vessels, because ground-glass opacity refers to an area of increased attenuation that does not completely obscure the underlying bronchial and vascular structures. However, this method is not objective and can lead to observer variability. This variability emphasizes the need for accurate and automated methods to classify nodule types. In response, this study employs commercial software (VUNO Med-LungCT AI) to evaluate its capability in classifying lung nodule types.

Methods: We collected data on 238 patients with nodules from a referral hospital in the United States. Two radiologists reviewed the images and identified 1,896 nodules by consensus. From these, 11 part-solid nodules were excluded. Out of the remaining 1,885 nodules, 1,413 (75%) were used to update the model, and 472 (25%) were used for testing. The test set included 422 (89%) solid nodules and 50 (11%) GGNs. This study used VUNO Med-LungCT AI for nodule type classification.

Results: The classification of 472 nodules yielded an area under the receiver operating characteristic (ROC) curve (AUC) of 0.972 (95% confidence interval [CI], 0.953-0.991). The accuracy was 98.3% for solid nodules (415 out of 422) and 86.0% for GGNs (43 out of 50). Figure 1.A shows the ROC curve, and Figure 1.B displays axial slice CT images from eight cases, incorrectly classified as the opposite type. The qualitative analysis indicates that most of the incorrectly classified nodules were difficult to categorize definitively even by clinicians, because they are small or have ambiguous HU values. This ambiguity means that while some clinicians might classify such nodules as solid, others could identify them as GGN. The classification of these 472 nodules was completed in under one second, demonstrating the software's efficiency in rapid processing.

Conclusions: VUNO Med-LungCT AI demonstrated impressive performance in nodule type classification. Future studies will expand the part-solid and cystic nodules according to the Lung-RADS 2022. With these enhancements, the VUNO Med-LungCT AI is expected to achieve superior performance in Lung-RADS categorization.



P4.04C SCREENING AND EARLY DETECTION - INNOVATIVE SCREENING TECHNOLOGY
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P4.04C.04 Epidemiological Characteristics of Incidental Pulmonary Nodules and in China: A Prospective Multicenter Trial of 10,560 Cases

W. Liang[1], D. Liu[2], C. Hu[3], W. Xiao[4], J. Zhang[5], M. Peng[6], S. Wu[6], B. Wang[6], J. He[1], J-B. Fan[7], N. Zhong[8], O. n Behalf of the NCT[03651986] Trial Investigators[9], [1]The First Affiliated Hospital of Guangzhou Medical University, Guangzhou/CN, [2]Department of Respiratory Medicine, West China Hospital of Sichuan University, Chengdu/CN, [3]Department of Respiratory Medicine, Xiangya Cancer Center, Xiangya Hospital, Central South University, Changsha/CN, [4]Department of Respiratory Medicine, QILU Hospital, Shandong University, Jinan/CN, [5]Department of Pulmonary Medicine, Xijing Hospital, Air Force Medical University of PLA, Xi'an/CN, [6]AnchorDx Medical Co., Ltd., Guangzhou/CN, [7]Department of Pathology, School of Basic Medical Science, Southern Medical University, Guangzhou/CN, [8]National Clinical Research Center for Respiratory Disease, State Key Laboratory of Respiratory Diseases, The First Affiliated Hospital of Guangzhou Medical University, Guangzhou/CN, [9]The First Affiliated Hospital of Guangzhou Medical University, Guangzhou Institute of Respiratory Disease & Health, China State Key Laboratory and National Clinical Research Center for Respiratory Disease, Guangzhou/CN

Introduction: We are conducting a large-scale prospective clinical trial study (NCT03651986) for assessment of the performance of ctDNA methylation markers for accurate diagnosis and surveillance of incidental pulmonary nodules screened by low dose computed tomography (LDCT) in China. Here we report the epidemiological characteristics of 10,560 pulmonary-nodule participants enrolled at baseline, and clarify the epidemiological and clinical risk factors associated with malignant features.

Methods: A prospective cohort of 10,560 participants with non-calcified pulmonary nodule sized in 5-30 mm indicated by LDCT or CT at 23 clinical centers in China were enrolled between October 2018 and May 2021. The demographic, clinical, CT imaging features and clinical diagnosis at baseline of all participants were collected. Prevalence and epidemiological characteristics were computed and the potential risk factors associated with lung cancer were evaluated by single and multiple factor binary logistic regression

Results: Females (56.6%) made up the majority of the pulmonary nodule patients and they were also younger (53 [45-62]) than the male patients (55 [46-63]) ($p<0.001$). Although 97.1% females and 37.8% males were non-smokers, up to 70% of them had ever been exposed to second-hand smoking. Increasing smoking and occupational exposing rates were observed in females under 30 years old. Benefited from high sensitivity of LDCT/CT, quite amount of small pulmonary nodules (78.2% at 5-10 mm and 17.8% at 10-20 mm) were detected, including 38.5% pure ground-glass nodules (pGGNs), 24.0% mixed ground-glass nodules (mGGNs) and 37.5% solid nodules (SNs), and most of them were solitary (81.24%). pGGNs and mGGNs dominated in females and non-smokers, whereas SNs dominantly in males and smokers. Both female patients and pGGNs had significantly higher rates of family history of cancers ($p\leq0.003$), indicating their unique genetic associations. Approximately 16.0% high-risk patients (median age 55 ([20-82]) were pathologically diagnosed, with 97.32% as lung adenocarcinoma and 90.35% at very early stages (AJCC stage 0-I). Age, female, education level (college or above), multiple target nodules, nodule size, nodule location (upper lobe), nodule type (mGGN and pGGN) and some CT imaging features were the independent risk factors associated with lung cancers. Notably, according to current NCCN guidelines and Chinese Expert Consensus, 13%-14% lung cancer patients were missed from screening and about 20% misdiagnosis rate was observed in SNs and small nodules.

Conclusions: We describe a representative profile of epidemiological characteristics of pulmonary nodules in a largest cohort from China till now. We identified the features related to different nodule types, and risk factors and trends of lung cancer incidence compared to previous studies, which providing a latest fundamental data for future precise clinical management of pulmonary nodules.

Keywords: Incidental Pulmonary Nodules, Epidemiological Characteristics, Prospective Multicenter Trial

P4.04C SCREENING AND EARLY DETECTION - INNOVATIVE SCREENING TECHNOLOGY
MONDAY, SEPTEMBER 9, 2024 - 18:30 - 20:00

P4.04C.05 AI-Assisted CXR Analysis in the Detection of Lung Nodules and Incidental Lung Cancers

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Introduction: The use of artificial intelligence (AI) in chest X-ray (CXR) analysis is growing in recent medical environments, and interest in its application is increasing. This study aimed to investigate whether utilizing AI for CXR analysis could lead to the unexpected detection of lung nodules, and to determine the impact of such detections on actual patient diagnosis and management.

Methods: Patients (> 18 years old) who underwent CXR at Yongin Severance hospital and between March 2021 and January 2023, and were identified to have lung nodules through AI software, were retrospectively included in this study. Commercially available AI-based lesion detection software (Lunit INSIGHT CXR, version 3, Lunit Inc., Korea) was used for lung nodule detection.

Results: During this period, 74,385 X-ray procedures were carried out in outpatient clinics excluding hospitalized patients. Out of 40,191 X-rays performed in other clinical departments, excluding respiratory medicine, thoracic surgery, oncology, health screening centers, and emergency rooms, 1,754 cases (4.4%) had lung nodules detected through AI. In the follow-up on this group, about one-third of these patients underwent a CT scan, while two-thirds did not, despite AI-identified abnormalities. Interestingly, the lung nodule abnormality scores, indicating the likelihood of actual nodules, showed no significant difference between the groups that did and did not undergo CT scans. Of the patients conducted CT scan, 71.5% had true nodules, and among these, lung cancer was incidentally discovered in 36 cases (7% of the CT group). These cancer patients, predominantly male with an average age of 74, mainly had adenocarcinoma (55.5%), with 33.3% at stage I and 44.4% at stage IV. The mean AI score for lung cancer was significantly higher (56.7) compared to the general nodule detection score (around 35), highlighting AI's potential in prioritizing high-risk patients.

Conclusions: This study highlights the potential role of AI CXR in lung nodule finding and incidentally detecting lung cancer. Furthermore, the findings emphasize the need for an improved medical information system to connect AI-detected abnormalities with patient examinations and management strategies.

Keywords: Lung cancer, CXR, AI

P4.04C SCREENING AND EARLY DETECTION - INNOVATIVE SCREENING TECHNOLOGY
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P4.04C.06 DNA Methylation Analysis in Plasma for Early Diagnosis Inlung Adenocarcinoma

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Introduction: Lung adenocarcinoma (LUAD) is the most common type of lung cancer. SHOX2 and RASSF1A methylation are confirmed to be crucial biomarkers for diagnosis and prognosis of lung cancer. Bronchoalveolar lavage fluid (BALF) has high specificity and sensitivity for the diagnosis of lung diseases, while difficulty obtaining and making patients uncomfortable. Clinically, plasma samples are easier than BALF in collection, but there is little research on the combined detection of SHOX2 and RASSF1A methylation in plasma. The aim of this study is to investigate the diagnosis value of combined promoter methylation assay for SHOX2 and RASSF1A in plasma of early LUAD.

Methods: BALF and blood samples were collected from 36 patients with early LUAD. Ten non-tumor patients served as the control group. The promoter methylation levels of SHOX2 and RASSF1A of all subjects were detected by human SHOX2 and RASSF1A gene methylation kit.

Results: The methylation detection rate of SHOX2 and RASSF1A in plasma was 61.11%, which was slightly lower than that in BALF (66.7%). The Chi-square test showed that there was no significant difference in the methylation rate between BALF and plasma ($p > 0.05$). The AUC of receiver operating characteristic (ROC) curve analysis of blood was 0.806 (95% CI, 0.677 to 0.900), while the AUC analysis of BALF was 0.781 (95% CI, 0.649 to 0.881). We also analyzed the correlation of SHOX2 and RASSF1A methylation level in plasma with gender, age, tumor differentiation, pathologic classification and other clinicopathological variables, which were found no significant correlation between them.

Conclusions: Measurement of SHOX2 and RASSF1A methylation level in plasma can be used as a promising noninvasive biomarker for auxiliary diagnosis of early LUAD, with good sensitivity and specificity.

Keywords: Lung adenocarcinoma, DNA methylation, SHOX2; RASSF1A

P4.04C SCREENING AND EARLY DETECTION - INNOVATIVE SCREENING TECHNOLOGY
MONDAY, SEPTEMBER 9, 2024 - 18:30 - 20:00

P4.04C.07 Improving the Efficiency of Lung Cancer Screening Through a Blood-based Lung Cancer Screening Test Prior to Low-Dose CT

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Introduction: Wide scale lung cancer screening (LCS) to detect early lung cancer (LC) with low dose computed tomography (LDCT) can strain already taxed health-systems, including the systems' radiology infrastructure, and the professionals and services involved in follow-up and evaluation of LDCT findings, including follow-up of incidental non-malignant actionable findings (NAFs). NAF's are common, occurring in 15-25% of scans, and can lead to specialist consultations, invasive work-up, repeated follow-up, and consume patient's time. It is possible that these burdens dampen the enthusiasm of health systems to ramp up LCS rates, which nationally remain below 20%. We evaluated whether initially evaluating screen-eligible individuals with an accessible blood-based screening test (BBT) could reduce the burden of LCS without reducing cancer detection.

Methods: We adapted the LungPLAN model developed by the American Cancer Society, National Lung Cancer Roundtable and The FiscalHealth Group, to a 2021 USPSTF LCS-eligible population with a 0.7% LC prevalence. We compared an LDCT-only screening strategy (A) to a blood-based test (BBT) first screening strategy (B). The LDCT-only strategy was modeled with 1,000 eligibles screened. We then determined how many individuals needed to be screened with a BBT-first strategy to either: (B1) identify the same number of LDCT screen-detected LCs or (B2) result in the same total number of screening LDCTs. In each, we evaluated the number needed to screen (NNS) to detect a LC, and the associated frequency of NAF detection. LDCT was modeled at 93% sensitivity, 76% specificity (99.9% NPV, 2.2% PPV), with 15% of scans identifying NAFs that required workup. We assumed the BBT had an 80% sensitivity, 58% specificity (99.8% NPV, 1.3% PPV) and that 100% and 0% of BBT positive and negative results followed on to LDCT, respectively.

Results: In strategy A, 1,000 LDCTs identified 7 LCs and 153 NAFs, (NNS=143, NAF:LC=22). In strategy B1, 1,250 BBTs resulted in 525 LDCTs identifying 7 LCs and 77 NAFs (NNS=76, NAF:LC=11). In strategy B2, 2,381 individuals received the BBT, followed by 1,000 LDCTs identifying 13 lung cancers and 147 NAFs (NNS=76, NAF:LC=11).

Conclusions: A BBT-first strategy can screen 2.4x more individuals, drive the same number of LDCTs as an LDCT-only strategy, find 1.9x more cancers and reduce the frequency of NAF detection per LC detected. An initial point of care BBT for LCS has the potential to improve the efficiency of screening and reduce the strain on health-systems.

Keywords: blood-based test, lung cancer screening, low-dose computed tomography (LDCT)

Screening Strategy	# of BBTs	# of LDCTs	# of Screen-detected Lung Cancers	Number needed to screen (NNS)	# Non-malignant actionable findings (NAF:LC)
(A) LDCT-alone	n/a	1,000	7	143	153 (21)
(B1) BBT-first: matched for LC detection	1,250	525	7	76	77 (11)
(B2) BBT-first: matched for LDCTs	2,381	1,000	13	76	147 (11)

P4.04C SCREENING AND EARLY DETECTION - INNOVATIVE SCREENING TECHNOLOGY
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P4.04C.08 Sensitivity of Artificial Intelligence in Low-dose Computed Tomography Screening for Lung Cancer

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Introduction: Artificial intelligence (AI)-based techniques have emerged as potential aids in the clinical workflow to reduce the burden on radiological specialist resources. The success of a lung cancer screening program is dependent on correct and timely reporting of CT findings, which places a demand on radiologist resources. Therefore, it is important to investigate the feasibility of using AI to optimize the radiological screening workflow as a primary CT reader or potentially as part of fully autonomous reading. In this manner, we have compared the sensitivity of two commercially available AI systems to an experienced radiologist reader in detecting lung cancer in the Norwegian lung cancer screening trial.

Methods: We included patients in whom lung cancer was detected by one thoracic radiologist reader with 10 years of experience in the first round of the Norwegian lung cancer screening pilot study using low-dose computed tomography (LDCT) reconstructed with a lung algorithm. These cases were blindly reviewed in terms of locating lung nodules retrospectively using two commercially available AI software packages designed to detect lung nodules. All nodules identified by the radiologist or clinically within 12 months with histologically confirmed malignancy were considered the gold standard.

Results: The first round of the Norwegian lung cancer screening pilot included 1000 patients, and 23 lung cancers were identified by the thoracic radiologist and clinically within 12 months of follow-up. The radiologist reader, AI software #1, and AI software #2 failed to detect one, four, and two cases, respectively, yielding sensitivity values of 95.7% (95% CI: 87.7-98.6%), 82.6% (95% CI: 71.7-89.9%), and 91.3% (95% CI: 82.0-96.0%), respectively. AI software #2 successfully detected the cancer missed by the radiologist, whereas AI software #1 did not. Only one cancer was missed by both AI software systems: a solid nodule located between emphysematous bullae. Three lesions overlooked by AI software #1 were larger than 3 cm, corresponding to masses. One lesion overlooked by AI software #2 was a ground-glass lesion.

Conclusions: This study indicates that the evaluated AI systems can fairly reliably assist radiologists in low-dose CT-based lung cancer detection in a screening program. However, they lack the sensitivity for autonomous CT readings to completely replace radiologist assessment.

Keywords: Artificial Intelligence, Low-Dose CT Screening, Lung Cancer

P4.04C SCREENING AND EARLY DETECTION - INNOVATIVE SCREENING TECHNOLOGY
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P4.04C.09 Exhaled VOC Detection in Lung Cancer Screening: A Comprehensive Meta-Analysis

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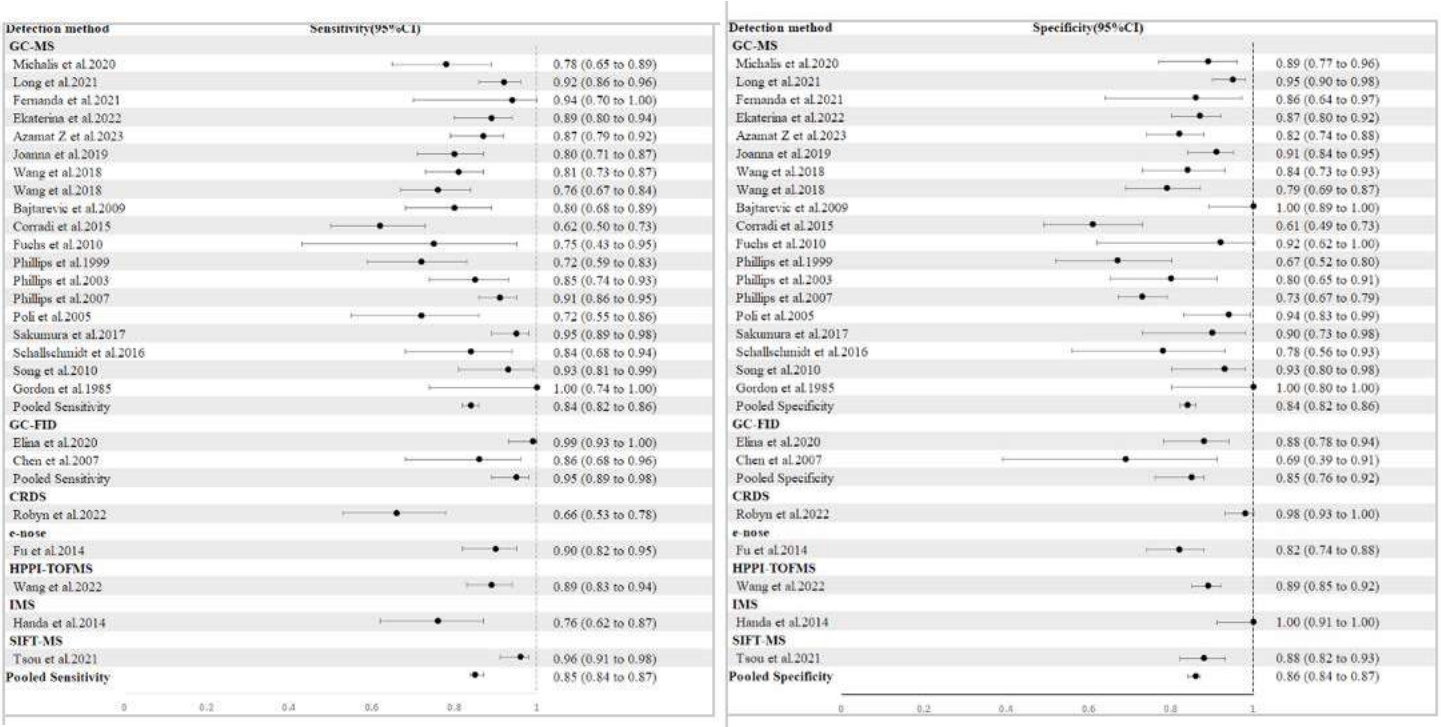
Introduction: Lung cancer (LC), characterized by high incidence and mortality rates, presents a significant challenge in oncology. Despite advancements in treatments, early detection remains crucial for improving patient outcomes. The accuracy of screening for LC by detecting volatile organic compounds (VOCs) in exhaled breath remains to be determined.

Methods: Our systematic review, following PRISMA guidelines and analyzing data from 25 studies up to October 1, 2023, evaluates the effectiveness of different techniques in detecting VOCs. We registered the review protocol with PROSPERO and performed a systematic search in PubMed, EMBASE and Web of Science. Reviewers screened the studies' titles/abstracts and full texts, and used QUADAS-2 tool for quality assessment. Then performed meta-analysis by adopting a bivariate model for sensitivity and specificity.

Results: This study explores the potential of VOCs in exhaled breath as biomarkers for LC screening, offering a non-invasive alternative to traditional methods. In all studies, exhaled VOCs discriminated LC from controls. The meta-analysis indicates an integrated sensitivity and specificity of 85% and 86%, respectively, with an AUC of 0.93 for VOC detection. We also conducted a systematic analysis of the source of the substance with the highest frequency of occurrence in the tested compounds. Despite the promising results, variability in study quality and methodological challenges highlight the need for further research.

Conclusions: This review emphasizes the potential of VOC analysis as a cost-effective, non-invasive screening tool for early LC detection, which could significantly improve patient management and survival rates.

Keywords: Volatile Organic Compounds, Lung cancer, Detection



P4.04C SCREENING AND EARLY DETECTION - INNOVATIVE SCREENING TECHNOLOGY
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P4.04C.10 Validation of LungFlag™ Prediction Model Using Electronic Medical Records (EMR) On Taiwan Data

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Introduction: Lung cancer (LC) is the leading cause of cancer death according to the WHO. In Taiwan, LC accounted for 9,629 deaths in 2020 and contributed one-fifth of total cancer deaths. More than 50% of those are among non-smokers. To reduce mortality rate, starting 2022, the Ministry of Health and Welfare launched the LC Early Detection Program to provide biennial low-dose computed tomography (LDCT) screening for high-risk groups. Multiple risk-scores were developed to identify high-risk populations, among those are dedicated questionnaire based PLCOm2012 and machine learning (ML) structured EMR based LungFlag™. The model was developed using data from Kaiser Permanente Southern California, USA.

Methods: From the National Taiwan University Hospital (NTUH) a dataset composed of individuals with diagnosed LC (cases) and randomly selected individuals without records of LC (controls) was extracted. To determine if EMR data in Taiwan could be used to identify individuals at higher risk of LC, we tested and compared the LungFlag™ model to the mPLCOm2012 model - both using the mentioned extracted EMR data. Inclusion was for ages 40 to 80 between 2010-2022 with minimal mandatory medical information captured in EMR (e.g., demographics, diagnosis, smoking information). Model performance was evaluated by AUC, Sensitivity, Odds-Ratio (OR) indexes for multiple false positive rate (FPR) cut-offs (top 3% and 10%) using bootstrap methodology.

Results: Total data of 65,882 individuals was extracted, 60,751 met the age criteria (10,557 Cases, 50,194 Controls). Average pack-years for ever smokers were 38 and 30 for cases and controls, respectively. Calculation of mPLCOm2012 and LungFlag™ was performed on the diagnosis date for cases, and on a randomly selected date for controls requiring at least 2 years of follow-up period to reduce the potential false negatives.LungFlag™ demonstrated statistically significant superiority over mPLCOm2012 with OR at 3% FPR of 11.7 vs. 5.9 among ever-smokers and 9.0 vs. 4.3 among USPSTF eligible, respectively. Furthermore, LungFlag™ had an OR of 9.9 at FPR of 3% for never smokers and 2.4 for individuals without smoking status.

Conclusions: LungFlag™ was actionable able to work on Taiwanese EMR data, presented superiority over mPLCOm2021. The results were comparable to the previous validation studies. LungFlag™ can potentially support Taiwan screening program in identifying elevated risk populations among ever- and never- smokers and would benefit from more historic data. A model retraining for never smokers using local data should be considered.

Keywords: AI, screening, Taiwan

Table 1: Performance per sub-population:

Sub-Population	Controls	Cases	Model	AUC	False Positive Rate 3%		False Positive Rate 10%	
					Sensitivity %	*Odds Ratio*	*Sensitivity %*	*Odds Ratio*
Ever smokers	4,986	911	$mPLCO_{20}$	0.697 [0.678 - 0.716]	15.3 [12.3 - 18.2]	5.9 [4.5 - 7.2]	33.2 [30.0 - 36.8]	4.5 [3.9 - 5.2]
			LungFlag	0.769 † [0.750 - 0.788]	26.5 † [23.0 - 31.0]	11.7 † [9.7 - 14.5]	46.6 † [42.8 - 50.7]	7.9 † [6.7 - 9.3]
USPSTF	1,035	342	$mPLCO_{20}$	0.702 [0.670 - 0.732]	11.6 [7.5 - 16.8]	4.3 [2.6 - 6.5]	27.2 [22.0 - 33.0]	3.4 [2.5 - 4.4]
			LungFlag	0.762 † [0.733 - 0.791]	21.6 [15.0 - 28.6]	9.0 † [5.8 - 13.0]	41.8 † [34.3 - 47.7]	6.5 † [4.7 - 8.2]
Never Smokers	19,372	2,207	LungFlag	0.649 [0.638 - 0.661]	13.6 [12.5 - 15.0]	9.9 [8.3 - 12.1]	26.6 [25.0 - 28.5]	3.4 [3.1 - 3.8]
Unknown smokers	26,589	7,439	LungFlag	0.581 [0.574 - 0.588]	6.9 [6.6 - 7.2]	5.9 [4.5 - 7.2]	* NA	* NA

* NA - Most patients only have sex and age information – causing same calculated score. Therefore, unable to select ~10% of the population.
† Statistically significance difference between LungFlag and mPLCOm2012 (P<0.05)

P4.04C SCREENING AND EARLY DETECTION - INNOVATIVE SCREENING TECHNOLOGY
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P4.04C.11 Pixel-Wise Pulmonary Nodule Growth Prediction on Low-Dose Computed Tomography with 3D-ConvLSTM Deep Neural Network

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Introduction: Lung cancer, characterized by high incidence and mortality rates, underscores the importance of early diagnosis for better patient outcomes and prolonged survival. Predicting pulmonary nodule growth through pixel-wise nodule mask forecasting from chest CT scans aids in malignancy assessment and treatment planning, holding significant clinical value. However, current methodologies primarily address tumor growth, neglecting specific nodule growth prediction. To fill this gap, we introduce a dedicated neural network designed for precise nodule growth forecasting using CT scans, aiming to enhance diagnostic accuracy and patient care.

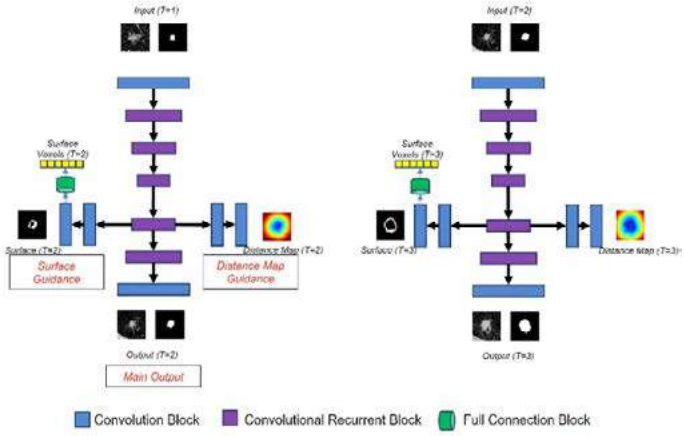
Methods: A novel pixel-wise nodule growth prediction network was proposed, featuring surface and distance guidance branches, as depicted in Figure 1(a). The surface-guidance-branch(SGB) captures nodule surface evolution by predicting post-growth surface contours, alongside key point coordinates extracted via PCA. In the distance-guidance-branch(DGB), we address surface clarity challenges in nodule images by predicting distance maps for segmentation results at subsequent time points. Our network was trained on a dataset of 299 patients, each patient with 3 follow-up CT scans, and tested on an independent dataset of 50 patients. All methods received nodule images and corresponding segmentation results at two-time points, tasked with predicting third-time-point outcomes. Dice, IoU and the MAE of the test set and the growth-only test set (nodules with volume growth over 50%) are calculated.

Results: Compared with existing methods such as 3D ResUNet and GM-AE, the quantitative results presented in Table 1 demonstrate the superior performance of our method over other approaches. This highlights the enhanced predictive capability of our model for nodule growth. Image results are depicted in Figure 1(b), showcasing our method's notably accurate predictions, particularly evident in the areas indicated by arrows.

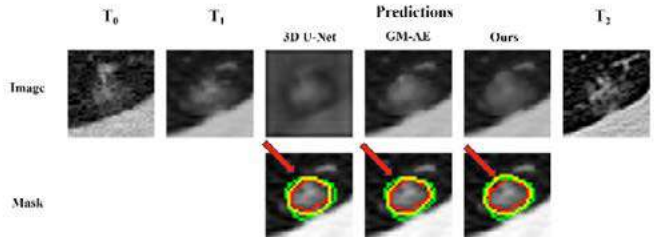
Conclusions: An innovative method was proposed for pixel-wise pulmonary nodule growth prediction and proved its superiority over existing methods on an independent dataset.

Keywords: Pulmonary Nodule Growth Prediction, Deep Convolutional Neural Network, Computed Tomography

(a)



(b)



Method	Dice	Dice G	IoU	IoU G	MAE	MAE G
3D ResUNet	75.95	72.99	61.93	58.18	0.6810	1.2970
GM-AE	76.16	73.44	62.14	58.74	0.6578	1.1744
3D-ConvLSTM(Ours)	**76.90**	**75.18**	**63.11**	**61.02**	**0.6141**	**1.0318**

P4.04D SCREENING AND EARLY DETECTION - REVISING LUNG CANCER SCREENING ELIGIBILITY
MONDAY, SEPTEMBER 9, 2024 - 18:30 - 20:00

P4.04D.01 Gender Disparities in Lung Cancer Screening: A Systematic Literature Review

E. Shum[1], N. Florez[2], J. Brahmer[3], C. Aggarwal[4], H. Wakelee[5], M. Chau[6], R. Shenolikar[6], R. Salomonsen[6], J. Chaieb[6], L. Luciani-Silverman[6], D. Guy[7], L. Woldmann[7], A-A. Ciritel[7], S. Peters[8], [1]NYU Perlmutter Cancer Center, New York/NY/USA, [2]Dana-Farber Cancer Institute, Boston/MA/USA, [3]Johns Hopkins Medicine, Baltimore/MD/USA, [4]University of Pennsylvania Medical Center - Abramson Cancer Center at Perelman Center for Advanced Medicine, Philadelphia/PA/USA, [5]Stanford University School of Medicine, Stanford/CA/USA, [6]AstraZeneca, Gaithersburg/MD/USA, [7]Amaris Consulting, Barcelona/ES, [8]CHUV, Lausanne University, Lausanne/CH

Introduction: Lung cancer screening can lead to earlier detection and reduced mortality. However, disparities in screening criteria, access, and utilization rates may limit the benefits of screening initiatives. Understanding these disparities is critical for optimizing screening strategies and improving lung cancer outcomes. This study seeks to inform more inclusive and effective lung cancer screening approaches that can benefit all individuals at risk, regardless of their smoking history or demographics.

Methods: A systematic literature review was conducted in January 2024 according to PRISMA guidelines to synthesize published observational or interventional literature reporting on gender differences in screening criteria, access, and utilization rates, considering additional factors such as age, race, ethnicity, histology, and socio-economic status. Embase, MEDLINE, MEDLINE In-Process, and Cochrane library databases were searched. Relevant conference proceedings and additional published literature from experts were also considered. English language studies published between January 2004 and February 2024 that reported statistically significant gender differences were included. Data were assessed before and after 2011, considering potential differences following the publication of the National Lung Screening Trial (NLST).

Results: We found 5,166 unique publications, of which 5,116 were excluded based on titles and abstracts, 50 were reviewed in full, of which, 24 were excluded due to lack of reporting on gender differences outcomes. Twenty-six studies covering over 1.4 million individuals were included. Of these studies, fifteen were from North America (NA), five were from Europe, three covered international regions, and two were from Asia. Screening rates were reported in ten studies, of which seven indicated that men in NA and Europe were more likely to undergo screening compared to women (range of OR 1.11 - 2.57). Five studies reporting on screening eligibility for low-dose computed tomography (LDCT) found that more men were eligible for screening than women using U.S. Preventive Services Task Force (USPSTF) criteria (USPSTF 2013: 56.8% - 70.3% vs 46.7% - 65%, USPSTF 2021: 51.4% - 71.8% vs 41.3% - 64.6 %). Two studies from NA suggested that women who had ever smoked were less likely to meet the 30-pack-year criterion than men who actively smoked or had stopped within six months of diagnosis (65.0% vs. 70.3%, p=0.033). Studies that included cases with 20+ pack-years showed a partial reduction in disparity between women's and men's eligibility criteria. This criteria was consistent with revised 2021 USPSTF criteria. Only one of the five studies reporting on screening eligibility included data from before 2011. Findings remained the same when results were assessed before and after NLST publication.

Conclusions: Fewer women are meeting lung cancer screening eligibility suggesting that current screening guidelines do not adequately capture factors affecting women's lung cancer risk. Further, lung cancer screening rates were found higher among men compared to women in NA and Europe. These exploratory findings suggest that further investigation into gender differences is needed.

Keywords: gender differences, lung cancer screening

P4.04D SCREENING AND EARLY DETECTION - REVISING LUNG CANCER SCREENING ELIGIBILITY
MONDAY, SEPTEMBER 9, 2024 - 18:30 - 20:00

P4.04D.02 Lung Cancer in Never Smokers and Individuals with a Family History of Lung Cancer: Missed Opportunities for Screening

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Introduction: Although smoking is the primary risk factor for lung cancer, a significant proportion of lung cancer cases occur in people who have never smoked. Recent research from Taiwan suggested that a family history of lung cancer among first-degree relatives significantly increases risk of lung cancer, particularly for women, and rate of invasive lung cancer with increasing age. However, current lung cancer screening eligibility criteria do not consider these factors. This study aims to examine the prevalence of people who have never smoked and individuals with a family history of lung cancer in the cohort of patients diagnosed and treated for lung cancer.

Methods: 1110 patients diagnosed with first primary lung cancer were enrolled in the prospective cohort, Initiatives for Early Lung Cancer Research on Treatment (IELCART), between 2016 and March 2024. We determined the prevalence of patients who have never smoked, those with a family history of lung cancer, and smokers who do not meet current screening guidelines, their demographic characteristics, and tumor histology.

Results: Among the 1110 patients with first primary lung cancer (45% male, 55% female; median age 70.5), 696 (62.7%) did not meet the current eligibility criteria for lung screening; 192 (27.6%) were never smokers, 333 (47.8%) smokers with <20 pack-years of smoking, and 171 (24.6%) former smokers with 20 or more pack-years but quit more than 15 years ago. Of these 696 patients, 126 (18.1%) had a family history of lung cancer, including 106 (84.1%) with one, 19 (15.1%) with two, and 1 (0.8%) with three or more first-degree relatives with lung cancer. 33 (26.2%) of the 126 were individuals who have never smoked, 57 (45.2%) smokers <20 pack-years, and 36 (28.6%) former smokers who quit more than 15 years ago. Tumor histology among these 126 patients were 13 (10.3%) squamous cell carcinoma, 3 (2.4%) small cell, 12 typical carcinoma (9.5%), 93 (73.8%) invasive adenocarcinoma, and 5 other (4%). Of the adenocarcinomas, 8 (8.6%) were adenocarcinoma-in-situ or minimally invasive adenocarcinoma, 7 (7.5%) were lepidic predominant adenocarcinoma, and 78 (83.9%) were other subtypes.

Conclusions: Our findings highlight that a significant proportion of diagnosed and treated lung cancer patients have never smoked or have a family history of lung cancer, but do not meet the current eligibility criteria for lung cancer screening. The detection of invasive lung cancers of these patients underscores the missed opportunities for early detection and potentially improved outcomes. This study suggests the need for the identification of more risk factors for lung cancer to inform future screening strategies.

Keywords: Lung Cancer Screening, Never Smokers, Family History

P4.04D SCREENING AND EARLY DETECTION - REVISING LUNG CANCER SCREENING ELIGIBILITY
MONDAY, SEPTEMBER 9, 2024 - 18:30 - 20:00

P4.04D.03 Lung Cancer in Those Who Never Smoked Study (luCNeSS) - Preliminary Analysis

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Introduction: Despite the increasing prevalence of lung cancer among those without a smoking history (LCNS), there is no proven screening modality approved for this population in the US. The Lung Cancer in those who Never Smoked Study (LuCNeSS) is designed to develop and validate an integrated clinical and biomarker-based risk prediction model for LCNS that will identify those likely to benefit from LDCT screening.

Methods: LuCNeSS aims to enroll at least 300 participants (100 with lung cancer, 200 no lung cancer; all <100 lifetime cigarettes) from the Beth Israel Lahey Hospital network to contribute survey data, blood samples, and nasal swabs. Tumor tissue will be collected when available from affected cases. LuCNeSS employs a survey based on an updated version of the PLCOall2014 risk model optimized for performance among those without a smoking history for the development of a clinical risk prediction model. This clinical risk model will be integrated with a methylation-based nasal epithelial biomarker panel to identify those at high risk for LCNS who may benefit from LDCT screening.

Results: Since November 2021, LuCNeSS has enrolled 26 case and 26 control participants with recruitment ongoing. As of this preliminary March 2024 data analysis, the average age of participants is 65 years, 63% are female. Among case participants, the average age at lung cancer diagnosis was 66 years with adenocarcinoma (ADC) histology predominant (69%). 62% of case participants presented with stage I-III disease (14/16 stage I/II) versus 35% with metastatic disease. Of those with ADC histology and advanced disease, 8/9 had actionable driver alterations (5 EGFR mutant; 2 MET exon 14 skipping; 1 ALK fusion). 9/26 case participants (vs 5/26 control) reported 1st or 2nd degree relatives with lung cancer history and 12/26 reported 1st degree relatives with non-lung cancer diagnoses (versus 11/26 among control participants). Reported environmental exposures linked to lung cancer risk were similar among case and control participants (9 case vs 7 control) as was reported exposure to secondhand smoke (18 case and 18 control). Blood and nasal swab epithelial samples were collected from 51 participants and tumor tissue from 10 case participants. Nasal swab epithelial sample methylation analysis is planned to begin once enrollment has reached 30 case and 60 control participants.

Conclusions: Preliminary results from LuCNeSS are presented here to highlight an ongoing effort to identify a clinical and biomarker-based risk profile for LCNS, emphasizing the role of environmental and potential genetic factors and strengthened by the case-control design. Continued accrual will allow for refining the clinical model (PLCOall2014) and integrated clinical and biomarker risk model (PLCOall2014PLUS) for prospective assessment in identifying a LCNS high-risk population likely to benefit from LDCT.

Keywords: Lung Cancer, Never Smoked, Screening

P4.04D SCREENING AND EARLY DETECTION - REVISING LUNG CANCER SCREENING ELIGIBILITY
MONDAY, SEPTEMBER 9, 2024 - 18:30 - 20:00

P4.04D.04 Efficiency of the Annual CT Screening Interval for Those at a Lower Risk of Lung Cancer - A CISNET Comparative Modelling Study

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Introduction: The United States Preventive Services Task-Force (USPSTF) recommends individuals aged 50-80 with 20 pack-years of smoking history and less than 15 years since smoking cessation to be screened annually. Other countries are issuing similar recommendations, with some opting for biennial screening out of concern for radiological capacity. Modelling studies have shown benefits and harms of annual relative to biennial screening, but it is unknown whether the benefits of annual screening can be preserved when adapting the screening interval to the age, sex and smoking exposure of participants.

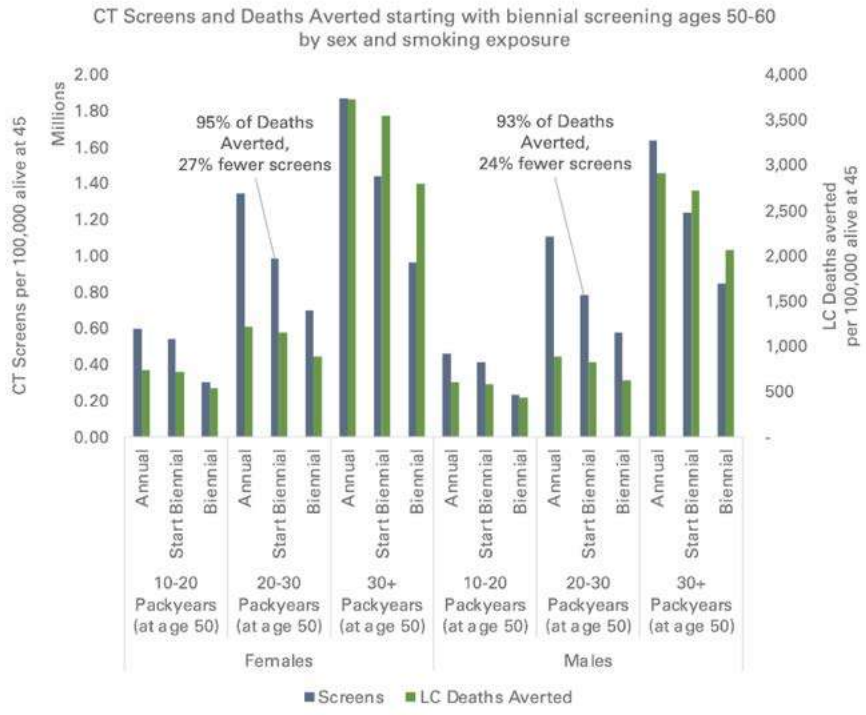
Methods: We perform a comparative modelling study with models from the Cancer Intervention and Surveillance Modeling Network (CISNET) lung working group. We evaluate screening strategies that adapt screening between annual and biennial intervals according to the age, sex and smoking exposure of participants. We consider a 1965 U.S. birth cohort, stratified by sex and smoking exposure at age 50 (<20, 20-30, 30+ packyears). Various age-adaptive strategies using USPSTF smoking eligibility criteria are simulated: annual screening ages 50-80, biennial screening ages 50-80, starting (ages 50-60) or ending (ages 70-80) with 10 years of biennial screening, or both starting and ending with 10 years biennial screening, but annual screening otherwise. To study cost-effectiveness, we calculate Quality-Adjusted Life-Years (QALYs) gained, and SEER-Medicare derived costs of treatment as well as costs of computed-tomography (CT) and follow-up. We assumed a willingness-to-pay threshold of $100k/QALY gained for cost-effectiveness.

Results: We find that starting with biennial screening for ages 50-60, followed by annual screening, retains most benefits with fewer CT scans (Figure 1). Particularly for those meeting USPSTF criteria at lower smoking exposure (e.g., 20-30 pack-years for women), this strategy preserves 95% of lung cancer deaths prevented from this strategy, compared to annual screening, with 27% fewer screens. Annual screening is cost-effective for men ages 50-80 with >30 pack-years (ICER $89,829). For females and males who smoked less, 10 years of biennial screening ages 50-60, followed by annual screening ages 61-80, is preferred over annual screening from ages 50-80.

Figure 1 reports estimated deaths prevented and required CT screens for annual screening (ages 50-80 per USPSTF), biennial screening ages 50-60 followed by annual screening, and biennial screening. Results are stratified by sex and smoking exposure at age 50, and scaled per 100,000 individuals alive at age 45.

Conclusions: In resource-constricted settings, CT scans every two years instead of annually for younger participants with less than 30 pack-years maintain screening effectiveness.

Keywords: screening, adaptive, Computed tomography



P4.04D.05 Family History is an Independent Predictor of Lung Cancer Detection in Women in a Predominantly Caucasian Screening Cohort

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Introduction: Lung cancer screening (LCS) with low dose computed tomography (LDCT) chest confers a mortality benefit in individuals at risk due to cigarette smoking. The importance of family history of lung cancer (FHx) has not been well-defined in this setting. We evaluated FHX as a predictive factor for lung cancer detection in participants in the International Lung Screen Trial (ILST), a prospective, multi-centre cohort study of LDCT in LCS (NCT02871856).

Methods: A post-hoc analysis of all Australian and Canadian participants compared lung cancer detection rates stratified by sex and family history. Univariable logistical regression was used to determine risk factors to include in the multivariable model from the following: age, body mass index (BMI), chronic obstructive pulmonary disease (COPD), personal history of cancer, FHx, smoking pack-years, years since smoking cessation and current smoking status. Risk factors with p-value<0.1 were included in the multivariable analysis to determine independent predictors of lung cancer detection. Continuous and categorical variables were reported as mean±standard deviation and count (%) respectively. Comparison of continuous and categorical variables were conducted using the Mann-Whitney U-test or Chi-Squared test respectively. A p-value <0.05 was deemed statistically significant.

Results: 4309 ILST participants were included of which 3941 (92%) were Caucasian and 2040 (47%) were female. 155 lung cancers were detected with an overall detection rate of 3.6%. There were no significant differences in detection rate based on sex [male 71 (3.1%) vs female 84 (4.1%), p=0.082] or FHx [Fhx 49 (4.3%) vs No Fhx 106 (3.3%), p=0.126]. The results of univariable and multivariable logistic regression analysis are presented in Table 1. Multivariable analysis identified two independent predictors of lung cancer detection in men: age [OR 1.06, 95% CI 1.04 -1.08, p=0.003] and smoking history [OR 1.01, 95% CI 1.01 - 1.02, p=0.001]. Multivariable analysis identified three independent predictors of lung cancer detection in women: age [OR 1.07, 95% CI 1.05 - 1.09, p<0.001], smoking history [OR 1.01, 95% CI 1.01 - 1.02, p=0.033] and FHx [OR 1.58, 95% CI 1.26 - 1.99, p=0.047].

Conclusions: Family history of lung cancer is an independent predictor of lung cancer detection in female participants of the ILST. The inclusion of family history in LCS selection criteria may optimize equity of access to future screening programs.

Keywords: Lung cancer screening, Family history, Women

Table 1: Univariable and multivariable logistical regression for predictors of lung cancer detection in the Australia and Canadian cohort of the International Lung Screening Trial (ILST)

	Female participants			
	Univariable		Multivariable	
Variable	Odds ratio	P-value	Odds ratio	P-value
Age (per 1-year)	1.07 (95% CI 1.05 – 1.09)	<0.001	1.07 (95% CI 1.05 – 1.09)	< 0.001
BMI (per unit increase)	1.01 (95% CI 0.83 – 1.22)	0.780	-	-
COPD	1.42 (95% CI 1.08 – 1.88)	0.206	-	-
Personal history of any cancer	0.86 (95% CI 0.63 – 1.16)	0.624	-	-
Family history of lung cancer	0.67 (95% CI 0.53 – 0.84)	0.080	1.58 (95% CI 1.26 – 1.99)	0.047
Smoking history (per 1-pack-years)	1.01 (95% CI 1.01 – 1.02)	0.021	1.01 (95% CI 1.01 – 1.02)	0.033
Years-quit smoking (per 1-year)	1.01 (95% CI 0.99 – 1.02)	0.637	-	-
Current smoker	1.09 (95% CI 0.87 – 1.36)	0.707	-	-
	Male participants			
	Univariable		Multivariable	
Variable	Odds ratio	P-value	Odds ratio	P-value
Age (per 1-year)	1.07 (95% CI 1.05 – 1.09)	<0.001	1.06 (95% CI 1.04 – 1.08)	0.003
BMI (per unit increase)	1.00 (95% CI 0.99 – 1.03)	0.900	-	-
COPD	1.65 (95% CI 1.23 – 2.22)	0.092	1.36 (95% CI 1.00 – 1.84)	0.313
Personal history of any cancer	0.86 (95% CI 0.64 – 1.16)	0.562	-	-
Family history of lung cancer	1.02 (95% CI 0.76 – 0.1.37)	0.951	-	-
Smoking history (per 1-pack-years)	1.02 (95% CI 1.01 – 1.02)	<0.001	1.01 (95% CI 1.01 – 1.02)	0.001
Years-quit smoking (per 1-year)	1.006 (95% CI 0.99 – 1.02)	0.646	-	-
Current smoker	0.85 (95% CI 0.67 – 1.08)	0.496	-	-

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P4.04D.06 Improving Lung Cancer Risk Prediction in Asbestos Exposed Individuals: An Ensemble Approach

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Introduction: Most lung cancer (LC) risk prediction models do not adequately account for risk due to asbestos exposure and none for the relative excess risk due to interaction (RERI) of asbestos and tobacco smoking. The aim of this study was to develop a LC risk model specific for asbestos exposed populations, by modelling complex interactions through ensemble machine learning.

Methods: Lung cancer risk models were trained on 1,357 participants from the Western Australian Asbestos Review Program (ARP), aged 45-90, with a smoking history (42 with lung cancer). All participants had ≥3 months asbestos exposure and underwent LDCT screening over 10-years. Validation was performed on 469 participants from the International Lung Screening Trial (ILST) with ≥3 months of asbestos exposure. Variables for risk prediction included: age, sex, body mass index (BMI), chronic obstructive pulmonary disease, tobacco exposure variables, family lung cancer and personal cancer history, and asbestos exposure duration.

Logistic regression and gradient boosted trees were used to build risk models in the training data using 10-fold cross-validation, with the 'best' performing model selected according to the AUC-ROC. Selected models were benchmarked against the performance of the PLCOm2012 model in the validation cohort. The predictions from the best performing models were selected and combined using weighted averaging to develop the ARP-1 ensemble model.

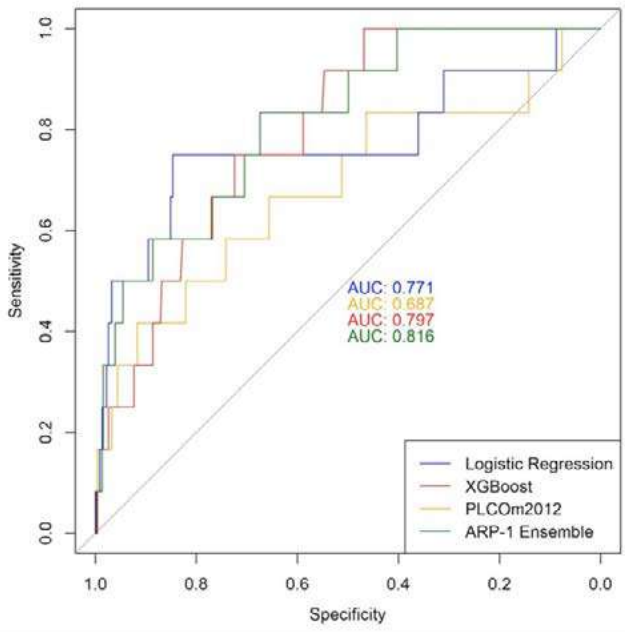
Results: The gradient boosted tree model was the best performing individual model in the validation data (AUC:0.797; 95%CI 0.693-0.901), improving over the PLCOm2012 model (AUC:0.687, 95%CI 0.502-0.872) in predicting the 12 cancers in ILST validation cohort. The logistic regression (LR) model performed better with asbestos exposure duration included solely as an interaction with smoking intensity (AUC:0.771; 95%CI 0.588-0.954), than as an independent variable (AUC:0.763; 95%CI 0.582-0.944). The variables: age, education, BMI, asbestos exposure duration and tobacco exposure duration/ intensity provided the strongest performance benefit in validation.

The best performing gradient boosted tree and LR models were combined using weighted averaging of predicted probabilities to develop the ARP-1 ensemble model: This model demonstrated improved performance over its constituent models in validation (AUC:0.816; 95%CI 0.698-0.935; Figure 1), with good mean calibration.

Conclusions: The ARP-1 model is the first LC prediction model to account for the RERI of asbestos and tobacco exposure. Given the widespread asbestos exposure in many countries, ARP-1's performance highlights the need for cohort specific models that account for interactions in lung cancer. Further external validation is required due to the small validation cohort.

Keywords: Lung Cancer Screening, Risk Prediction, Asbestos Exposure

Figure 1. ROC curves comparing the discriminative performance of the $PLCO_{m2012}$, the best performing Logistic Regression Model, the best performing Gradient Boosted Tree Model and the developed ARP-1 ensemble model in predicting lung cancer in ILST participants with asbestos exposure.



P4.04D.07 Lung Cancer Biomarkers in Nonsmokers: Diagnostic and Prognostic Use of Liquid Biopsy for Metabolites Found in the Urine

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Introduction: Ten to thirteen percent of lung cancer cases in the United States are caused by nonsmokers. Etiology is linked to several risk variables, such as exposure to secondhand smoke, asbestos, environmental pollution, and radon, but these exposures are not within the current eligibility criteria for early lung cancer screening by low-dose computed tomography (LDCT).

Methods: The urine samples were collected from two independent cohorts comprising 846 participants (exploratory cohort) and 505 participants (validation cohort). Liquid chromatography-mass spectrometry was used to analyze and quantify the cancer urine biomarkers, creatine riboside (CR) and N-acetylneuraminic acid (NANA), to identify and distinguish non-smoker cases from sex and age-matched controls in comparison with tobacco smoker cases and controls. This could lead to more precise eligibility criteria for LDCT screening.

Results: Urinary levels of CR and NANA were significantly higher and comparable in non-smokers and tobacco smoker cases as compared to population controls in both cohorts as shown in Figure 1. Receiver Operating Characteristics (ROC) analysis for combined CR and NANA levels in non-smokers of the exploratory cohort resulted in better predictive performance with the area under the curve (AUC) of 0.94, whereas the validation cohort never-smokers had an AUC of 0.80. Kaplan-Meier survival curves demonstrated that high levels of these biomarkers corresponded with an increase in cancer-specific mortality in both non-smokers and tobacco smokers. Biomarkers metabolite category factor and stage were significant independent predictors of survival in multivariate analyses for both cohorts as shown in Figure 2.

Conclusions: Prospective investigations of these biomarkers are warranted, since measuring them in urine liquid biopsies may identify nonsmokers at high risk for lung cancer and make them candidates for LDCT screening.

Keywords: Biomarker, Metabolomics, Non-smoker

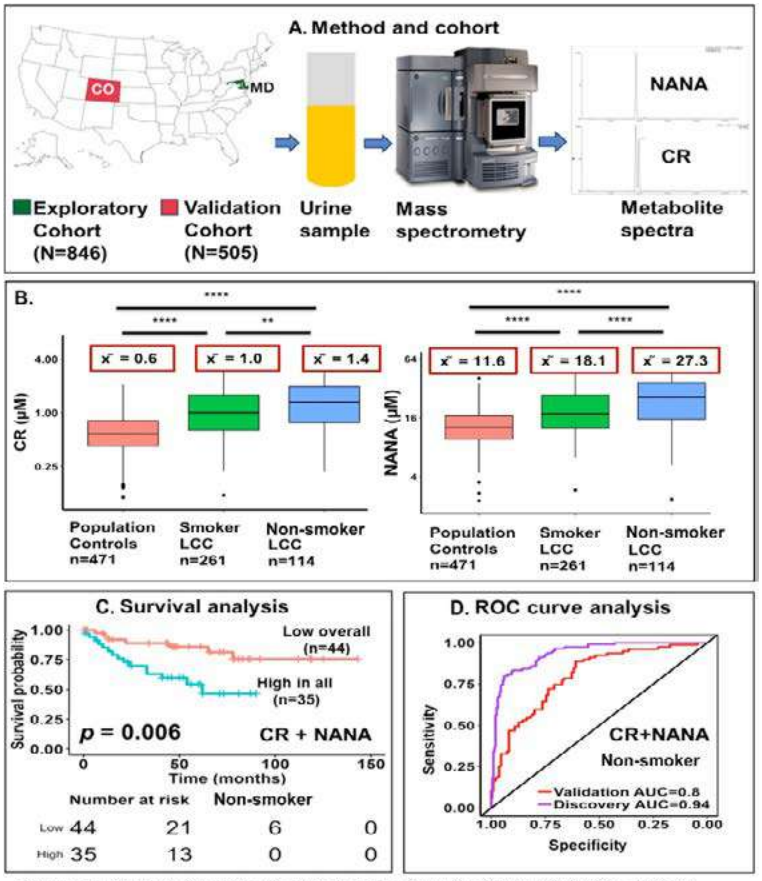

Figure 1. A. Study design and methodology **B.** Box plots showing the distribution of urinary metabolite levels of CR and NANA **C.** K-M plots of overall survival of lung cancer cases stratified by the median cutoff value of CR and NANA for non-smokers **D.** ROC curves represent the accuracy of metabolite in combination with AUC for non-smokers in both discovery as well as exploratory cohorts

Exploratory Cohort			Univariable			Multivariable		
Factors	**Levels**	**N**	**HR[1]**	**95% CI[1]**	**p-value**	**HR[1]**	**95% CI[1]**	**p-value**
CR + NANA category	Low; High	114	1.79	0.99, 3.24	**0.041**	2.74	1.40, 5.38	**0.001**
Stage	Early Stage (I & II); Late Stage (III & IV)	107	3.26	1.99, 5.33	**<0.001**	3.83	2.26, 6.51	**<0.001**
Histology	Adenocarcinoma; Squamous cell carcinoma	114	1.62	0.74, 3.55	0.26	3.44	1.49, 7.95	**0.011**
Age	n=114	114	0.99	0.97, 1.00	0.086	0.99	0.98, 1.01	0.4
Sex	Male; Female	114	0.95	0.59, 1.52	0.82	0.85	0.50, 1.47	0.6
Race	African American; European American	114	0.84	0.26, 2.67	0.77	0.39	0.12, 1.33	0.2

Validation Cohort			Univariable			Multivariable		
Factors	**Levels**	**N**	**HR[1]**	**95% CI[1]**	**p-value**	**HR[1]**	**95% CI[1]**	**p-value**
CR + NANA category	Low; High	114	1.79	0.99, 3.24	**0.041**	2.74	1.40, 5.38	**0.001**
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Age	n=114	114	0.99	0.97, 1.00	0.086	0.99	0.98, 1.01	0.4
Sex	Male; Female	114	0.95	0.59, 1.52	0.82	0.85	0.50, 1.47	0.6
Race	African American; European American	114	0.84	0.26, 2.67	0.77	0.39	0.12, 1.33	0.2

Figure 2. Univariate and multivariate regression analysis for factors associated with survival in never-smokers from both cohorts

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P4.04D.08 Natural History Model for Second Primary Lung Cancer Among Lung Cancer Survivors: Utilizing the U.S. SEER Cancer Registries

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Introduction: Recent advances in early detection and treatment have doubled survival rates for lung cancer patients. This extended survival gives rise to a subsequent risk of second primary lung cancer (SPLC), which may require tailored screening strategies. Evaluating the potential benefits of computed tomography screening for SPLC relies on the ability to ascertain when tumors are detected at a curable size. A natural history model (NHM) can provide a mechanistic framework that predicts the expected time course of tumor growth of SPLC, which may differ from initial primary lung cancer (IPLC). Further, an NHM can be incorporated into a microsimulation model that can evaluate efficient screening strategies by simulating individual-level outcomes in the absence or presence of hypothetical screening strategies. However, at this time, SPLC lacks an NHM, with existing NHMs for lung cancer developed using survival data that include patients with both single and multiple primary lung cancers for model parameter estimation. This study aims to develop a separate NHM for SPLC vs. IPLC and to compare their tumor characteristics.

Methods: We utilized data from 250,380 patients diagnosed with primary lung cancer between 1992-2013 in SEER database for 13 registries (i.e., SEER-13). The original Stanford NHM for lung cancer—that did not separate IPLC and SPLC—was previously developed using SEER for 9 registries (i.e., SEER-9; 1988-2003). Using SEER-13, we re-fitted the NHM for IPLC using lung cancer survival data (by stage and tumor size) from patients who had a single diagnosis (i.e., IPLC) in their lifetime, thus separating out SPLCs. Then, we newly developed an NHM for SPLC using data from patients who developed SPLC after ≥5 years from IPLC. The model parameters were estimated using a stepwise maximum-likelihood by histology and sex. We compared the estimated outcomes (survival, stage, tumor size) using the NHMs vs. observed data from SEER-13.

Results: The estimated survival using the NHMs from IPLC and SPLC closely resembled those observed in SEER-13 (log-rank P>0.1). After separating out SPLCs, the TVDT of the IPLC-specific NHM was shorter (i.e., fast-growing) vs. the original NHM (e.g., 65 vs. 128 days for male-adenocarcinoma), which was expected because the latter NHM included those who survived extended time (≥5 years) until developing SPLC. When comparing the NHMs for SPLC vs. IPLC, we observed a larger proportion of SPLCs that were clinically detected at an early-stage vs. IPLC (e.g., 71.0% vs. 56.6% in male-adenocarcinoma in SEER), with a smaller median tumor size at clinical detection (e.g., 2.5cm vs. 3.8cm in male-adenocarcinoma in SEER). However, the TVDT of SPLC was similar to IPLC (e.g., 64 vs. 67 days for male-adenocarcinoma), suggesting that once SPLC is developed, its tumor growth rate may be similar to IPLC.

Conclusions: We developed an NHM for SPLC by separating it from the natural history of IPLC. The tumor growth rate of SPLC may be comparable to IPLC, although SPLC tends to be detected earlier potentially due to post-diagnosis surveillance. This work can serve as a foundation for future microsimulation studies to evaluate tailored screening for SPLC.

Keywords: Natural history of cancer, Second primary lung cancer, Modeling

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P4.04D.09 Assessing the Risk of Second Primary Lung Cancer in Women after Previous Breast Cancer

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Introduction: Advances in early diagnosis and treatment have improved breast cancer (BC) patients' prognosis and prolonged survival, also increased risk for developing a new (second) cancer compared to non-BC survivors. Lung cancer (LC) is of particular concern as it is the most common cancer among BC survivors, but it is unclear whether a history of BC is an independent risk factor for LC.

Methods: Women aged 54 to 75 were identified from prostate, lung, colorectal, and ovarian (PLCO) screening trial. Pre-PLCO BC diagnosis as well as incident breast cancer during follow-up through 2017 were ascertained. We then calculated unadjusted incidence rates of LC among BC survivors. BC was then included as a time-updated exposure in a multivariable Cox regression modeling LC incidence, adjusting for established LC risk factors

Results: The study included 75,951 female PLCO participants, of whom 8,504 (11.2%) were BC survivors, including 5,808 with BC diagnosed after enrollment in PLCO and 2,696 with BC diagnosed prior to enrollment. The median follow-up for BC survivors was 13.37 years. BC survivors were slightly older (p<0.0001), more likely to be white non-Hispanic (WNH), college graduates or with advanced degree, former cigarette smokers (all p<0.05) than non-BC survivors. Overall, unadjusted incidence rate (IR) of 191.7 per 100,000 person-years (95% confidence interval [CI]; 167 -219) compared to IR of 143 per 100,000 person-years non-BC survivors (95% CI; 136 -150). The adjusted hazard ratio (HR) associated with BC for LC was 1.26 (95%CI: 1.09, 1.45) compared to female subjects without BC.

Conclusions: Our results suggest that the history of BC is an independent risk factor for the incidence of LC. BC survivors may therefore have increased benefit from LC prevention interventions including low-dose computed tomography screening.

Keywords: Lung cancer, Breast cancer

Parameter		Adjusted hazard ratio (AHR)	Estimate	95% CI		Std Error	Pr > |t|
Age		1.63	0.491	0.293	0.689	0.101	<.0001
Age^2		1.00	-0.003	-0.005	-0.002	0.001	<.0001
Race	Black, non-Hispanic	1.10	0.098	-0.084	0.280	0.093	0.29
	Hispanic	0.67	-0.403	-0.833	0.028	0.220	0.07
	Asian	1.03	0.034	-0.230	0.297	0.134	0.80
	Others	1.30	0.259	-0.122	0.639	0.194	0.18
Education	College and above	0.84	-0.179	-0.266	-0.093	0.044	<.0001
	< 12 Years or completed high School	1	Reference				
With BC history	Yes	1.26	0.23	0.089	0.371	0.072	0.0014
	No	1	Reference				
BMI		0.97	-0.027	-0.035	-0.018	0.005	<.0001
History of COPD	Yes	1.38	0.319	0.201	0.437	0.06	<.0001
	No	1	Reference				
LC family history	Yes	1.54	0.434	0.331	0.536	0.052	<.0001
	No	1	Reference				
Smoking status	Never smoked	1	Reference				
	Former smokers	3.6	1.281	1.136	1.425	0.074	<.0001
	Current smoker	10.14	2.317	2.160	2.473	0.08	<.0001
pack_years		1.02	0.016	0.015	0.018	0.001	<.0001

Characteristics		No breast cancer history	Breast cancer history	P-value
		N=67,447	N=8,504	
Age (years)		62.51	62.79	<0.0001
Age group, N [%]				0.0003
	<=59	23,220(34.43%)	2,742(32.24%)	
	60-64	20,352(30.17%)	2,591(30.47%)	
	65-69	14,737(21.85%)	1,943(22.85%)	
	>=70	9,138(13.55%)	1,228(14.44%)	
BMI at baseline		(Missing n= 975)	(Missing n= 115)	0.05
		27.1	26.98	
Race, N [%]		(Missing n= 25)	(Missing n= 2)	<0.0001
	White, non-Hispanic	59,610(88.38%)	7,651(89.97%)	
	Black, non-Hispanic	3,961(5.87%)	359(4.22%)	
	Hispanic	1,089(1.61%)	120(1.41%)	
	Asian	2,265(3.36%)	298(3.50%)	
	Pacific islander	312(0.46%)	58(0.68%)	
	American Indian	185(0.27%)	16(0.19%)	
Education, N [%] (Missing n=193)				<0.0001
	Less than high school	4,535(6.74%)	438(5.17%)	
	High school graduate	27,437(40.78%)	3,200(37.74%)	
	College	25,640(38.11%)	3,347(39.47%)	
	Postgraduate	9,666(14.37%)	1,495(17.63%)	
With personal history of COPD, N [%]		4,977(7.38%)	500(5.88%)	<0.0001
With personal history of emphysema, N [%]		1,420(2.12%)	127(1.50%)	0.0002
Lung cancer family history, N [%]		9,031(13.39%)	1,090(12.82%)	0.14
Pack-years (excluded never smokers)		30.3	29.76	0.23
Smoking status, N [%]				<0.0001
	Never smoked cigarettes	37,659(55.83%)	4,609(54.20%)	
	Current cigarette smoker	6,638(9.84%)	740(8.70%)	
	Former cigarette smoker	23,150(34.32%)	3,155(37.10%)	
Follow-up time (years)		18.87	13.37	<0.0001
Lung cancer incidence, N [%]		1,820(2.70%)	218(2.56%)	0.47

P4.04D SCREENING AND EARLY DETECTION - REVISING LUNG CANCER SCREENING ELIGIBILITY
MONDAY, SEPTEMBER 9, 2024 - 18:30 - 20:00

P4.04D.10 Risk-Based LDCT Screening for Non-smokers in Taoyuan, Taiwan, Y-L. Liu1, C-y. Yeh1, Y-c. Yu1, T-M. Huang1, H-H. Lin1, K-J. Chuang2, 1Department of Public Health, Taoyuan, Taoyuan/TW, 2Taiwan Association of Medical Screening, Taipei/TW

Introduction: Lung cancer poses a significant challenge to global health, affecting not only smokers but affecting never-smokers, especially in Asia Female. While current evidence supports the use of LDCT for heavy smokers, the design and implementation of LDCT screening for non-smoker remain in debate, even in the face with soaring disease burden among this group. To address this issue, a risk-based low-dose computed tomography (LDCT) screening program was initiated for non-smokers in Taoyuan, Taiwan.

Methods: The Taoyuan City lung cancer screening program targets non-smokers aged 40 to 74 with specific risk factors such as long-term occupational exposure to carcinogens (asbestos, arsenic, cadmium, nickel, and dust), family history of lung cancer, personal breast cancer history, and household passive smoke exposure. It provides triennial LDCT scans for early lesion detection. Eligibility extends to individuals in industrial areas or exposed to pollution, including Police, Fire Department, Funeral Management Office personnel, night market workers exposed to cooking oil fumes, and temple workers exposed to incense, with over a decade of exposure. Utilizing the Lung-RADS system, it identifies positive scans (category 3 and above) for further diagnostics to confirm lung cancer diagnoses, aiming to enhance early detection and management in Taoyuan.

Results: The Taoyuan City lung cancer screening program for non-smokers, conducted from March 1 to December 31, 2023, accessed 13,446 residents, with 949 testing positive (7.06% positivity rate) and 74 diagnosed with lung cancer (0.55% detection rate). Notably, females, older residents (55+ years), and those with junior to senior high school education had higher detection rates. A significant risk increase was observed in individuals with a family or personal history of cancer, specifically lung (0.93% vs. 0.53%) and breast cancer (2.05% vs. 0.51%). Long-term exposure (10+ years) to cooking oil fumes and carcinogenic substances, along with household passive smoke exposure, also correlated with elevated detection rates. Multivariable logistic regression analysis revealed a statistically significant higher risk of lung cancer among attendees with a family history (aOR: 3.27, 95% CI: 1.43-7.50) and a history of breast cancer (aOR: 4.63, 95% CI: 1.86-11.5). Occupational exposure to carcinogenic substances (aOR: 4.06, 95% CI: 0.52-31.9) and exposure to cooking oil fumes (aOR: 1.58, 95% CI: 0.60-4.16) showed increased risks, albeit not statistically significant. Similar trends were observed for industrial workers (aOR: 1.58, 95% CI: 0.82-3.03) and field personnel of the Police and Fire Departments (aOR: 1.36, 95% CI: 0.48-3.82), indicating a need for targeted screening in high-risk groups. The results Bayesian Hierarchical model taking into account relevant factors with the concentration of PM2.5 as a township level factor showed the significant risk of lung cancer detection in the five townships (Guishan, Luzhu, Taoyuan, Bade, Dayuan) for female and two townships for male (Taoyuan, Daxi), showing the necessity of a gender-specific strategy to enhance lung cancer screening for residents in these areas.

Conclusions: The Taoyuan risk-based LDCT screening program proves the effectiveness in identifying lung cancers among non-smokers. This informs targeted LDCT screenings to address increasing lung cancer rates in Asia, aiming to improve early detection and reduce mortality.

Keywords: Lung cancer, Low-dose CT screening, non-smoker

P4.07D EARLY-STAGE NON-SMALL CELL LUNG CANCER - CLINICAL TRIALS IN PROGRESS
MONDAY, SEPTEMBER 9, 2024 - 18:30 - 20:00

P4.07D.01 Neoadjuvant Osimertinib Followed by Radiation And/or Surgery in Stage III EGFR-Mutant NSCLC: An Open-Label, Single-Arm, Phase 2 Study

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Introduction: The standard treatment for unresectable, locally advanced stage III non-small cell lung cancer (NSCLC) harboring epidermal growth factor receptor (EGFR) mutations involves concurrent chemoradiation therapy (cCRT) followed by durvalumab. The consolidation treatment might change to osimertinib following the announced positive results of the LAURA study. This study aimed to assess the potential advantages of using neoadjuvant osimertinib as an alternative therapeutic option and to minimize the radiation field.

Methods: This ongoing study is an open-label, single-arm, phase 2, prospective, proof-of-concept, investigator-initiated study. The study focused on patients diagnosed with treatment-naïve unresectable, stage III EGFR+ NSCLC. Participants received 80 mg of oral osimertinib daily for 12 weeks before undergoing definitive radiation therapy (RT) and/or surgery. Response assessments occurred at weeks 6 and 12, with responders proceeding to sequential definitive RT and/or surgery and nonresponders transitioning to cCRT. Patients were monitored for 2 years following RT ± surgery or CRT. The primary endpoint is the objective response rate (ORR), for which data collection will continue until March 31, 2024. The secondary endpoints included safety evaluations and measurements of gross tumor volume (GTV), planned tumor volume (PTV), and the percentage of total lung volume minus the GTV exceeding 20 Gy (V20%) before and after osimertinib treatment. Exploratory analyses involved assessing the presence of plasma circulating tumor-free DNA before osimertinib treatment, at weeks 6 and 12, at RT completion, and at 6 weeks post-RT.

Results: The study enrolled 34 patients, including 26 women, with a median age of 71 years (range: 48-83). Of these, 18 had EGFR exon 19 deletions, and 16 had EGFR exon 21 mutations. Participants had stage IIIA (13), IIIB (10), or IIIC (11) disease. Three patients withdrew from the study and were consequently excluded from the analysis. The ORR to osimertinib was 94% (26 partial responses, 3 complete responses, 1 stable disease, and 1 progressive disease). Initial assessment of 19 patients revealed that the median GTV, PTV and V20% before osimertinib treatment were 47.4 ± 76.9 cm3, 227.0±258.8 cm3, and 27.1±16.4%, respectively. After osimertinib treatment, these values changed to 27.5 ± 42.3 cm3 (representing a reduction of 48 ± 20%; P = .02), 181.9 ± 198.4 cm3 (representing a reduction of 31 ± 20%; P = .01), and 21.8 ± 11.7% (representing a reduction of 24 ± 40%; P = .04), respectively. The reduction in PTV/GTV/V20% correlated with tumor size and central location. No significant adverse events were reported during the osimertinib or radiation phases.

Conclusions: Neoadjuvant osimertinib in stage III EGFR+ NSCLC patients who received definitive radiation and/or surgery was shown to be feasible in this pilot study, achieving an impressive ORR of 94% along with a favourable safety profile. The 12-week induction of osimertinib before definitive radiation (without chemotherapy) notably decreased the radiation field by almost 50%, demonstrating a direct correlation with tumor size. Additional studies are necessary to evaluate the long-term efficacy of this chemotherapy-free strategy.

P4.07D EARLY-STAGE NON-SMALL CELL LUNG CANCER - CLINICAL TRIALS IN PROGRESS
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P4.07D.02 Furmonertinib as Adjuvant Therapy in Postoperative EGFR-Mutated Stage IB-IIA NSCLC with High-Risk Pathological Factors

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Introduction: Non-small cell lung cancer (NSCLC) patients with high-risk pathological factors such as micropapillary (MP), solid (S), and spread through air spaces (STAS) have shown poor prognosis in previous studies. Furmonertinib (AST2818) is a novel, promising oral third-generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI), which has demonstrated efficacy in tumors harboring sensitive EGFR mutations and T790M resistance mutation. Here, we investigated the efficacy and safety of furmonertinib as adjuvant therapy in postoperative EGFR-mutated NSCLC patients with high-risk pathological factors.

Methods: Patients who underwent radical lung cancer surgery with both EGFR mutations and MP/S/STAS were enrolled and received furmonertinib 80mg daily. The disease-free survival (DFS), safety and tolerability were evaluated.

Results: This study has prospectively enrolled 52 patients who were pathologically confirmed adenocarcinoma, EGFR mutation positive (exon 19 deletion/L858R), stage IB-IIA NSCLC. All of them had at least one high-risk pathological factor. There were 37 patients with MP, 6 with S, and 33 with STAS. By the cut-off date of March 1, 2024, all patients were alive and with no radiographic recurrence. The median follow-up time was 16.5 months. During therapy, 15 (28.8%) patients had treatment-related adverse events (TRAEs) of any grade. The most common TRAEs were rash (13, 25%), diarrhea (4, 7.7%) and mouth ulcer (1, 1.9%). Only 1 (1.9%) patient had TRAEs of grade 3 or higher.

Conclusions: This is the first prospective study to demonstrate that furmonertinib has good efficacy and a tolerable safety profile as adjuvant therapy in EGFR-mutated early NSCLC patients with high-risk pathological factors who underwent radical lung cancer surgery.

Keywords: Early NSCLC, Postoperative adjuvant therapy, EGFR-TKI

Table. Patient demographic characteristics and safety events.

Variables	Values
Age, years	58 (24, 73)
Sex	
Female	30
Male	22
Type of surgery	
Lobectomy	39
Sub-lobectomy	13
Stage	
IB	41
IIA	11
High-risk factor	
MP	37
S	6
STAS	33
EGFR mutation	
19del	7
L858r	45
AE	
Any AEs	15 (28.8%)
CTCAE ≥ Gr 3	1 (1.9%)
Rash	13 (25.0%)
Diarrhea	4 (7.7%)
Mouth ulcer	1 (1.9%)

P4.07D EARLY-STAGE NON-SMALL CELL LUNG CANCER - CLINICAL TRIALS IN PROGRESS
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P4.07D.03 Phase 2 Peri-Operative Study of Fianlimab+Cemiplimab+Chemotherapy vs Cemiplimab+Chemotherapy in Resectable Early-Stage NSCLC

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Introduction: Co-blockade of lymphocyte-activation gene 3 (LAG-3) may enhance the efficacy of anti–programmed cell death-1 (anti–PD-1) therapies. Fianlimab (anti–LAG-3) and cemiplimab (anti–PD-1) are high-affinity, fully human, IgG4 monoclonal antibodies. In a Phase 1 study (NCT03005782), fianlimab + cemiplimab showed promising clinical activity with durable responses and an acceptable risk-benefit profile in patients with advanced non-small cell lung cancer (NSCLC) who were anti–PD-1/L1-naïve. The use of IO + chemotherapy in the peri-operative setting is established as a new standard of care, but is still under active investigation to potentially improve outcomes in early-stage disease.

Methods: This is a randomized, multicenter, double-blind, Phase 2 peri-operative study (NCT06161441) in patients with early-stage resectable stage II to stage IIIB (N2), squamous or non-squamous histology, operable, treatment-naïve NSCLC, to be treated with neoadjuvant therapy, followed by surgery and subsequent adjuvant therapy. The aim of this study is to investigate the efficacy and safety of fianlimab + cemiplimab + chemotherapy versus cemiplimab + chemotherapy as peri-operative treatment. The study will be conducted globally at approximately 130 sites. Key inclusion criteria: 1) age ≥18 years; 2) newly diagnosed, histologically confirmed, fully resectable stage II to IIIB (N2) NSCLC; 3) for patients with evidence of mediastinal adenopathy on imaging, mediastinal lymph node sampling is required; 4) no evidence of distant metastases on imaging; 5) evaluable PD-L1 immunohistochemistry results; 6) no cancer treatment within the prior 3 years, except adjuvant hormone therapy for hormone-sensitive cancers in long-term remission; 7) Eastern Cooperative Oncology Group Performance Status ≤1; 8) no known EGFR mutations or ALK aberrations; 9) adequate organ and bone marrow function. All patients enrolled in the study will be stratified by clinical TNM stage at randomization (stage II versus stage III), histology (non-squamous versus squamous), and PD-L1 expression (<1%, 1–49%, ≥50%). Approximately 180 patients will be randomized (1:1:1) to the following study arms for the neoadjuvant period (up to 4 cycles; each cycle is every 3 weeks): Arm A: placebo + cemiplimab 350 mg + platinum doublet chemotherapy; Arm B: fianlimab Dose 1 + cemiplimab 350 mg + platinum doublet chemotherapy; Arm C: fianlimab Dose 2 + cemiplimab 350 mg + platinum doublet chemotherapy. After surgery, in the adjuvant period (up to 14 cycles), all arms will continue study treatment at the same dose and schedule according to prior randomization, without platinum doublet chemotherapy. Patients will be treated for up to approximately 12 months (12 weeks of neoadjuvant therapy + 42 weeks of adjuvant therapy), or until recurrence of disease, unacceptable toxicity, patient's decision, or investigator's decision. The primary endpoint is pathological complete response by blinded independent pathological review (BIPR). The key secondary endpoints are event-free survival by investigator assessment, major pathological response by BIPR, tumor response by investigator assessment, safety, pharmacokinetics, immunogenicity, and patient-reported outcomes. In addition, there are two Phase 2/3 studies (NCT05785767 and NCT05800015) exploring fianlimab + cemiplimab ± chemotherapy in first-line patients with metastatic NSCLC.

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P4.07D.04 Trofuse-019: A Phase 3 Study of Adjuvant Pembrolizumab with or without Sac-TMTfor Resectable Stage II-IIIB (N2) NSCLC

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Introduction: The phase 3 KEYNOTE-671 study demonstrated significantly improved clinical outcomes with neoadjuvant immunotherapy plus chemotherapy followed by surgery and adjuvant immunotherapy versus neoadjuvant chemotherapy alone followed by surgery in patients with resectable early-stage non-small-cell lung cancer (NSCLC). However, patients in both treatment arms in KEYNOTE-671 who did not achieve a pathological complete response (pCR) had worse outcomes. Additional treatment in the adjuvant setting may improve long-term outcomes in patients who do not achieve pCR following neoadjuvant immunotherapy plus chemotherapy followed by surgery and adjuvant immunotherapy. Trophoblast cell-surface antigen 2 (TROP2; cell-surface glycoprotein) is overexpressed in several cancers, including NSCLC. Sacituzumab tirumotecan (sac-TMT; formerly MK-2870/SKB264) is an antibody-drug conjugate composed of humanized anti-TROP2 monoclonal antibody, a hydrolytically cleavable linker, and the cytotoxic drug KL610023. In a phase 2 study, sac-TMT demonstrated encouraging antitumor activity and manageable toxicity in patients with advanced NSCLC. Here, we describe the phase 3 TroFuse-019 study (NCT06312137) evaluating adjuvant pembrolizumab with versus without sac-TMT in patients with resectable stage II-IIIB (N2) NSCLC who did not achieve pCR after neoadjuvant pembrolizumab and platinum-based doublet chemotherapy followed by surgery.

Methods: In this global, randomized, open-label, phase 3 study, patients will be enrolled into an initial neoadjuvant study period. Initial eligibility criteria include histologically confirmed stage II-IIIB (N2) NSCLC without EGFR mutations, ECOG PS 0 or 1, and ability to undergo surgery and neoadjuvant treatment with pembrolizumab plus platinum-doublet chemotherapy. Documented ALK gene rearrangements are not permitted (if ALK status unknown/undetermined, testing not required). Patients will receive 4 cycles of neoadjuvant therapy with pembrolizumab 200 mg Q3W and platinum-doublet chemotherapy and then undergo potentially curative resection. Approximately 780 patients who complete definitive surgery (with postoperative radiation therapy for R1 resection status as indicated), do not achieve pCR by local review, and are disease-free per radiologic assessment by blinded independent central review (BICR) will be randomized in the adjuvant study period. Eligible patients must also have a tumor tissue sample from the surgical resection for biomarker analysis and ECOG PS 0 or 1. Patients will be randomized 1:1 to receive either sac-TMT 4 mg/kg Q2W for 20 doses plus pembrolizumab 400 mg Q6W for 7 doses or pembrolizumab 400 mg Q6W as monotherapy for 7 doses. Randomization will be stratified by histology (squamous vs nonsquamous), PD-L1 tumor proportion score (<50% vs ≥50%), disease stage (stage II vs stage III), and TROP2 expression (no or low vs medium vs high vs unknown). Tumor imaging will be performed within 2 weeks before surgery, within 28 days before randomization in the adjuvant period, then Q12W after randomization. The primary endpoint is disease-free survival (time from randomization to any recurrence, occurrence of new primary NSCLC, or death) as assessed by BICR. Secondary endpoints include OS, distant metastasis-free survival (time from randomization to first documented distant metastasis by investigator review or death), disease-free survival by investigator review, lung cancer-specific survival (time from randomization to death due to lung cancer), safety, and patient-reported outcomes. Enrollment into this study will begin in April 2024.

Keywords: Antibody-drug conjugate (ADC), Topoisomerase I inhibitor, Adjuvant therapy

P4.07E EARLY-STAGE NON-SMALL CELL LUNG CANCER - DEVELOPMENTS IN SURGICAL PATHOLOGY AND MICROENVIRONMENT
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P4.07E.01 A Revised International Association for the Study of Lung Cancer Grading System: The Inclusion of Invasive Mucinous Adenocarcinomas

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Introduction: The International Association for the Study of Lung Cancer (IASLC) grading system doesn't include lung invasive mucinous adenocarcinoma (LIMA). However, we encounter mixed lung adenocarcinoma and LIMA in clinical work. Our study proposed to introduce the LIMA into the IASLC grading system, and aimed to measure the validity of its modification in lung invasive adenocarcinoma (ADC).

Methods: This retrospective study included 553 patients with lung invasive adenocarcinoma with or without LIMA components (stage I-III) from Shanghai Chest Hospital and 6962 patients in the SEER database. We introduced the LIMA and re-classified the IASLC grading system. The validity of the revised grading, derived from the training cohort, was measured in the validation cohort (the SEER database), using the concordance index (Harrell C-index), time-dependent receiver operating characteristic (ROC) curves and area under the curves (AUCs). Overall survival (OS) curves were estimated by a Kaplan-Meier method and log-rank test was performed to compare differences.

Results: The LIMA was classified as predominant tumor patterns in the IASLC grading system, and mucinous predominant tumors with no or less than 20% of high-grade patterns (solid, micro papillary, and/or complex glandular patterns) were classified as the Grade 2 (moderately differentiated, Table 1). The C-index and AUCs of the revised IASLC system were 0.754 and 0.729 in the training cohort and 0.716 and 0.682 in the validation cohort, respectively. Moreover, the revised grading showed a 5-year OS rate of 88.6% in Grade I group, 76.1% in Grade II group, 65.5% in Grade III group in the training cohort (P<0.001, Table 2). The revised grading also showed a promising performance in distinguishing patients in the validation cohort (5-year OS rate: 85.4% vs. 69.8% vs. 60.1%, P<0.001, Table 2).

Conclusions: The revised IASLC grading system was practical and prognostic for lung invasive adenocarcinoma with or without LIMA component, and the introduction of LIMA could improve its applicability.

Keywords: Lung Cancer, Mucinous Adenocarcinoma, Pathologic Grading

Table 1. The Revised Grading Scheme for Invasive Pulmonary Adenocarcinomas.

Grade	Differentiation	Patterns
1	Well-differentiated	Lepidic predominant with no or less than 20% of high-grade patterns
2	Moderately differentiated	Acinar or papillary or **mucinous** predominant with no or less than 20% of high-grade patterns
3	Poorly differentiated	Any tumor with 20% or more of high-grade patterns

Table 2. Performance Measurements of Revised Grading Scheme in Overall Survival.

Scheme	Training cohort				Validation cohort			
	C-index (95%CI)	AUC (95%CI)	5-year OS rate	P value	C-index (95%CI)	AUC (95%CI)	5-year OS rate	P value
Revised Grading	0.754(0.727-0.783)	0.729(0.696-0.754)		< 0.001	0.716(0.682-0.745)	0.682(0.656-0.711)		< 0.001
Grade 1			88.6%				85.4%	
Grade 2			76.1%				69.8%	
Grade 3			65.5%				60.1%	

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P4.07E.02 Genomic Profiling of Pre-invasive and Early-Stage Lung Adenocarcinoma Delineates Gene Signatures of Different Adenocarcinoma Subtypes

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Introduction: Adenocarcinoma represents the predominant type of lung cancer. The major non-mucinous subtypes are acinar, papillary, micropapillary, lepidic, and solid. The presence of solid, and micropapillary patterns is associated with a poor prognosis. Understanding the genomic landscape of preinvasive lung adenocarcinoma (LAD) and subtypes of early-stage invasive LAD might provide important insight and promote development of novel strategies for early intervention and adjuvant treatment. This study explored clinical features and genomic landscape of preinvasive LAD and different subtypes of early-stage invasive LAD.

Methods: Patients with non-small cell lung cancer were prospectively recruited at Taipei Veterans General Hospital from May 2021 to December 2022. The tumor tissues and paired peripheral blood specimens were sequenced using whole-exome sequencing (WES). De-identified data, including genomics, pathology findings, and patients' clinical features were reviewed. For WES analysis, a predefined pipeline was utilized for sequence quality control, alignment, and variant calling, which was conducted using GATK Mutect2, MuSE, VarScan, and Pindel. A mutation was annotated when identified by at least two callers.

Results: This study enrolled 180 patients, of whom 58 and 122 patients had stage 0 and stage I LAD, respectively. Patients with stage I LAD were older than those with stage 0 LAD (64.7 vs. 55.0 years, p<0.001). In patients with stage I LAD, there were more ever-smokers(p=0.013), and more tumors in peribronchial site (p=0.025) compared to stage 0 LAD. As for WES analysis, EGFR was the most common mutation among both groups(41% and 70% for stage 0 and stage I LAD, respectively). Patients with family history of lung cancer had lower tumor mutation burden (TMB) compared to those without(p=0.033). Stage I LAD had a significantly higher TMB compared to stage 0 LAD (p<0.001). TMB of minimally invasive adenocarcinoma (MIA) was higher than that of adenocarcinoma in situ (AIS)(p<0.001). TMB of MIA was lower than that of acinar-, and solid-predominant adenocarcinoma(p=0.0026, and 0.027, respectively). The TMB of micropapillary-predominant adenocarcinoma (MPA) was higher than that of AIS, and MIA(p<0.001, and p=0.0053, respectively). Tumors with spread through air space (STAS) exhibited a higher TMB than those without(p<0.001). The gain and loss proportion of copy number variation (CNV) were higher in stage I LAD compared to stage 0 LAD(both p<0.001). Significant differences in the gain and loss proportion of CNV among different adenocarcinoma subtypes (p<0.001) were also found. Tumors with STAS had higher gain and loss proportion of CNV compared to those without (both p<0.001). Oncogene pathways enrichment analysis for MPA demonstrated the main signaling pathways, including RTK-RAS, WNT, and NOTCH. The mutational enrichment analysis for MPA showed an enrichment of mutations in PCLO, ZNF831, TP53, and PLEKHO1, warranting further research.

Conclusions: The stage I LAD is characterized by a higher TMB, and more significant copy number variations compared to stage 0 LAD. These genetic differences are linked to clinical features, and specific functional morphologies of tumor cells. WES analysis revealed significant genomic disparities between stage 0 LAD and various subtypes of stage I invasive LAD, warranting further investigation into the underlying pathophysiology.

Keywords: non-small cell lung cancer, early-stage lung adenocarcinoma, whole-exome sequencing

NON-SMALL CELL LUNG CANCER; DEVELOPMENTS IN SURGICAL PATHOLOGY AND MICROENVIRONMENT
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P4.07E.03 Real-World Data on Early Lung Cancer in Never-Smokers and Light Smokers-Prevalence, Family History, and Molecular Alterations

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Introduction: The proportion of early-stage lung cancer patients who are never-smokers or have a history of light smoking is on the rise. This study aims to explore the prevalence of never-smokers and light smokers among patients undergoing surgical resection for early-stage lung cancer, along with their family history and the frequency and type of molecular alterations.

Methods: We analyzed data from the Initiative for Early Lung Cancer Research for Treatment (IELCART), a prospective multi-institutional cohort study initiated in 2016. This study included patients who underwent surgery for lung tumors measuring 30 mm or smaller. Our objective was to describe the frequencies of never-smoker patients and light smokers (≤ 20 pack-years), and to report their family history of lung cancer, as well as the distribution of molecular alterations. Additionally, we aimed to compare these distributions among different racial groups.

Results: In the prospective treatment cohort of 957 patients diagnosed with lung cancer, who underwent surgery for tumors measuring 30 mm or less in maximum diameter in the Initiative for Early Lung Cancer Research on Treatment (IELCART), 354 (37%) were never-smokers or had a smoking history of less than 20 pack-years.

Among the 354 patients, 65 (18.4%) reported a family history of lung cancer. Among these, 27 out of 65 patients (41.5%) had a father diagnosed, 33.8% had a mother diagnosed, and 26.2% had a sibling affected. For five out of 65 patients (7.7%), the specific family relationship was not specified.

Oncogenic driver mutation analysis was performed in 248 out of 354 patients (70.1%). Clinically actionable variants were identified in 159 (64.1%) out of 248 patients Among them, 108 out of 248 patients (43.5%) showed EGFR gene mutations, including 82 (75.9%) patients harboring classical mutations such as deletions of exon 19 (39 patients) and the L858R mutation in exon 21 (43 patients). Additionally, 24 (9.7%) presented with a KRAS G12C mutation. Furthermore, there were 12 (4.8%) with MET exon 14 deletions, five patients (2%) with targetable ROS1 mutations, four (1.6%) with RET fusions, three (1.2%) with ALK fusion and three (1.2%) and three with a BRAF V600E.

Our cohort comprises 15.5% patients self-identifying as Asian, 18.4% as Afro-American, 55.9% as White, and 10.2% identifying as other races. The distribution of oncogenic driver mutations varied significantly based on patient race, with a notably significantly higher prevalence of EGFR mutations observed among Asian patients (28/42 patients, 66%) (Fisher test, p-value <0.01).

Conclusions: Among 957 patients with resected lung cancer ≤30mm, 37% were never- or light-smokers. 18.4% had a family history of lung cancer. EGFR mutations were prominent (43.5%), with a higher prevalence of 66% observed among Asian patients. This rate remains below the 85% reported in a Taiwanese cohort dominated by never-smoking patients, mostly females, with early-stage NSCLC, emphasizing the racial heterogeneity of our cohort. Our results underline that many never- or light smokers with lung cancer harbor driver alterations, suggesting an alternative model of carcinogenesis. These patients are not targeted by traditional screening programs, necessitating further studies on screening in these populations.

Keywords: Never-smoker and light smokers, Family history of lung cancer, Molecular alterations

P4.07E.04 Pathological Grading of Early-Stage Lung Cancers Through CT-to-PET Translation and Co-Learning Model

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Introduction: The wide application of chest CT screening is increasing the detection of early-stage lung cancer. Early-stage lung cancers vary in morphology, progression, and prognosis depending on different stages. However, CT screening has limits, such as high false-positive rates and overdiagnosis. Positron emission tomography (PET) examination can help stratify the pathological subtype of nodules, but it is expensive, radioactive, and technically demanding. We propose a new methodology that may accomplish pathological grading for patients with lung cancer by producing PET pictures and the accompanying metabolic characteristics with CT images.

Methods: We have 642 individuals who had preoperative chest CT scans, PET/CT examinations, and matching nodules (≤30 mm and ≥4 mm) with surgically proven definitive pathology, with a 1:2 distribution between the train cohort (cohort A) and the validation cohort (cohort B). Additionally, we proposed a generative adversarial networks-based image-to-image translation model to achieve CT-to-PET translation (CPT) and predict tumor metabolic characteristics. Thus, to accomplish lung cancer pathological grading, we integrate the metabolic features and the CT and PET pictures into the multi-modal co-learning model.

Results: The synthetic images and real target images in the CPT model show a low mean square error (MSE = 0.015, p<0.01) and a high similarity structural index measure (SSIM = 0.956, p<0.01). Furthermore, we evaluated and computed the metabolic parameters, including SUVmax, using synthetic PET. The correlation plot shows a strong connection (r = 0.79) between the projected SUVmax and the actual data. And the evaluated SUVmax achieved an AUC of 0.658 in cohort A, performed similar efficacy with the one using real SUVmax in cohort A (AUC:0.660), and evaluated SUVmax in cohort B (AUC:0.654) (see Figure1.a-c). Based on the CPT model, we developed a multimodal co-learning model for lung cancer pathological grading. The proposed model using CT, synthetic PET, and evaluated SUVmax achieve an AUC of 0.942 ([95%CI 0.936-0.952], p< 0.0001), performed similar efficacy with the one using CT, real PET, and real SUVmax (0.941 [95%CI 0.939-0.9444], p< 0.0001), better than the one using only CT (0.929 [95%CI 0.924-0.930]) and the one using only PET (0.853[95%CI 0.850-0.869])(ROC curves see Figure1.d).

Conclusions: By expanding the capabilities of CT scans, this model broadens the boundaries of CT images, providing a more accurate, economical, and noninvasive approach for improving early detection and providing appropriate treatment approaches.

Keywords: Early-stage lung cancer, Pathological grading, Generative adversarial network

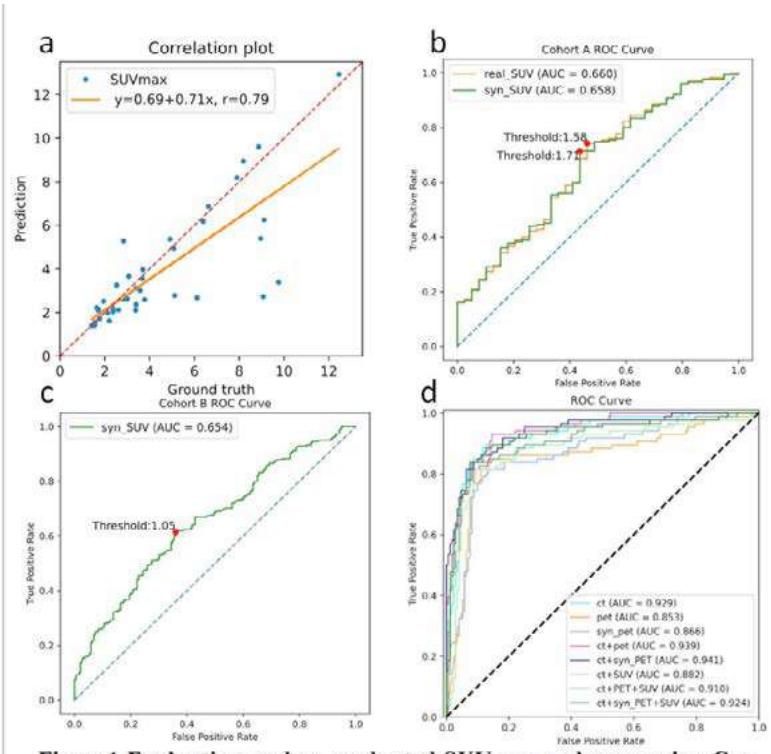

Figure1.Evaluating real vs. evaluated SUVmax and comparing Co-learning pathological grading models.
(a) Correlation plot of predicted SUVmax in CPT model;(b. c) Classification result using SUVmax in Cohort A and Cohort B;(d) ROC curves and AUC values generated by different modality of co-learning pathological grading mode.

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P4.07E.05 Insights from Molecular Profiling after Second Lung Surgeries in Early-Stage NSCLC - Recurrence or New Primary Tumor?

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Introduction: In patients with early-stage non-small-cell lung cancer (NSCLC), surgery aims to be curative; however, local recurrence may occur, posing challenges in distinguishing between a new primary tumor and an intrapulmonary metastasis. This study aims to investigate the role of genomic profiles of tumors from patients who underwent curative surgery twice.

Methods: We utilized data from a prospective multi-institutional cohort study, the Initiative for Early Lung Cancer Research for Treatment (IELCART), and included patients treated twice surgically with curative intent and subjected to genomic testing between 2014 and 2022. Next-generation sequencing (NGS), histopathological characteristics, demographics and outcomes of patients were collected. NGS profiles were compared and correlated with outcomes.

Results: 30 patients (17 females) underwent surgery after previous resected NSCLC with pathological and genetic analyses. The majority were white (77%), current or former smokers (90%) and had median age of 68.6 years. Mean time between the two procedures was 27 months (SD 21). None had germline mutations.

For their first surgery, 34 adenocarcinomas were resected (4 patients had 2 distinct adenocarcinomas). All patients had stage I NSCLC and none received adjuvant treatment. The mean tumor size was 1.72 cm (SD 0.84). The most frequently mutated genes were KRAS (56%), TP53 (18%), and EGFR (15%). For the 4 patients with 2 separate NSCLC, NGS was discordant in 3 cases.

For the second surgery, 33 adenocarcinomas were resected (3 patients had 2 distinct adenocarcinomas). 7 patients underwent resection in the same lobe and 23 in a different lobe. The mean tumor size was 1.75 cm (SD 0.97). 16/30 patients presented a concordant NGS result between the first and second surgeries. 4 patients received adjuvant chemotherapy.

For patients re-resected in the same lobe, NGS profiles were similar to the first in 6/7 patients. 2 patients subsequently developed a third lung tumor in another lobe, with the same NGS profile (KRAS in both cases).

For patients re-resected on a different lobe, NGS was similar to the first tumor for 10/23 and discordant in 13/23. 10 patients developed a third lung tumor in another lobe, and 2 patients developed distant metastasis.

The localization of the second cancer showed no significant correlation with NGS similarity (exact Fisher test, p=0.086), however with a trend of higher NGS concordance (86% versus 43%) among patients who underwent surgeries in similar lobes.

The size of the initial tumor demonstrated a significant correlation with a concordant NGS profile identified in the tumor from the second surgery (Welch Two Sample t-test, p=<0.05).

Post-surgical outcomes were similar between patients with NGS concordance and discordance (recurrence: 44% vs 50%).

Conclusions: In a cohort of 30 patients with early-stage NSCLC undergoing sequential surgeries, NGS revealed concordance within the same lobe but discrepancies across lobes. Tumor size correlated with NGS concordance, suggesting potential in distinguishing a new primary tumor from intrapulmonary metastasis. Post-surgery outcomes showed no significant difference based on NGS concordance, and the optimal integration of clinical, pathological, radiological, and molecular features for differentiation remains unclear. Future NGS studies may help evaluate its predictive role.

Keywords: Multiple primary lung cancers, Intrapulmonary metastasis, Genetics

P4.07E.06 Distinct Genomic and Immune Microenvironment Features of Solid or Micropapillary Predominant Subtype in Stage I Lung Adenocarcinomas

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Introduction: Lung adenocarcinomas (LUAD) exhibit histological heterogeneity among various pathology patterns. Numerous studies have indicated that the solid or micropapillary predominant subtypes (S/MP+) are associated with unfavorable prognoses in LUAD patients. However, limited research has specifically focused on the S/MP+ subtype in stage I LUAD, and the molecular factors contributing to malignant potential and tumor immune microenvironment in this high-risk subgroup remain poorly understood.

Methods: In this study, we collected clinical information and survival data from 2382 patients diagnosed as stage I LUAD. Patients are defined as S/MP+ if the total proportion of solid and micropapillary subtypes exceeds any other subtypes. To further explore the genetic signatures of S/MP+ pattern, whole exome sequencing and RNA sequencing were performed on another 36 patients with sufficient tissue samples. Multiple immunofluorescence staining (MAP) for PD-1, PD-L1, CD3, CD8, and panCK was also performed to investigate the tumor immune microenvironment. Immune cell infiltration was assessed using Cibersort, Xcell, and single-sample gene set enrichment analysis (ssGSEA).

Results: We found that S/MP+ patients showed significantly poorer overall survival (HR: 0.24 [95% CI: 0.13-0.44], P<0.001) compared to those grouped as S/MP-. This difference remained significant after adjusting for covariates such as gender, smoke, surgery type and adjuvant chemotherapy (HR: 0.22 [95% CI: 0.13-0.44], P < 0.001). In 36 LUAD cases with multi-omics data, 47.2% (N=17) were classified as solid or micropapillary predominant (S/MP+). We found significant differences in driver mutation profiles and immune characteristics between S/MP+ and S/MP- subtypes. S/MP- patients had a significantly higher prevalence of EGFR activating mutations, while S/MP+ subtype showed more RAS(G12X/13X/Q61X) and MAPK pathway mutations, higher tumor mutation burden (TMB) (median, 2.71 mut/MB vs 0.89 mut/MB), tumor neoantigen burden (TNB), and chromosomal instability (P<0.05). Signature 4, a smoking-related signature, was also significantly enriched in S/MP+ patients, suggesting a potential link between high TMB and smoking in this subtype. In total, we identified 1284 differentially expressed genes (DEGs) through RNA sequencing, including 715 upregulated genes and 569 downregulated genes in S/MP+ group. The biological processes of most upregulated DEGs were associated with chromosome organization, cell division and nuclear division. The immune cell infiltrates were comparable between the two groups, but S/MP+ patients exhibited higher tumor proliferation rates, stromal remodeling, and epithelial-mesenchymal transition features (P<0.05). Additionally, S/MP+ patients had significantly higher numbers of cancer-associated fibroblasts (CAF), NK cells, M1 and M2 macrophages, while CD4+ immune cell count was lower (P<0.05).

Conclusions: Our findings suggest that the S/MP+ histologic subtype demonstrates distinct genomic and immune characteristics compared to the S/MP- patients, indicating a worse prognosis in patients with surgically resected stage I LUAD. These findings contribute to defining prognostic subgroups and identifying specific LUAD treatment population that may benefit from evolving therapeutic strategies.

Keywords: Stage I NSCLC, Biomarkers, Immune microenvironment

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P4.07E.07 Spatial Memory B Cells Activation by CXCL13+ Th Cells via the MIF(CD74-CXCR4) Axis may Improve Immunotherapy Efficacy in HER2 Mutant NSCLC

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Introduction: The clinical benefits and underlying mechanism of neoadjuvant PD-1 blockade plus chemotherapy (nICT) or Trastuzumab Deruxtecan (nT-Dxd) remain unclear for HER2-mutant non-small cell lung cancer (NSCLC).

Methods: We reported the clinical results of nICT or nT-Dxd in resectable NSCLC patients with HER2 mutation, including objective response rate (ORR), major pathologic response (MPR) and complete pathologic response (PCR) rate. We combined spatial transcriptomics (ST) with single-cell RNA (scRNA) sequencing and multiplexed immunofluorescence (mIHC) of HER2-mutant NSCLC after nICT or nT-Dxd treatment to identify the specific tumor microenvironment (TME) factors related to treatment efficacy. Lasso regression was performed to construct a prognostic risk model and validated by external cohort in TCGA.

Results: Overall, 14 patients treated with nICT and 2 with nT-Dxd were enrolled. The ORR for nICT and nT-Dxd group were both 50.0%. Fifteen out of sixteen patients underwent a complete resection. Among them, 42.9% (6/14) of patients in nICT group and 0% (0/2) in nT-Dxd group achieved MPR, while the PCR rate in patients treated with nICT was 28.6% (4/14). Furthermore, we performed combined analysis of ST (n=5) and scRNA (n=6) data and revealed the enrichment of CD27+ memory B cells (Bm) in tumors with better response to nICT, which is characterized by increased immunoglobulin production and antigen presentation activity. Spatial analysis demonstrated a phenomenon of mutually exclusive distribution between Bm and tumor cells. Then, we dissected the ligand-receptor networks between T and B cells to elucidate the Bm cell activation process; that is, CXCL13+ T helper (Th) cells activate Bm cells via MIF (CD74-CXCR4) crosstalk, which subsequently stimulate the secretion of Immunoglobulin (Ig) G and A, thereby enhancing the antitumor immune response. CXCL13+ Th cells in this process show an elevated ability of CXCL13 production and MHC II binding. A predictive model was developed based on this crosstalk genes, which was associated with favorable outcome. Additionally, the nT-Dxd-treated patient displays a paradoxical TME characterized by significant infiltration of both effector and suppressive immune cells. Immune checkpoint genes are upregulated in the boundary of the tumor.

Conclusions: Our findings demonstrate the potential feasibility of nICT or nT-Dxd for resectable NSCLC with HER2 mutation. Bm cells may serve as a predictor biomarker for favorable outcome in HER2-mutant NSCLC treated with nICT. Furthermore, we have uncovered a novel mechanism of Bm cell activation and provided a fresh insight into the nT-Dxd-treated TME.

Keywords: Neoadjuvant, HER2 mutant non-small cell lung cancer, Single cell and spatial transcriptomics

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P4.07E.08 Single-Cell TCR Barcoding and RNA Sequencing Illuminate Distinct Tumor-Draining Lymph Node T Cell Responses to Neoadjuvant PD-1 Blockade

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Introduction: Leveraging insights from Phase III trials on the efficacy of PD-1 targeted immune checkpoint inhibitors (ICIs) in early-stage NSCLC, the precise mechanisms driving primary tumor responses remain elusive. In this study, we apply advanced machine learning algorithms to analyze single-cell sequencing data of TCR-barcoded CD8+ T cells, aiming to unravel the tissue and treatment-specific clonal dynamics within our "live T cell" biobank from patients receiving neoadjuvant ICIs. This approach illuminates the pivotal role of tumor-draining lymph node-derived T cells in mediating the tumor's pathologic response to therapy.

Methods: At Weill Cornell Medicine, we profiled four early-stage NSCLC patients undergoing surgical resection, with three receiving anti-PD-1 and platinum-based chemotherapy. Treatment outcomes varied: one non-responder (90% viable tumor), one partial responder (30% viable tumor), and one complete responder. We analyzed four tumors and five lymph nodes from these patients, utilizing pathological evaluation, flow cytometry, and scRNA/TCR-seq of CD3+CD8+ T cells. Employing single-cell TCR barcoding and RNA sequencing, we traced T cell responses to PD-1 blockade. Through machine learning, we elucidated the impact of neoadjuvant anti-PD-1 therapy combined with chemotherapy on T cell dynamics.

Results: In our analysis of 19,059 CD8+ T cells from nine tissue samples, we combined single-cell TCR CDR3 amino acid sequencing with the transcriptional profiling of 24,500 genes per cell. T cells from tumor-draining lymph nodes (tdLN) that were clonally related to the tumor predominantly resided in quiescent clusters, characterized by high expression levels of SELL, TCF7, and CCR7. Conversely, tumor-associated T cells from the tumor were localized in clusters indicative of a more differentiated, activated, and exhausted state, marked by the expression of effector-like markers and inhibitory receptors, such as TOX and PDCD1. By applying a mix of supervised and unsupervised machine learning techniques, we identified a transcriptional signature associated with a favorable primary tumor response to PD-1 blockade in T cells within the tdLN ($p < 0.05$). This signature was further validated in an immunocompetent murine model, demonstrating an initial tumor response to neoadjuvant PD-1 treatment ($p < 0.05$).

Conclusions: Employing single-cell TCR barcoding for comprehensive multi-tissue deep clonal tracking in conjunction with single-cell RNA sequencing, we reveal that T cells originating from draining lymph nodes exhibit a unique response to PD-1 blockade, potentially impacting the primary tumor's response to neoadjuvant immune checkpoint inhibitors (ICI).

Keywords: TCR Clonal Tracking, Machine Learning/AI, Early Stage NSCLC

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P4.07E.00 The Impact of PD-1/PD-L1 Inhibitor on GGN Lesion: An Exploratory and Retrospective Study

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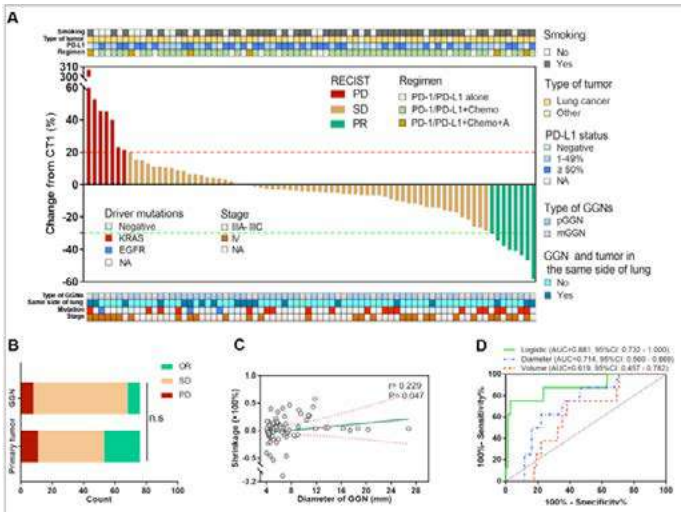
Introduction: Ground-glass nodules (GGNs) are common early signs of lung cancer in CT imaging. Immunotherapy improved the prognosis for patients with advanced lung cancer. However, clinical evidence for the effectiveness of immunotherapy in GGNs is insufficient, especially for cases presenting with GGNs as multiple primary lung cancers.

Methods: Patients receiving PD-1/PD-L1 inhibitors for primary malignant tumors coexisting with GGNs at the Second Xiangya Hospital from January 1, 2016, to June 30, 2021 were included. The inclusion criteria are as follows: 1. Received PD-1/PD-L1 inhibitors for ≥ 2 cycles; 2. Underwent thin-slice (1 mm) chest CT before immunotherapy; 3. Pre-immunotherapy CT suggested the presence of GGNs measuring 4-30 mm in maximum diameter; 4. Underwent CT imaging within 1 month after completing PD-1/PD-L1 inhibitor treatment. The last CT images before (CT1) and after (CT2) PD-1/PD-L1 inhibitor treatment were collected to evaluate changes in GGNs.

Results: A total of 76 GGNs from 39 patients were included. Although almost all GGNs exhibited changes after immunotherapy, there were no significant changes in their maximum diameter, maximum solid proportion, volume, density, or the maximum of the solid component. After PD-1/PD-L1 inhibitor treatment, 74.6% of GGNs classified as Lung-RADS 2 or 3 remained unchanged, while 80% of GGNs classified as Lung-RADS 4 were downgraded to category 2 or 3. When evaluating the efficacy of immunotherapy for GGNs, the objective response rate was 11.8%, with 9 GGNs achieving partial response, 59 achieving stable disease, and 8 achieving progressive disease (Figure 1). The ORR for primary malignant tumors was 36.8%, and the efficacy of 44.7% of GGNs was consistent with that of the primary tumors. The maximum diameter and volume of GGNs were positively correlated with the efficacy of immunotherapy ($p<0.05$), and GGNs ≥8 mm could benefit from PD-1/PD-L1 inhibitor. GGN density ($p=0.012$) and volume ($p=0.039$) were independent predictors of the efficacy of PD-1/PD-L1 inhibitor treatment, with GGNs having a volume ≥70 mm^3 achieving more significant efficacy.

Conclusions: PD-1/PD-L1 inhibitors show limited activity on GGNs in patients with malignant tumors. GGNs with a maximum diameter ≥8 mm and with a volume ≥70 mm^3 may potentially benefit from immunotherapy.



A, Overview of clinicopathological charteristics and clinical outcome of GGNs treated with PD-1/PD-L1 inhibitor.
B, The efficacy of PD-1/PD-L1 inhibitor in GGNs and primary malignant tumor.
C, Correlation between the maximum diameter of GGNs before immunotherapy and shrinkage of GGNs after immunotherapy. Spearman correlation was used to measure the relevance.
D, ROC curve based on the volume and maximum diameter of GGNs before immunotherapy and Logistic regression model of multiple clinicopathological factors (volume and maximum diameter and driver mutation).
OR, objective response = complete response and partial response; SD, stable disease; PD, pregression disease; NA, no assess.

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P4.07F.01 Real World Characteristics and Distant Metastasis Free Survival of Patients with Early NSCLC Treated with Chemoimmunotherapy

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Introduction: Chemoimmunotherapy (CIO) is an established treatment option for resectable early non-small cell lung cancer (eNSCLC) in both the adjuvant and neoadjuvant setting. However, little is known about its real world (rw) utilization. We described adjuvant and neoadjuvant CIO use and rw outcomes in eNSCLC patients.

Methods: Patients with stage II-IIIA, surgically resected NSCLC diagnosed 1/1/2020-7/31/2023 were selected from the Flatiron Health nationwide electronic health record (EHR)-derived, de-identified database, and categorized based on neoadjuvant (CIO prior to surgery) or adjuvant (CIO within 12 weeks post surgery) therapy receipt. Data cut off was 1/31/2024. Clinical characteristics were extracted via machine learning models and compared with chi-square and Wilcox tests. Rw distant metastasis free survival (DMFS), defined as time to distant metastasis or death from first neoadjuvant or adjuvant chemoimmunotherapy, was estimated for both cohorts by the Kaplan Meier estimator. Hazard ratios (HRs) within treatment groups were evaluated using Cox models adjusted for age, race/ethnicity, gender, practice type, smoking status, stage, PD-L1 status and histology.

Results: Among 256,269 patients diagnosed with NSCLC, 4771 patients with stage II-IIIA NSCLC underwent surgical resection in the relevant time period, of which 1008 received CIO in the neoadjuvant or adjuvant setting. Baseline characteristics are shown in the Table; notably biomarker testing rates were lower prior to neoadjuvant than adjuvant CIO. CIO was uncommon among resected stage II-IIIA patients in 2022, but increased in 2023 from 9.0% to 17.0% and 18.9% to 23.9% for neoadjuvant and adjuvant CIO, respectively. DMFS at 18 months for neoadjuvant patients was 77.6% (95% CI, 70.0%-86.2%), compared to 83.2% (95% CI, 79.7%-86.9%) for adjuvant patients. DMFS did not differ by clinical covariates, except for non-squamous versus squamous histology in neoadjuvant patients (HR, 2.96; 95% CI, 1.13-7.73) and stage IIIA versus stage II in adjuvant patients (HR, 2.62; 95% CI 1.58-4.37). Both neoadjuvant (n=19) and adjuvant (n=57) patients who developed distant disease had similar distribution of brain, bone and liver metastasis.

Conclusions: CIO use was associated with favorable rwDMFS, in line with clinical trial outcomes. While rw CIO usage increased in 2022 and 2023, fewer than half of surgically resected patients received CIO at end of study period, and biomarker testing was inconsistently done particularly in the neoadjuvant setting. Further study of factors influencing clinical adoption of CIO and biomarker testing in eNSCLC is needed.

Keywords: eNSCLC, Chemoimmunotherapy, Real world

Table 1: Baseline Characteristics

	Neoadjuvant Cohort (n = 298)	Adjuvant Cohort (n = 710)	*P* value
Age (years), median (IQR)	67.0 (62.0, 72.8)	68.0 (63.0, 74.0)	0.060
Gender, n (%)			0.3
Female	142 (47.7)	363 (51.1)	
Male	156 (52.3)	347 (48.9)	
History of Smoking, n (%)	272 (91.3)	663 (93.4)	0.3
Follow-up time from initial diagnosis (months), median (IQR)	11.2 (8.4-15.8)	15.2 (10.3-21.4)	<0.001
Time from initial diagnosis to treatment (months), median (IQR)	1.3 (0.9-1.8)	2.7 (1.9-3.6)	<0.001
Stage, n (%)			0.001
Stage II	137 (46.0)	406 (57.2)	
Stage IIIA	161 (54.0)	304 (42.8)	
Histology, n (%)			0.002
Squamous	111 (37.3)	186 (26.2)	
Non-squamous	184 (61.7)	517 (72.8)	
Unknown	3 (1.0)	7 (1.0)	
Practice Type, n (%)			0.2
Academic	70 (23.5)	138 (19.4)	
Community	228 (76.5)	572 (80.6)	
Biomarker Testing prior to CIO receipt, n (%)			
EGFR	148 (49.7)	483 (68.0)	<0.001
ALK	149 (50.0)	429 (60.4)	<0.003
PD-L1	153 (51.3)	515 (72.5)	<0.001
PD-L1 Status, n (%)			<0.001
<1%	43 (14.4)	74 (10.4)	
1-49%	64 (21.5)	256 (36.0)	
≥50%	46 (15.4)	185 (26.1)	
Not Tested/Unknown	145 (48.7)	195 (27.5)	

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P4.07F.02 Invasiveness Diagnosis by Intraoperative Frozen Section Guides Resection Strategy Amomg ≤2cm Non-Small-Cell Lung Cancer

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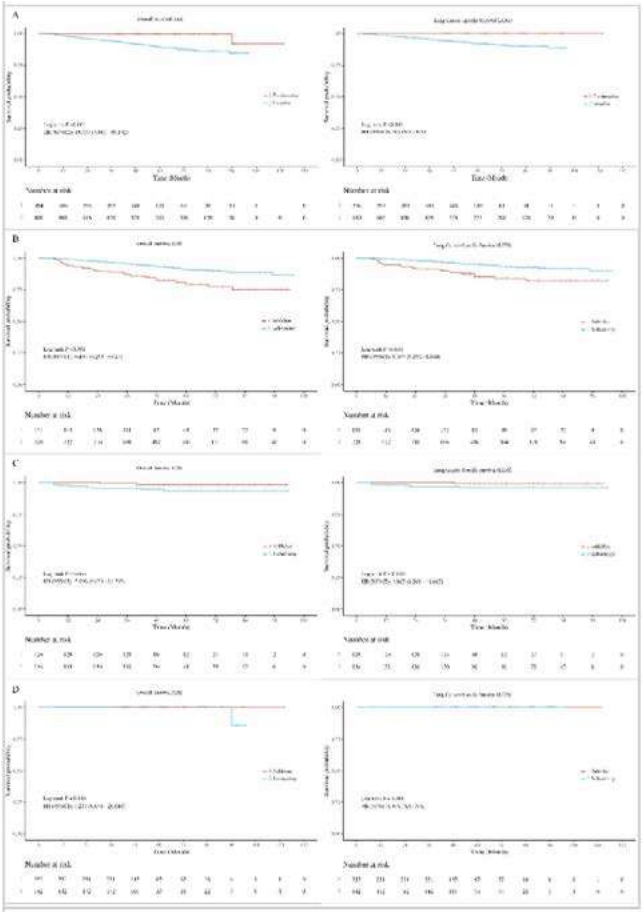
Introduction: The JCOG (Japan Clinical Oncology Group) studies, including JCOG0804, JCOG1211, and JCOG0802, suggest a more favorable long-term survival trend for ≤2cm non-small-cell lung cancer (NSCLC) with sublobar resection, despite increased risks of recurrence and metastasis. This implies that not all nodules within this size range may be suitable for sublobar resection. Therefore, this study aims to determine if intraoperative frozen section diagnosis can accurately identify candidates benefiting more from lobectomy over sublobar resection among individuals meeting JCOG study criteria.

Methods: This retrospective study involved patients diagnosed with NSCLC who underwent surgical resection at the Department of Thoracic Surgery, First Affiliated Hospital of Guangzhou Medical University, between September 2009 and January 2019. Patient data, including preoperative CT images, surgical procedures, frozen section, and follow-up information, were collected from the hospital's electronic medical record system. Kaplan-Meier survival analysis was utilized to compare overall survival (OS) and lung cancer-specific survival (LCSS) between patients with invasive and pre-invasive NSCLC. Meanwhile, based on frozen section diagnosis, OS and LCSS were evaluated in patients undergoing sublobar resection versus lobectomy.

Results: A total of 1,539 patients who underwent surgical resection for NSCLC were included in this study, with a median follow-up time of 54 months. The frozen section diagnosis and the final pathological diagnosis were consistent for both pre-invasive NSCLC and invasive NSCLC, with a concordance rate of 80.90%. Among patients with ≤2cm NSCLC, those whose frozen section indicated invasive lung cancer exhibited inferior overall survival (OS) (HR=19.737, P<0.001) compared to patients with pre-invasive NSCLC, and the patients diagnosed with pre-invasive NSCLC, the LCSS rate is 100%. Among patients with intraoperative frozen section indicated pre-invasive NSCLC, there were no lung cancer-related deaths observed in either sublobar resection or lobectomy group. Among patients with intraoperative frozen section indicated invasive NSCLC, those who underwent lobectomy demonstrated better LCSS compared to those who underwent sublobar resection (HR=0.378, P<0.001). When the invasion status could not be determined by intraoperative frozen section, there was no significant difference in survival between sublobar resection and lobectomy (OS: HR=3.906, P=0.063; LCSS: HR=4.867, P=0.11).

Conclusions: In summary, intraoperative frozen section significantly influences the choice of sublobar resection for ≤2cm NSCLC. Lobectomy demonstrates superior survival for patients with intraoperative frozen section indicating invasive NSCLC, while both sublobar resection and lobectomy show favorable outcomes for those with pre-invasive NSCLC.

Keywords: Intraoperative Frozen Section, sublobar resection, invasion status



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P4.07F.03 A Cost-Effective Tumor-Informed ctDNA Analysis for MRD Detection in Resected NSCLC With Common Driver Genes

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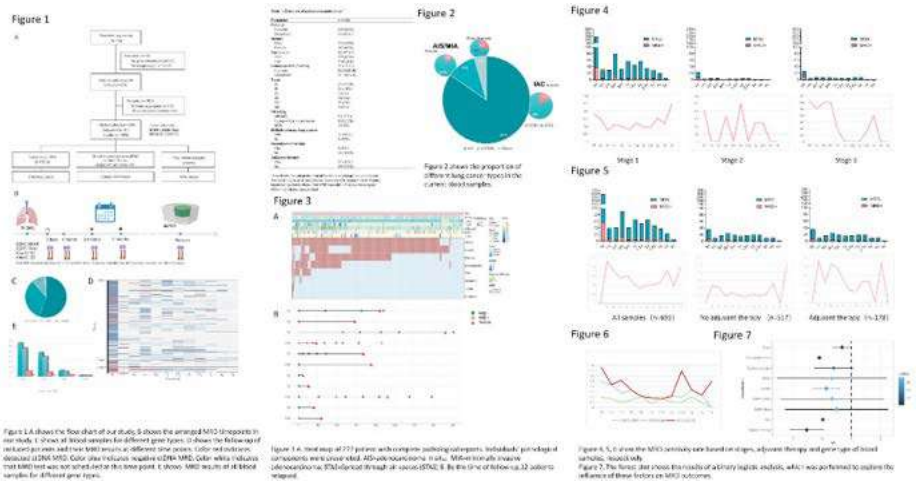
Introduction: The potential of Circulating Tumor DNA (ctDNA) for Molecular Residual Disease (MRD) detection in predicting relapse among resected Non-Small Cell Lung Cancer (NSCLC) patients is promising. Digital droplet PCR (ddPCR) has been shown to be highly specific in detecting individual mutations in cell-free DNA (cfDNA). This study aims to identify specific driver gene mutations for MRD monitoring using ddPCR, focusing on epidermal growth factor receptor (EGFR) or Kirsten rat sarcoma viral oncogene homologue (KRAS) mutations in ctDNA from resected NSCLC patients.

Methods: This is an ongoing prospective observational study that enrolled patients with stage I to III resected NSCLC. The study only included patients who were confirmed to have EGFR or KRAS G12 C/D mutations, which were pathologically confirmed through whole exome sequencing (WES) or PCR. Plasma samples were collected from the patients at regular intervals, every 3 or 6 months postoperatively depending on patients' MRD results. A single point assay according to patients' specific gene mutation (EGFR or KRAS) was used to detect ctDNA by ddPCR. The results of MRD analysis in each blood sample were evaluated along with possible influencing factors such as patient age, type of lung cancer, type of gene mutation, postoperative time, and TNM stage.

Results: As of Jan 2024, 695 blood samples were included in our MRD analysis. A total of 300 NSCLC patients were enrolled; 54% of the patients had EGFR L858R mutation, 34% had the EGFR 19del mutation, 10% had KRAS mutation, and the remaining 1% had more than two of the aforementioned mutations. The majority of the participants were diagnosed with Stage IA NSCLC (72%), while 14% had Stage IB, 7% had Stage II, and 7% had Stage III. The follow-up time lasted 3 years, with a median time of 40 months, and 12 patients relapsed. Subgroup analyses of MRD positivity rates were conducted based on different MRD time points, TNM stage, adjuvant therapy and gene type.

Conclusions: Our updated findings from different subgroup analyses the feasibility of utilizing ddPCR technology for evaluating ctDNA MRD in patients with resected NSCLC harboring common mutations such as EGFR L858R, EGFR 19del, KRAS G12C, or KRAS G12D. Considering the high prevalence of the aforementioned mutations within the Chinese population, our targeted, tumor-informed strategy that focuses on specific mutations could offer a cost-effective tool for MRD monitoring. Further research is needed to validate its effectiveness and practical utility in clinical settings.

Keywords: MRD, NSCLC, ctDNA



P4.07F EARLY-STAGE NON-SMALL CELL LUNG CANCER - PROFILING FOR RECURRENCE
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P4.07F.04 Ground Glass Nodules with Scattered or Eccentric Island-Shaped Consolidations may have Poor Outcomes

M. Li, J. Xi, M. Feng, Q. Wang, Zhongshan Hospital Fudan University, Shanghai/CN

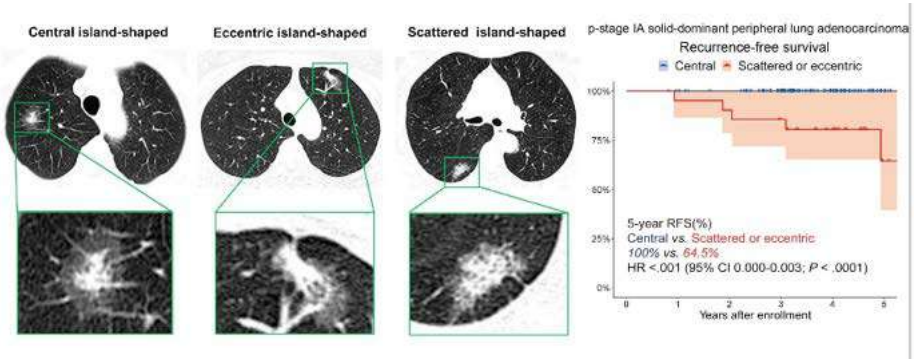
Introduction: To explore the effect of scattered or eccentric shaped types of ground glass opacity (GGO) on outcomes of patients with solid-dominant peripheral lung adenocarcinoma.

Methods: We evaluated patients with solid-dominant peripheral lung adenocarcinoma, who underwent radical surgery at Zhongshan Hospital, Fudan University, between January 2013 and December 2015. Morphologically heterogeneous solid-dominant lung adenocarcinoma in imaging findings was based on the last preoperative computed tomography (CT) scans. Endpoints were recurrence-free survival (RFS) and overall survival (OS). Kaplan-Meier analysis and the log-rank test were used to estimate survival differences. Impact factors were assessed by univariable logistic regression analysis.

Results: We retrospectively collected data from 200 patients, including 170 patients with central island-shaped CT imaging, 18 patients with scattered shaped CT imaging, and 12 patients with eccentric shaped CT imaging. Eleven patients experienced recurrence or metastases. Kaplan-Meier survival curves showed significant survival differences between the central island-shaped type and scattered shaped or eccentric shaped type for OS (c-stage IA: 5-year OS: 100% vs. 92.1%; HR = 0.019, p = 0.0025; p-stage IA: 100% vs. 95.2%; HR = 0.146, p = 0.1139) and RFS (c-stage IA: 5-year RFS: 100% vs. 59.7%; HR = 0.001, p < 0.0001; p-stage IA: 100% vs. 64.5%; HR < 0.001, p < 0.0001). Univariable logistic regression analysis showed that scattered and eccentric shaped types were related to poor outcomes (p < 0.012, odds ratio = 18.8).

Conclusions: Relative spatial position of GGO and solid components may affect patient outcomes. Patients with scattered or eccentric shaped GGO may have a poor prognosis.

Keywords: ground glass opacity, scattered or eccentric island-shaped, prognosis



P4.07F EARLY-STAGE NON-SMALL CELL LUNG CANCER - PROFILING FOR RECURRENCE
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P4.07F.05 Low OLFM1/BMP6 Expression Identifies High-Risk Stage I Non-Squamous Non-Small Cell Lung Cancer after Pulmonary Resection

K. Suda[1], Y. Yoshida[2], H. Sato[3], A. Hamada[1], M. Yotsukura[2], K. Shiraishi[4], R. Hamamoto[4], Y. Chiba[5], T. Kohno[4], Y. Yatabe[2], S-I. Watanabe[2], Y. Tsutani[1], T. Mitsudomi[1], [1]Kindai University Faculty of Medicine, Osaka-Sayama/JP, [2]National Cancer Center Hospital, Chuo-ku, Tokyo/JP, [3]Yamagata University Well-Being Institute, Yamagata/JP, [4]National Cancer Center Research Institute, Chuo-ku, Tokyo/JP, [5]Kindai University Hospital, Osaka-Sayama/JP

Introduction: Pathological stage I (pStage I) non-small cell lung cancer (NSCLC) is the representative of lung cancers with good prognosis; however, it is also true that a certain number of pStage I NSCLC patients experience disease recurrence after surgery. Identification of poor prognostic markers in pStage I NSCLC may facilitate further personalized perioperative treatment by expanding the candidates for novel adjuvant treatment. Because NSCLC patients with ground-glass opacity have excellent survival outcomes, in this study, we explored prognostic biomarkers focusing on pure solid non-squamous NSCLC.

Methods: RNA sequence was performed using frozen tumor specimens obtained from 33 non-squamous NSCLC patients who experienced disease recurrence (recurrence group) and 33 counterparts (control group) who were extracted from patients without disease recurrence for at least 5 years using propensity score matching (Cohort 1). The prognostic role of candidate genes (either expression or mutation) was evaluated using an independent Cohort 2a (N=125). Furthermore, survival analysis was performed in patients with EGFR mutation after adding an independent Cohort 2b (N=24).

Results: We identified 101 differently expressed genes between recurrence group and control group in Cohort 1. In addition, we found 5 genes of which mutation frequencies were different between these two groups. In the validation analysis using Cohort 2a, we found that lower expression of 6 genes (BMP6, KCNK3, NFASC, OLFM1, PEG3, and TNXB) was associated with disease recurrence. Prognostic impact of these 6 genes were also confirmed using TCGA lung adenocarcinoma database. Multivariable proportional hazard analysis further revealed that lower expression of BMP6 and OLFM1 were independent prognostic factors, and expression status of these two genes was significantly associated with recurrence-free survival in Cohort 2a (Figure 1A). In addition, we observed that the expression status of these two genes was also prognostic in EGFR mutation positive group extracted from a combined cohort (Figure 1B).

Conclusions: In pure solid non-squamous NSCLC patients, low BMP6/OLFM1 status will identify high risk pStage I NSCLC patients after pulmonary resection.

Keywords: Prognostic biomarker, lung adenocarcinoma, pathological stage I

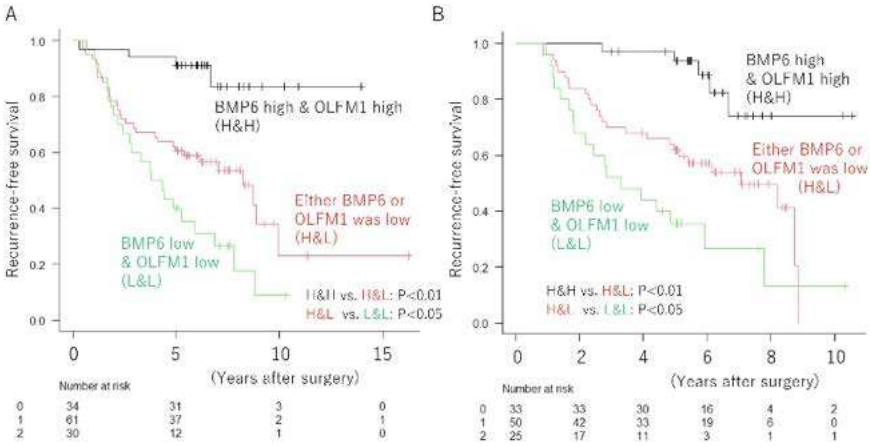

Figure 1. Recurrence-free survivals based on BMP6 and OLFM1 expression status in Cohort 2a (A) and in the EGFR mutated cohort obtained from Cohort 1, Cohort 2a, and Cohort 2b (B).

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P4.07F.06 CT-Based Deep Learning Model for Predicting Visceral Pleural Invasion in NSCLCs with Tumor Diameter Less Than 3cm

M-W. Lin, L-W. Chen, M-S. Hsieh, Y-C. Chang, J-S. Chen, C-M. Chen, National Taiwan University, Taipei City/TW

Introduction: Sublobar resection is significantly associated with poor prognosis in early-stage non-small cell lung cancer (NSCLC) with visceral pleural invasion (VPI). Therefore, preoperative VPI prediction is crucial for guiding surgical strategies. The utilization of deep learning models for VPI prediction remains limited with suboptimal performance. This study aims to develop a computed tomography (CT)-based VPI deep learning (VPI-DL) prediction model for NSCLC with tumor sizes less than 3 cm.

Methods: This study consecutively retrospectively enrolled NSCLC patients with tumor size less than 3cm who underwent complete lung resection at Institute 1 from 2011 to 2015 and Institute 2 from 2017 to 2019, respectively (Figure). A CT-based VPI-DL model was developed for predicting VPI. The proposed VPI-DL model underwent external validation and was compared with the three other methods: the previously established DL model, consolidation-to-tumor (C/T) ratio, and assessment by three board-certified thoracic surgeons. The performance of the models was evaluated using the area under the curve (AUC), accuracy, and specificity.

Results: Among the total 835 enrolled patients from two institutes, 127 patients (15.2%) had positive VPI. We included 691 patients (VPI +/- = 104:587) from institute 1 in the training and internal validation sets, and 144 patients (VPI +/- = 23:121) from institute 2 in the external validation set. The proposed VPI-DL model outperformed other methods on the external validation set, achieving an AUC of 0.91 and an accuracy of 83.0%. The AUC of this proposed model in the external validation cohort was significantly superior to the other three methods, including the previously established DL model (0.77), C/T ratio (0.85), and the thoracic surgeons' average (0.74) (Table).

Conclusions: The proposed VPI-DL model exhibited expert-level performance and shows significant promise in preoperatively predicting VPI, providing valuable assistance in surgical planning for early-stage NSCLC.

Keywords: Visceral pleural invasion, non-small cell lung cancer, computed-tomography

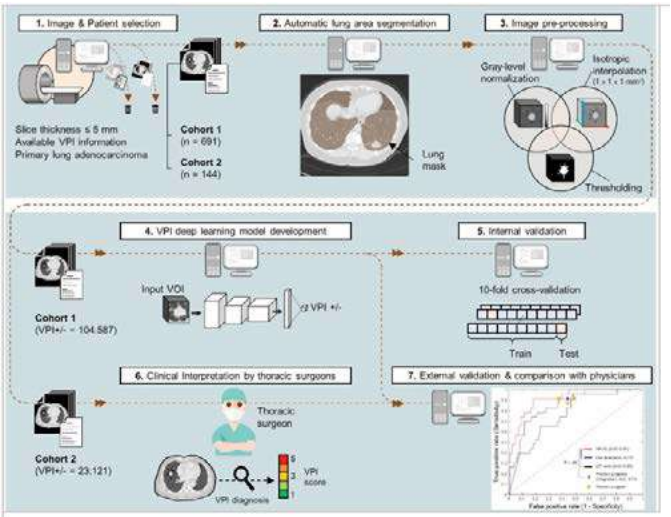

Table. Performance of the proposed VPI-DL prediction model and other methods in training set and external validation set.

A. Performance of three methods based on 5-fold cross-validation in training set. (while operating with 89% [93/104] sensitivity)

	Methods		
Parameters	The proposed VPI-DL model	The previously established DL model	C/T ratio
Accuracy	66.0 (318/691) [62.0, 69.0]	38.0* (507/691) [35.0, 42.0]	62.0* (348/691) [58.0, 65.0]
Specificity	62.0 (362/587) [58.0, 65.0]	29.0* (173/587) [26.0, 33.0]	57.0* (334/587) [53.0, 61.0]
AUC	0.83 [0.78, 0.88]	0.69* [0.63, 0.75]	0.79 [0.74, 0.84]

Note.—Unless otherwise specified, data are percentages, with numbers/images in parentheses and 95% confidence intervals in brackets. C/T ratio: consolidation-to-tumor ratio; AUC: area under the receiver operating characteristic curve; VPI-DL: visceral pleural invasion deep learning.
*$P < .05$ compared with VPI-DL by paired Student *t* test.

B. Performance of four methods based in external validation set. (while operating with 91% [21/23] sensitivity)

	Methods			
Parameters	The proposed VPI-DL model	The previously established DL model	C/T ratio	Thoracic surgeons (integrated)
Accuracy	83.0 (43/144) [76.0, 89.0]	60.0* (77/144) [51.0, 68.0]	67.0* (66/144) [59.0, 75.0]	62.0* (74/144) [53.0, 70.0]
Specificity	82.0 (99/121) [74.0, 88.0]	54.0* (65/121) [45.0, 62.0]	63.0* (76/121) [54.0, 71.0]	56.0* (68/121) [48.0, 64.0]
AUC	0.91 [0.83, 0.99]	0.77** [0.65, 0.89]	0.85** [0.75, 0.95]	0.74** [0.61, 0.86]

Note.—Unless otherwise specified, data are percentages, with numbers / images in parentheses and 95% confidence intervals in brackets. C/T ratio: consolidation-to-tumor ratio; AUC: area under the receiver operating characteristic curve; VPI-DL: visceral pleural invasion deep learning.
*$P < .05$ compared with VPI-DL by McNemar's chi-square test.
**$P < .05$ compared with VPI-DL by DeLong's test.

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P4.07G.01 Incidence of and Outcomes of Second Primary Lung Cancer after Resection for Screen-Detected Lung Cancer

A. Potter, S. Venkateswaran, Q. Guo, P. Senthil, D. Wang, P. Furlow, M. Lanuti, C-F.J. Yang, Massachusetts General Hospital, Boston/MA/USA

Introduction: Patients who undergo surgery for initial primary lung cancer (IPLC) detected via lung cancer screening remain at risk for the development of second primary lung cancers (SPLC); however, the incidence and outcomes of SPLC in this population are unknown. We evaluated the incidence of, and long-term outcomes associated with, SPLC among patients with resected IPLC detected via screening in the National Lung Screening Trial (NLST).

Methods: Patients who underwent surgery and were diagnosed with pathologic stage I IPLC detected via screening in the NLST from 2002-2009 were identified for analysis. The NLST collected data on the incidence of any SPLC diagnosed among study participants through the end of 2009. For the present study, we obtained an updated dataset with mortality data extended through 2015. The incidence rate of synchronous SPLC and of metachronous SPLC were evaluated. The 5-year cumulative incidence of metachronous SPLC was examined; subgroup analyses were performed by IPLC histology, pack-year smoking history, smoking status, and age at IPLC diagnosis. Lastly, 5-year overall and lung cancer-specific survival after the date of SPLC diagnosis were assessed.

Results: Of 337 patients in the study cohort, 23 patients were diagnosed with SPLC. The incidence of synchronous SPLC was 3.0% (n=10). During a median follow-up of 4.8 years after surgery for IPLC, 13 patients were diagnosed with metachronous SPLC, representing an incidence rate of 0.8 (95% CI: 0.5-1.5) per 100 person-years. The 5-year cumulative incidence of metachronous SPLC in the overall cohort was 3.5% (95%: 1.9-5.7), but varied notably by patient subgroup (Figure). The majority of synchronous (80.0%, n=8) and metachronous (61.5%, n=8) SPLCs were diagnosed at stage I. Five-year overall survival, from the date of SPLC diagnosis, was 80.0% (95% CI: 40.9-94.6) for synchronous SPLC and 53.9% (95% CI: 24.8-76.0) for metachronous SPLC. Five-year lung cancer-specific survival, from the date of SPLC diagnosis, was 88.9% (95% CI: 43.3-98.4) for synchronous SPLC and 61.5% (95% CI: 30.8-81.8) for metachronous SPLC.

Conclusions: In this analysis of patients who underwent surgery and were diagnosed with pathologic stage I IPLC in the NLST, the incidence of synchronous SPLC was 3.0% and the 5-year cumulative incidence of metachronous SPLC was 3.5%. There were notable differences in the stage at diagnosis and long-term survival of synchronous vs. metachronous second primaries.

Keywords: Lung cancer, Lung cancer screening, Early-stage

Figure. Five-year cumulative incidence of second primary lung cancer among patients who underwent surgery and were diagnosed with pathologic stage I initial primary lung cancer detected via screening in the National Lung Screening Trial stratified by histologic subtype, age at initial primary lung cancer diagnosis, smoking pack-years, and smoking status.

Group	Five-year Cumulative Incidence of Lung Cancer
Histologic Subtype	
Adenocarcinoma	5.1% (95% CI: 2.2 - 9.7)
Squamous Cell Carcinoma	2.9% (95% CI: 0.5 - 9.0)
Age at IPLC Diagnosis	
<65 years	4.0% (95% CI: 1.6 - 8.1)
≥ 65 years	2.6% (95% CI: 0.9 - 6.1)
Smoking Pack-years	
<50 pack-years	2.6% (95% CI: 0.7 - 6.8)
≥ 50 pack-years	3.8% (95% CI: 1.7 - 7.3)
Smoking Status	
Former	2.1% (95% CI: 0.6 - 4.4)
Current	4.4% (95% CI: 1.9 - 8.5)

P4.07G.02 Prediction of Relapse-free Survival of NSCLC Patients Through Multimodal Data Fusion Using Deep Learning Model

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Introduction: The use of deep learning(DL) models has emerged as a superior approach for the diagnosis, treatment, and prognosis of lung cancer. However, current DL models predominantly rely on a single modality, such as textual clinical data, CT images, or omics data, each offering a restricted viewpoint of lung cancer. The aim of this study is to improve the prediction of relapse-free survival by integrating CT images and clinical data through a proposed DL model, namely IC-TCA-Net.

Methods: The dataset used in this study included clinical variables and preoperative chest CT images of 166 NSCLC patients who underwent curative surgical resection (Figure 1(a)). A total of 17 clinical variables, recognized for their prognostic significance, were collected from patient's basic information, laboratory results, and pathology examinations. Initially, univariate, and multivariate analysis were conducted to identify the optimal set of clinical features significantly associated with recurrence. Subsequently, IC-TCA-Net extracted deep image features, which are multi-scale features focused on tumor location, through the tumor-centric attention module and dual branches from CT images and tumor masks. Finally, clinical features and deep image features were concatenated for multimodal feature fusion, and provided recurrence prediction using a classifier composed of two fully connected layers (Figure 1(b)).

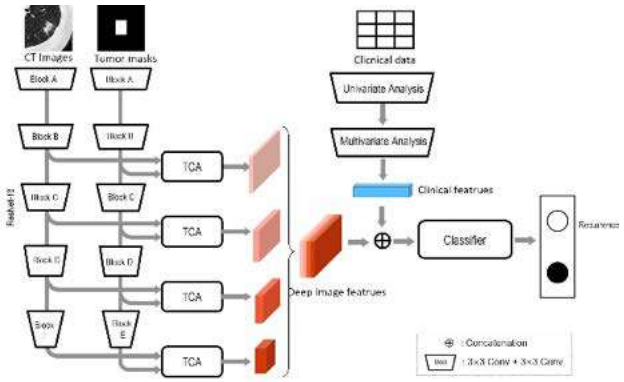
Results: We conducted 3-fold cross-validation to assess the performance of our proposed network using the entire dataset. In comparison to TCA-Net, which utilizes only CT images and tumor masks, IC-TCA-Net achieved the overall performance improvement in accuracy, balanced accuracy, sensitivity and AUC by 5.46%p, 4.3%p, 12.86%p and 0.05, respectively. Additionally, the Kaplan-Meier curves of IC-TCA-Net showed better separation than those of TCA-Net.(Figure 2)

Conclusions: This study demonstrated the effectiveness of deep learning-based data fusion, such as IC-TCA-Net. (This work was supported by the NRF grant funded by the Korea government MIST (No. RS-2023-00214043) and the Ministry of Education (No. 2021R1F1A1051297))

Keywords: Multimodal fusion, Deep-learning, relapse-free survival

Patient characteristics	CML (n=166)
Age	66 ± 10.28 (38–85)
Gender	
Male	86 (52%)
Female	80 (48%)
Histology	
Adenocarcinomas	145 (87%)
Squamous cell carcinomas	21 (13%)
T stage	
T1	92 (55%)
T2	51 (31%)
T3	21 (13%)
T4	2 (1%)
N stage	
Nx	7 (4%)
N0	123 (74%)
N1	18 (11%)
N2	16 (10%)
N3	2 (1%)
Recurrence	
Non-recurrence	99 (60%)
Recurrence	67 (40%)

(a)



(b)

Figure 1. The overview of the method in this study (a) Patient characteristics and (b) The structure of the proposed IC-TCA-Net (Integrated Clinical data with Tumor Centric Attention Network). TCA module effectively leverages the tumor mask to amplify characteristics in the CT image related to the tumor.

(a)

Method	Fold	TP	TN	FP	FN	Accuracy	Balanced Accuracy	Sensitivity	Specificity	AUC
TCA-Net (CT image features)	A	17	24	8	7	73.21	72.92	70.83	79.03	0.79
	B	12	31	3	11	71.68	75.44	52.17	91.18	0.79
	C	18	24	9	2	79.25	81.36	90	72.72	0.85
	Total	47	79	20	20	74.71	76.57	71	**80.98**	0.81
IC-TCA-Net (Clinical features + CT image features)	A	20	27	5	4	83.93	83.85	83.33	84.38	0.88
	B	18	25	9	5	75.44	75.89	78.26	73.53	0.82
	C	18	25	8	2	81.13	82.88	90	75.76	0.88
	Total	56	77	22	11	**80.17**	**80.87**	**83.86**	77.89	**0.86**

(b)

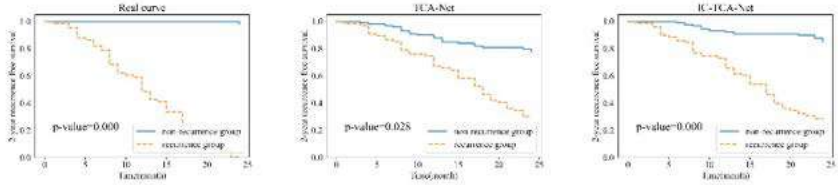


Figure 2. Results of two-year relapse free survival on the entire dataset. (a) Performance evaluation of our proposed network, IC-TCA-Net, in terms of accuracy, balanced accuracy, sensitivity, specificity, and AUC compared to TCA-Net, an identical model except for clinical features. (b) Kaplan-Meier curves for two-year relapse-free survival.

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P4.07G.03 Real-World Clinical Outcomes and the Association Between EFS and OS in Early-Stage NSCLC Treated with Primary SBRT

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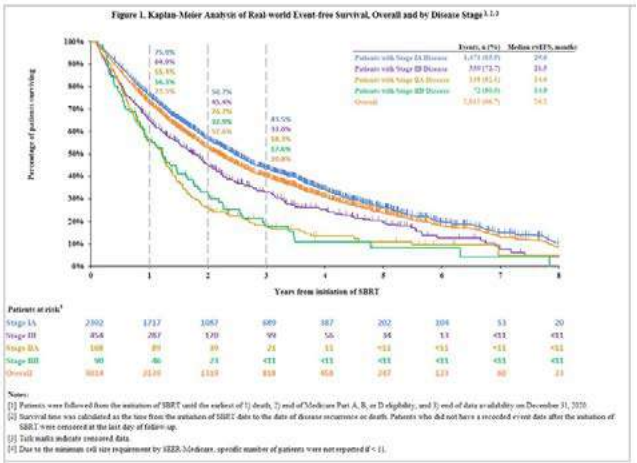
Introduction: Stereotactic body radiotherapy (SBRT) is the standard of care for unresectable early-stage non-small cell lung cancer (NSCLC), yet there are limited real-world clinical outcomes data. While intermediate endpoints (e.g., event-free survival [EFS]) have shown good correlation with overall survival (OS) in NSCLC clinical trials, few studies have quantified this correlation using real-world data. This study assessed clinical outcomes and association between real-world EFS (rwEFS) and OS among patients with early-stage NSCLC treated with SBRT.

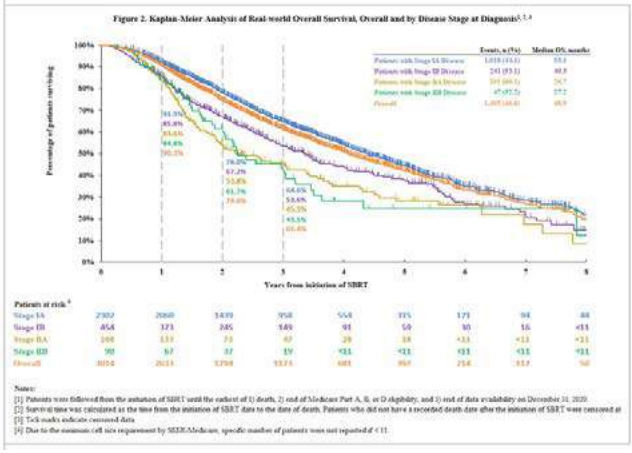
Methods: This retrospective, observational analysis of SEER-Medicare database (2007-2020) included patients with newly diagnosed, stage I-II (N0) NSCLC (AJCC 8th edition) who received primary SBRT, with index date defined as initiation of SBRT. Patient characteristics were summarized. rwEFS and OS, overall and by stage, were described using Kaplan-Meier analyses. Data by recurrence status will be presented in the poster. Correlation between rwEFS and OS was assessed using the normal scores rank correlation.

Results: 3,014 patients with stage I-II NSCLC met eligibility criteria with a median follow-up of 2.4 years. Median age at diagnosis was 77.0 years; 37.7 % males, 86.9% whites, and mean Charlson comorbidity index was 2.4. The median rwEFS for the overall population was 26.2 months with 5-year rwEFS survival rate of 23.8%; data by stage shown in Figure 1. The median OS for the overall population was 48.9 months with 5-year OS survival rate of 42.3%; data by stage shown in Figure 2. The normal scores rank correlation demonstrated moderate but statistically significant correlation between rwEFS and OS (0.74; 95%CI: 0.72-0.77; P<0.001).

Conclusions: Among patients with early-stage NSCLC who received primary SBRT, modest survival outcomes were observed, highlighting the potential for novel strategies such as the incorporation of immunotherapy to augment outcomes for this patient population. Additionally, significant positive correlation between rwEFS and OS suggests rwEFS may predict OS.

Keywords: early-stage unresected NSCLC, real world event-free survival, overall survival





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P4.07G.04 BML is Associated with Potential Survival Advantages in Patients with Solid-Dominant Stage I NSCLC

W. Wang, L. Zhang, Sun Yat-sen University Cancer Center, Guangzhou/CN

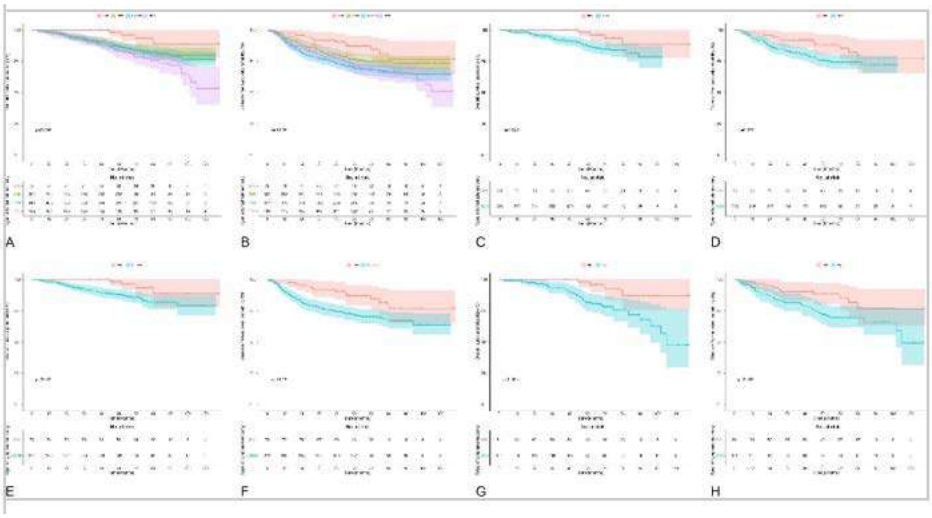
Introduction: The optimal lymphadenectomy approach for solid-dominant stage I non-small cell lung cancer (NSCLC) is controversial. We compared postlobectomy survival outcomes to elucidate.

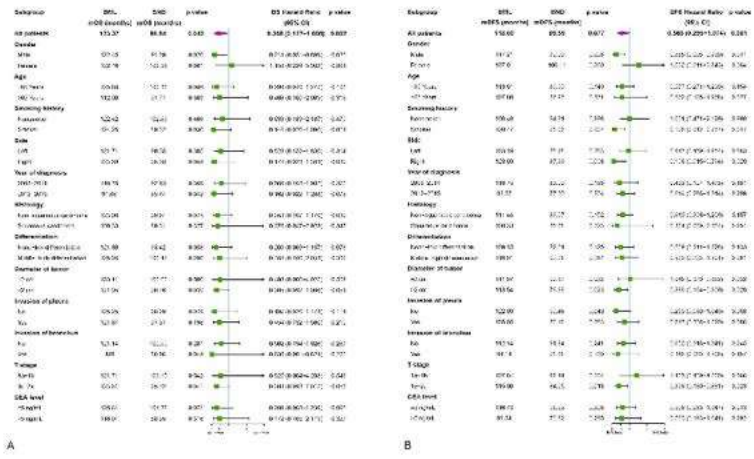
Methods: Patients diagnosed with solid-dominant stage I NSCLC between 2008 and 2015 were included and grouped according to the mode of lymphadenectomy. Disease-free survival (DFS) and overall survival (OS) were compared, and survival analysis was performed among the groups. Cox analysis was used to identify independent prognostic factors. Nomograms for survival prediction based on the lymphadenectomy mode were constructed and internally calibrated. Propensity score matching (PSM) was used to account for potential confounders. Subgroup comparisons between bilateral mediastinal lymphadenectomy (BML), systematic nodal dissection (SND), lobe-specific lymph node dissection (LSND) and systematic nodal sampling (SNS) were conducted.

Results: In total, 983 patients were included. The 5-year OS rates were 98.2%, 86.9%, 86.4%, and 82.8% (p=0.006), and the 5-year DFS rates were 87.1%, 76.4%, 69.5%, and 70.9% (p=0.008) in the BML, SND, LSND and SNS groups, respectively. Given PSM, patients who underwent BML had longer OS (HR, 0.358; 95% CI, 0.127-1.008; p=0.052) and DFS (HR, 0.563; 95% CI 0.295-1.074; p=0.081) than patients who underwent SND with marginal significance. Compared with L-SND and SNS, BML was associated with significantly improved OS (HR=0.343; 95% CI=0.123-0.958; p=0.041 and HR=0.250; 95% CI=0.088-0.709; p=0.009, respectively) and DFS (HR=0.474; 95% CI=0.258-0.868; p=0.016 and HR=0.467; 95% CI=0.232-0.938; p=0.032, respectively). Subgroup analyses demonstrated that in male patients and those whose tumours were larger or more advanced, BML was associated with significantly better OS and DFS than other types of lymphadenectomy.

Conclusions: BML may be associated with improved survival in patients with solid-dominant stage I NSCLC, and BML is recommended for such patients, especially those with large tumours or more advanced disease.

Keywords: non-small cell lung cancer, bilateral mediastinal lymphadenectomy, propensity score matching





P4.07G EARLY-STAGE NON-SMALL CELL LUNG CANCER - UNDERSTANDING LONG-TERM OUTCOMES
MONDAY, SEPTEMBER 9, 2024 - 18:30 - 20:00

P4.07G.05 Prediction of Quality-of-Life Results after Lung Stereotactic Body Radiotherapy Using Functional Mapping on Gallium-68 Perfusion PET/CT

F. Lucia[1], J. Lamour[2], M. Geier[1], V. Bourbonne[1], U. Schick[1], M. Nebbache[1], F. Pinot[1], O. Pradier[1], G. Le Gal[1], S. Hennebicq[1], M. Mauguen[1], K. Kerleguer[1], F. Blanc-Beguin[1], D. Bourhis[1], P-Y. Salaun[1], P-Y. Le Roux[1], [1]University Hospital of Brest, Brest/FR, [2]University of Brest, Brest/FR

Introduction: The PEGASUS trial was the first study to evaluate and demonstrate the benefits of 68Ga-perfusion PET/CT in the lung stereotactic body radiotherapy (SBRT) planning process in preserving functional lung volumes while respecting target volume coverage and doses to other organs at risk. Here we report the prespecified exploratory endpoint of SBRT on health-related quality of life (HRQoL).

Methods: In this a single-center prospective study, we recruited patients planned to be treated in the radiotherapy department at the Brest University Hospital, France, with SBRT for primary or secondary lung tumors. PROs were assessed at the first visit, 1 month, 3 months and every 3 months until 12 months after SBRT using the European Organisation for the Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 items (QLQ-C30), the EORTC Quality of Life Questionnaire Lung Cancer 13 items (QLQ-LC13), and the European Quality of Life 5 Dimensions-5 Level (EQ-5D-5L) questionnaire. The key exploratory HRQoL endpoints (analyzed for all patients who completed at least QLQ-C30 at least one time point after SBRT) were baseline-to-early change (between 1 month and 3 month) and baseline-to-late change (between 6 month and 12 month) in the QLQ-C30 global health status (GHS)/quality-of-life (QoL) score and in the deterioration of the dyspnea (patient-reported lung toxicity). Explorative analysis of the impact of baseline HRQoL, patient- and SBRT-related characteristics, including PET perfusion-based functional parameters, on the change in QoL from baseline was analyzed using univariate analysis.

Results: Of the 60 patients included, 39 were analyzable as early-onset and 22 as late-onset. Thirteen (33%) and 7 (32%) patients had a deterioration of QoL. In univariate analysis, maximal dose to the heart, doses to the functional lung volume and pulmonary functional test parameters were significantly associated with the early deterioration of HRQoL. Only doses to the functional lung volume were significantly associated with the late deterioration of HRQoL.

Conclusions: In our study, increased radiation doses in functional lung volume PET bases dose parameters were significantly associated with decreased of HRQoL unlike anatomic lung parameters. Functional lung avoidance planning guided by perfusion PET/CT may be a simple and noninvasive method to improve HRQoL in patients treated with lung SBRT.

Keywords: Radiation therapy, health-related quality-of-life, perfusion PET/CT

P4.11D METASTATIC NON-SMALL CELL LUNG CANCER - IMMUNOTHERAPY - CLINICAL TRIALS IN PROGRESS
MONDAY, SEPTEMBER 9, 2024 - 18:30 - 20:00

P4.11D.01 TRITON: Tremelimumab + Durvalumab + Chemotherapy (CT) vs Pembrolizumab + CT in mNSCLC with STK11, KEAP1 and/or KRAS Mutations

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Introduction: Mutations in STK11 and KEAP1, present in approximately 20% and 15% of patients respectively with non-squamous metastatic NSCLC (mNSCLC), lead to an immunosuppressive tumor microenvironment and are associated with inferior clinical outcomes with anti-PD-(L)1-based chemo-immunotherapy, especially when co-mutated with KRAS. Patients with tumors bearing STK11, KEAP1 and/or KRAS mutations may benefit from combinations with CTLA-4 inhibitors, aimed at increasing immune responses. In the phase 3 POSEIDON trial (NCT03164616), first-line tremelimumab (T) + durvalumab (D) + CT significantly improved overall survival (OS; HR 0.77 [95% CI 0.65-0.92]; P=0.0030) vs CT. These results were maintained after a median follow-up of >5 years. Subgroup analyses showed sustained OS improvement with T+D+CT vs CT in patients with mNSCLC with STK11 (non-squamous), KEAP1 (all histologies, due to small sample size), and KRAS (non-squamous) mutations (HR [95% CI] 0.57 [0.32-1.04), 0.43 [0.16-1.25], and 0.55 [0.36-0.83], respectively). The TRITON study will further investigate the signal of efficacy observed in the POSEIDON subgroup analysis. TRITON will compare T+D+CT vs pembrolizumab (P) + CT (a standard treatment for non-squamous mNSCLC) in patients with STK11, KEAP1 and/or KRAS mutations. The results will help to inform clinical practice and to establish a biomarker-driven treatment strategy for these difficult-to-treat patients.

Methods: TRITON (NCT06008093) is a phase 3b, multicenter, open-label, 2-arm parallel randomized study. Eligible patients, aged ≥18 years, must have non-squamous mNSCLC (no EGFR or ALK alterations), with STK11, KEAP1, or KRAS mutations/co-mutations, no prior systemic therapy for mNSCLC, and ECOG performance status of 0/1. Approximately 280 patients will be randomized 1:1 to receive either T+D+CT or P+CT. In the T+D+CT arm, patients will receive T (75 mg) + D (1500 mg) + carboplatin (AUC 5 or 6)/cisplatin (75 mg/m2) + pemetrexed (500 mg/m2) every 3 weeks (Q3W) for 4 cycles (a fifth dose of T [75 mg] will be given in combination with D, post-platinum at week 16), followed by maintenance D (1500 mg) + pemetrexed (500 mg/m2) Q4W until disease progression. In the P+CT arm, patients will receive P (200 mg) + carboplatin (AUC 5 or 6)/cisplatin (75 mg/m2) + pemetrexed (500 mg/m2) Q3W for 4 cycles, followed by maintenance P (200 mg) + pemetrexed (500 mg/m2) Q3W until disease progression, for up to 24 months.

Randomization is stratified by mutation type (KRAS [without STK11 or KEAP1] mutations are capped at 33% of the total sample) and tumor PD-L1 expression (≥1% vs <1%). Primary endpoints are OS in all patients and in the subset with STK11 or KEAP1 mutations/co-mutations. Key secondary endpoints include OS rates at 12 and 24 months, progression-free survival, objective response rate, duration of response (all RECIST v1.1; investigator-assessed) and safety/tolerability (CTCAE v5.0). The study will include up to 75 sites across the USA; as of April 5, 2024, there are 10 active sites and the first patient has been enrolled.

Keywords: Durvalumab, Tremelimumab, TRITON

P4.11D METASTATIC NON-SMALL CELL LUNG CANCER - IMMUNOTHERAPY - CLINICAL TRIALS IN PROGRESS
MONDAY, SEPTEMBER 9, 2024 - 18:30 - 20:00

P4.11D.02 Phase 3 Trofuse-007 Study: Sacituzumab Tirumotecan Plus Pembrolizumab vs Pembrolizumab Alone for NSCLC with PD-L1 TPS ≥50%

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Introduction: Pembrolizumab (anti-PD-1) monotherapy is a standard of care first-line treatment for advanced or metastatic non-small-cell lung cancer (NSCLC) with PD-L1 TPS ≥50% without actionable genetic alterations; however, some patients do not respond to therapy or experience disease progression. Trophoblast cell-surface antigen 2 (TROP2) is another candidate for anticancer treatment and overexpression of TROP2 is associated with poor prognosis in patients with NSCLC. Sacituzumab tirumotecan (sac-TMT; also known as MK-2870/SKB264) is an antibody-drug conjugate (ADC) composed of the humanized TROP2 monoclonal antibody, a hydrolytically cleavable linker, and the cytotoxic drug KL610023. In patients with relapsed or refractory locally advanced or metastatic NSCLC, monotherapy with sac-TMT showed encouraging antitumor activity with a manageable safety profile. The complementary mechanisms of action of sac-TMT and pembrolizumab may provide more potent antitumor activity when given in combination compared with each therapy alone. To investigate this further, the TroFuse-007 study will evaluate the efficacy and safety of the addition of sac-TMT to pembrolizumab vs pembrolizumab alone in patients with previously untreated metastatic NSCLC with PD-L1 TPS ≥50%.

Methods: Approximately 614 eligible patients aged ≥18 y with previously untreated histologically or cytologically confirmed stage IV (per American Joint Committee on Cancer version 8.0) NSCLC, PD-L1 TPS ≥50% and no EGFR, ALK, or ROS1 alterations (nonsquamous only); ECOG PS 0 or 1; and measurable disease per RECIST version 1.1 will be enrolled. Patients with well-controlled HIV are permitted. Patients will be randomized 1:1 to receive either pembrolizumab 400 mg Q6W for up to 18 cycles plus sac-TMT 4 mg/kg Q2W or pembrolizumab 400 mg IV Q6W alone until progressive disease, intercurrent illness, patient withdrawal, unacceptable toxicity, prolonged interruption of study drug, or until maximum number of cycles (18 cycles for pembrolizumab). Randomization stratification factors include ECOG PS (0 vs 1), histology (squamous vs nonsquamous), TROP2 expression (low vs medium vs high), and geographic region (East Asia vs North America/Western Europe/Australia vs Rest of World). The primary endpoint is OS. Secondary endpoints include PFS, ORR, and duration of response per RECIST v1.1 by blinded independent central review, patient-reported outcomes (PROs), and safety. Tumor imaging will occur at baseline, Q6W until week 48, and Q12W thereafter until PD, start of new anticancer treatment, or withdrawal of consent. PD-L1 TPS will be assessed centrally using PD-L1 IHC 22C3 pharmDx (Agilent Technologies, Carpinteria, CA). PROs will be assessed using the European Organisation for Research and Treatment of Cancer (EORTC) Quality of life questionnaire core 30 (QLQ-C30); EORTC quality of life questionnaire and lung cancer module 13 (QLQ-LC13); NSCLC symptom assessment questionnaire (NSCLC-SAQ); and EuroQol 5-dimension, 5-level (EQ-5D-5L) questionnaires. AEs will be graded according to National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0. Enrollment began in December 2023 and is currently ongoing.

Keywords: Pembrolizumab, Antibody-drug conjugate (ADC), Topoisomerase II inhibitor

P4.11D METASTATIC NON-SMALL CELL LUNG CANCER - IMMUNOTHERAPY - CLINICAL TRIALS IN PROGRESS
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P4.11D.03 Trial in Progress: Phase 1/2 Study of OBX-115 Engineered Tumor-Infiltrating Lymphocyte (TIL) Cell Therapy in Patients with Advanced Solid Tumors

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Introduction: Immune checkpoint inhibitors (ICI) have improved outcomes for patients with solid tumor malignancies; however, most patients relapse, after which options are limited. Non-engineered TIL cell therapy has shown promising efficacy in patients with ICI-resistant melanoma (Rohaan NEJM 2022, Chesney JITC 2022) and non-small cell lung cancer ([NSCLC] Creelan Nat Med 2021, Schoenfeld Cancer Discov 2024), but requires co-administration of systemic high-dose IL2, which has well-described high-grade toxicity frequently requiring specialized management and limiting patient eligibility. OBX-115 is a tumor-derived autologous T-cell immunotherapy (TIL cell therapy) expanded from patient tumor tissue and engineered with a transgene to express membrane-bound human IL15 (mbIL15), regulated by acetazolamide (ACZ), eliminating the need for high-dose IL2 (Figure 1). A first-in-human single-institution study (NCT05470283) evaluating the safety of OBX-115 in metastatic melanoma is ongoing (Amaria AACR 2024). The current study (NCT06060613) is enrolling patients with NSCLC and melanoma at multiple US sites using centralized manufacturing.

Methods: This phase 1/2, single-arm, open-label, nonrandomized, multicenter study will assess the safety, tolerability, and efficacy of the OBX-115 engineered autologous TIL cell therapy regimen in patients with metastatic NSCLC previously treated with an approved systemic therapy for metastatic disease (including an ICI-based regimen and/or targeted therapy where applicable) and progressed, no longer deriving benefit, or unable to continue due to treatment intolerance OR histologically confirmed unresectable Stage IIIC, IIID, or Stage IV metastatic melanoma (excluding uveal) with documented radiographic progression after systemic therapy containing an anti-PD-1/PD-L1 agent (if adjuvant, progression during or within 12 weeks after the last dose) and received a BRAF inhibitor ± MEK inhibitor if BRAF V600 mutation-positive. Patients may have treated and asymptomatic brain metastases. Patients must have ECOG PS of 0 or 1 and life expectancy >~6 months. Patients must have ≥1 lesion suitable for OBX-115 manufacturing (≥1.5 cm) and ≥1 RECIST v1.1-measurable lesion remaining after tumor tissue procurement. Primary objectives of Phase 1 are to characterize safety and tolerability and identify a recommended Phase 2 dose of OBX-115 + ACZ; Phase 2 will evaluate efficacy of the regimen (ORR using RECIST v1.1 per investigator). Cryopreserved OBX-115 is generated from the patient's own tumor tissue procured by surgical excision or core needle biopsy and is infused after standard- or low-dose lymphodepletion (cyclophosphamide and fludarabine), based on clinical status and prior treatments (Figure 2). No systemic high-dose IL2 is administered. ACZ is administered at cohort-defined doses once daily for up to 14 days starting day of OBX-115 infusion, with additional ACZ dosing at Week 6 for up to 14 days; patients with NSCLC with investigator-assessed suboptimal response may receive additional ACZ dosing at Weeks 12 and 18. ACZ may be redosed (melanoma or NSCLC) upon progression when new anticancer therapy is not immediately warranted. Four sites are open and recruiting, with additional sites being activated.

Keywords: non-small cell lung cancer, adoptive cell therapy, tumor-infiltrating lymphocytes

Figure 1. OBX-115 Mechanism of Action

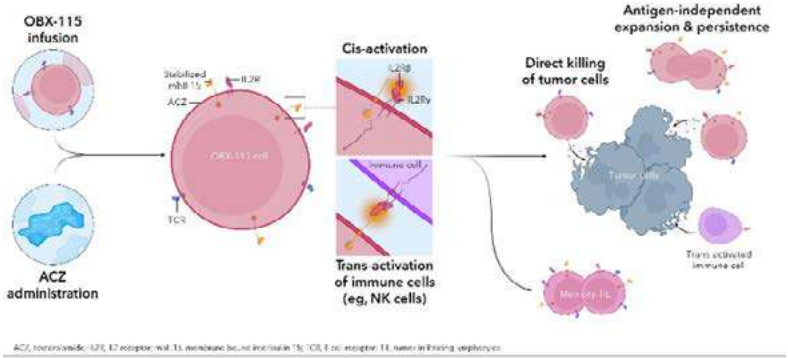
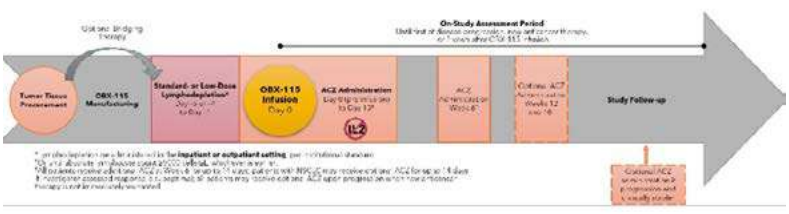


Figure 2. Study Treatment Schema



P4.11D METASTATIC NON-SMALL CELL LUNG CANCER - IMMUNOTHERAPY - CLINICAL TRIALS IN PROGRESS
MONDAY, SEPTEMBER 9, 2024 - 18:30 - 20:00

P4.11D.04 A Phase 1/2 Study of REGN7075 (EGFRÃ-CD28) Combined with Cemiplimab (anti-PD-1) In NSCLC: Trial in Progress Update

M.L. Johnson[1], E. Girda[2], D. Sohal[3], N.J. Lakhani[4], A.J. Olszanski[5], L. Fong[6], M. Kinnaman[7], H. Han[7], A. Moesta[7], Y. Hao[7], S. Li[7], S. Ganguly[7], F. Seebach[7], M. Mathias[7], N.H. Segal[8], [1]Sarah Cannon Research Institute, Tennessee Oncology, Nashville/TN/USA, [2]Division of Gynecologic Oncology, Rutgers Cancer Institute of New Jersey, New Brunswick/NJ/USA, [3]Division of Hematology/Oncology, University of Cincinnati Cancer Center, Cincinnati/OH/USA, [4]START Midwest, Grand Rapids/MI/USA, [5]Department of Hematology/Oncology, Fox Chase Cancer Center, Philadelphia/PA/USA, [6]Division of Hematology and Oncology, University of California San Francisco, San Francisco/CA/USA, [7]Regeneron Pharmaceuticals, Inc., Tarrytown/NY/USA, [8]Department of Medicine, Memorial Sloan Kettering Cancer Center, New York/NY/USA

Introduction: There is a need to develop novel immunotherapies to enhance response rates to immune checkpoint blockade and in patients who progress on epidermal growth factor receptor (EGFR)-targeted therapies. REGN7075 is a human costimulatory bispecific antibody that bridges EGFR-expressing tumor cells with CD28+ T cells to further support T-cell activation by endogenous tumor antigens.

Methods: Open-label, Phase 1/2, first-in-human, global study to evaluate the safety, pharmacokinetics (PK), and efficacy of REGN7075 + cemiplimab in patients with advanced solid tumors (NCT04626635). Here, we focus on three non-small cell lung cancer (NSCLC) cohorts in the dose expansion phase. The study includes a dose escalation (Part 1) and dose expansion (Part 2) phase. Part 2 consists of tumor-specific expansion cohorts, including three cohorts of patients with metastatic/locally advanced NSCLC who are not candidates for curative surgery/radiation: (1) patients who are treatment-naïve with no targetable driver mutation (ALK/ROS1/EGFR/RET-fusion/MET exon 14 skipping) with any programmed cell death-ligand 1 expression level (cohort 1; n=95); (2) patients with an EGFR mutation (exon 19 deletion/L858R/exon 20 insertion/exon 18/21 atypical mutation) who received a third generation tyrosine kinase inhibitor (TKI; cohort 2; n=61); and (3) patients with an EGFR mutation who received a third generation TKI and prior platinum-doublet chemotherapy (cohort 3; n=56). Patients in cohorts 1 and 2 will receive four cycles of platinum-based chemotherapy concurrently with REGN7075 + cemiplimab. Eligible patients must have an Eastern Cooperative Oncology Group performance status of 0/1 and have received no prior immunotherapy. Primary objectives: safety and tolerability of REGN7075 ± cemiplimab (Part 1); objective response rate (REGN7075 + cemiplimab ± chemotherapy; Response Evaluation Criteria in Solid Tumors v1.1; Part 2). Secondary objectives: PK for REGN7075; overall survival, progression-free survival, duration of response, complete response, and disease control rates; patient-reported outcomes per the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Lung Cancer 13 (Part 2). As of February 23, 2024, 122 patients were enrolled in Part 1. The study is ongoing and open to enrollment.

Keywords: REGN7075, cemiplimab, NSCLC

P4.11D METASTATIC NON-SMALL CELL LUNG CANCER - IMMUNOTHERAPY - CLINICAL TRIALS IN PROGRESS
MONDAY, SEPTEMBER 9, 2024 - 18:30 - 20:00

P4.11D.05 EGFR Neoantigen Peptide Vaccine Combined with Tislelizumab and Chemotherapy for Advanced NSCLC Resistant to EGFR-TKI Therapy

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Introduction: The therapeutic efficacy of PD-1 monoclonal antibody combined with chemotherapy in EGFR-TKI resistant patients is still controversial. At present, neo-antigen vaccine shows a good prospect in NSCLC treatment. The neo-antigens produced by EGFR mutations have strong immunogenicity and are ideal antigens for vaccine. The combination of ICI and neo-antigen vaccine is expected to have a synergistic effect which can improve the immune suppression microenvironment and further enhance the anti-tumor immune response. This study aimed to explore the efficacy and safety of neo-antigen vaccine with tislelizumab (TIS) and chemotherapy in the treatment of advanced NSCLC resistant to previous EGFR-TKI treatment(NCT06095934).

Methods: This is a single arm, open, single center study with plans to enroll 20 patients. Eligible participants were adults aged ≥18 years with stage IIIB-IV EGFRmut NSCLC progressed after EGFR-TKI based treatment. Participants received chemo-immune induction (TIS plus pemetrexed or nab-paclitaxel plus carboplatin), combination(chemo-immune and 9 doses neo-antigen vaccine), and maintenance treatment (TIS with or without pemetrexed or nab-paclitaxel) until disease progression or intolerable toxic effects. Primary endpoint were safety and objective response rate (ORR); secondary endpoints included progression-free survival (PFS), disease control rate (DCR), 6-month and 1-year PFS rate and overall survival (OS). The study will also explore the prediction of biomarkers as well as antigen-specific response.

Results: At present, 15 patients have been enrolled in the study and a total of 11 patients have been vaccinated with EGFR neoantigen vaccine. 5 patients achieved PR (partial response) and 6 achieved SD (stable disease) according to RECIST-v1.1, within 45.45% of ORR and 100% of DCR. The longest PFS was over 21 months till present. Aside from transient fever, rash, and fatigue observed in 5 patients, no severe adverse events related to vaccine injection were observed. The 1-2 grade TRAEs are consistent with known immuno and chemotherapy, while no ≥3 grade AEs were observed. 7 patients have been explored biomarkers related to immune response. Notably, immune monitoring showed that 6/7 patients (85.7%) demonstrated vaccine-induced T cell responses against EGFR neo-antigen peptides and up-regulation of Th1 cytokines including IL-2,IFN-α,TNF-α post vaccination in serum of patients with PFS >4.9 months. Furthermore, the percentage of effect-memory T cells (CD45RO+CD62L-) increased in both peripheral blood CD4+T cells (P=0.0424,P<0.05) and CD8+ T cells (P=0.0242,P<0.05) post vaccination.

Conclusions: This ongoing study with small samples has shown that EGFR neo-antigen vaccine with tislelizumab and chemotherapy for TKI resistant EGFRmut NSCLC has preliminarily confirmed safety and feasibility. The clinical and immune responses were observed following the combination therapy, suggested that shared immunogenic EGFR neoantigen are promising immunotherapeutic strategy for large population of EGFR-TKI resistant NSCLC patients and further efficacy needs to be evaluated in the future.

Keywords: Neoantigen vaccine, EGFR mutation, NSCLC

P4.11D METASTATIC NON-SMALL CELL LUNG CANCER - IMMUNOTHERAPY - CLINICAL TRIALS IN PROGRESS
MONDAY, SEPTEMBER 9, 2024 - 18:30 - 20:00

P4.11D.06 A Phase II Trial of Restorative Microbiota Therapy with Chemoimmunotherapy in Metastatic Non-Small Cell Lung Cancer

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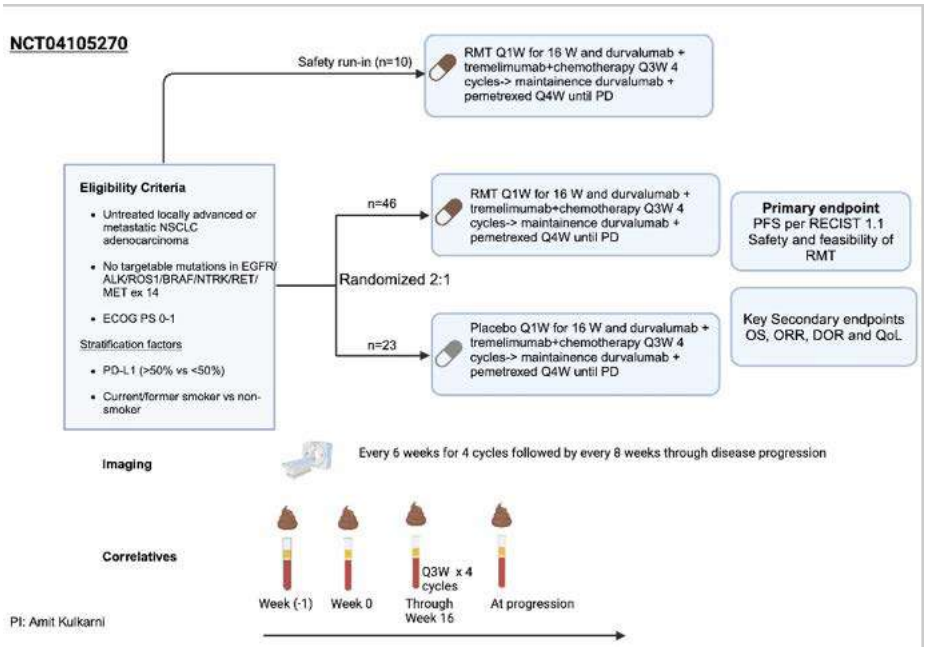
Introduction: Immune checkpoint inhibitors (ICI) with or without platinum doublet chemotherapy form the backbone of treatment in advanced or metastatic non-small cell lung cancer (NSCLC). Despite the success of ICI in lung cancer treatment, only a fraction of patients have durable response to ICI and others develop treatment resistance. Pre-clinical and clinical studies provide compelling evidence that the composition of the gut microbiome modulates immunotherapy response and clinical outcomes of ICI in metastatic melanoma and lung cancer. Recently, studies in patients with melanoma have provided preliminary evidence that manipulating the gut microbiome using fecal microbiota transplant is feasible and has demonstrated promising results that may overcome resistance to ICI. We hypothesize that adding microbiota transplant therapy i.e restorative microbiota therapy (RMT), which involves repeated oral administration of encapsulated healthy donor microbiota to immunotherapy improves the gut microbiome diversity and augments anti-tumor efficacy and improves treatment outcomes.

Methods: This is a multicenter, randomized, double-blind Phase II trial of oral RMT or placebo combined with durvalumab plus tremelimumab and platinum doublet chemotherapy in patients with advanced or metastatic NSCLC (NCT04105270). RMT is administered as an oral encapsulated formulation of freeze-dried fecal microbiota (compound MTP-101C) prepared from the stool of healthy donors and manufactured using GMP protocols at the University of Minnesota Microbiota Therapeutics Program. The clinical trial will run in 2 phases. The first phase is the open-label safety component where 10 patients are directly assigned to the RMT capsules with durvalumab and tremelimumab plus standard platinum-doublet chemotherapy. If no safety concerns are noted, the study then moves to the second phase i.e double-blind randomized (RMT vs Placebo) portion where approximately 69 patients are randomized 2:1 to receive either RMT or placebo capsules. In the study, all patients receive RMT or placebo capsules weekly for 16 weeks, along with durvalumab and tremelimumab with platinum doublet chemotherapy every 3 weeks for 4 cycles followed by maintenance durvalumab and pemetrexed every 4 weeks until disease progression, treatment intolerance or up to 2 years whichever occurs earlier. Patients are evaluated for treatment response at 6 weeks and 12 weeks, and then every 8 weeks thereafter with radiographic imaging until disease progression. The primary objective of the study is to evaluate the safety and efficacy of RMT in combination with durvalumab plus tremelimumab and chemotherapy using progression-free survival (PFS) per Response Evaluation Criteria in Solid Tumors (RECIST v1.1) as assessed by the investigator. We will collect stool and blood samples at baseline and longitudinally during treatment.

Keywords: Non small cell lung cancer, Immunotherapy, Gut microbiome



P4.11D METASTATIC NON-SMALL CELL LUNG CANCER - IMMUNOTHERAPY - CLINICAL TRIALS IN PROGRESS
MONDAY, SEPTEMBER 9, 2024 - 18:30 - 20:00

P4.11D.07 A Single Arm, Exploratory Study Oftislelizumab Intrapleural Therapyin NSCLC Patients with Malignant Pleural Effusion

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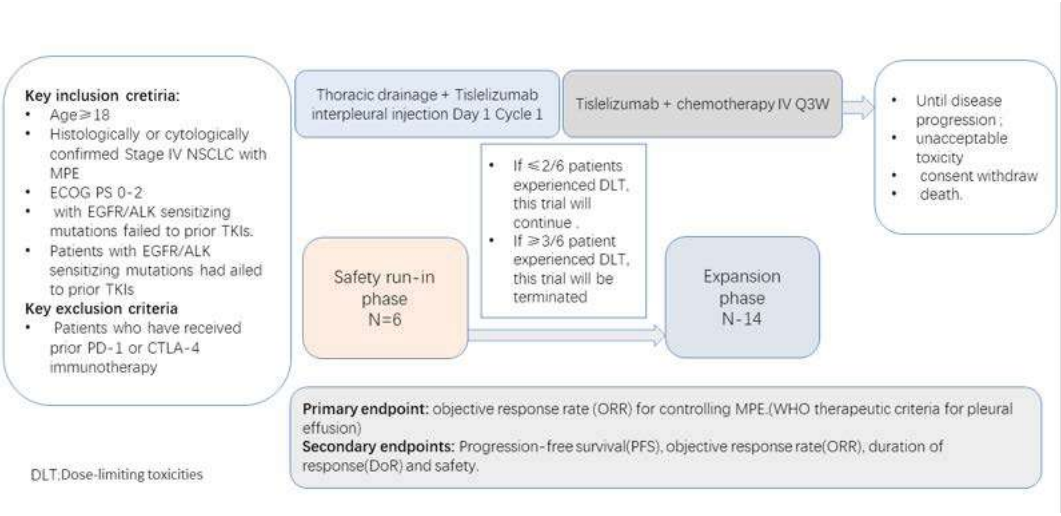
Introduction: Lung cancer is the most frequent cause of cancer worldwide, about 85% are non-small-cell lung cancer (NSCLC). Malignant pleural effusion (MPE) occurs in approximately 40% of advanced NSCLC patients and more frequently in adenocarcinoma. The presence of malignant effusion causes significant symptoms and result in decrease the quality of life and a poor prognosis. Herein, we conduct this study to evaluate the efficacy and safety of Tislelizumab intrapleural therapy combine immunochemotherapy in NSCLC patients with MPE.

Methods: This is a phase II, single arm, exploratory study conducting in the first affiliated hospital of Soochow University in China. Key inclusion criteria: stage IV NSCLC patients with symptomatic MPE, age≥18,ECOG PS 0-2, with EGFR/ALK sensitizing mutations patients should be failed to prior TKIs treatment. Patients who have received prior PD-1 or CTLA-4 immunotherapy will be excluded. All enrolled patients will receive Tislelizumab intrapleural administration in Day1 cycle 1 followed by Tislelizumab plus chemotherapy IV Q3W. We perform this study initially six enrolled patients in safety run-in phase followed by enrolled 14 patients in expansion phase. If 2 or less out of 6 patients experienced DLT in safety run-in phase, the trial will continue. All enrolled patients will receive immunochemotherapy until progression or unacceptable toxicity, consent withdraw or death. Primary endpoint: objective response rate (ORR) for controlling MPE. (WHO therapeutic criteria for pleural effusion).Secondary endpoints: Progression-free survival(PFS), objective response rate(ORR), duration of response(DoR) and safety.

Keywords: PD-1, malignant pleural effusion, intrapleural therapy



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P4.11D.08 Tislelizumab in Combination with Anlotinib as First-Line Treatment for Advanced Pulmonary Sarcomatoid Carcinoma: A Phase II Study

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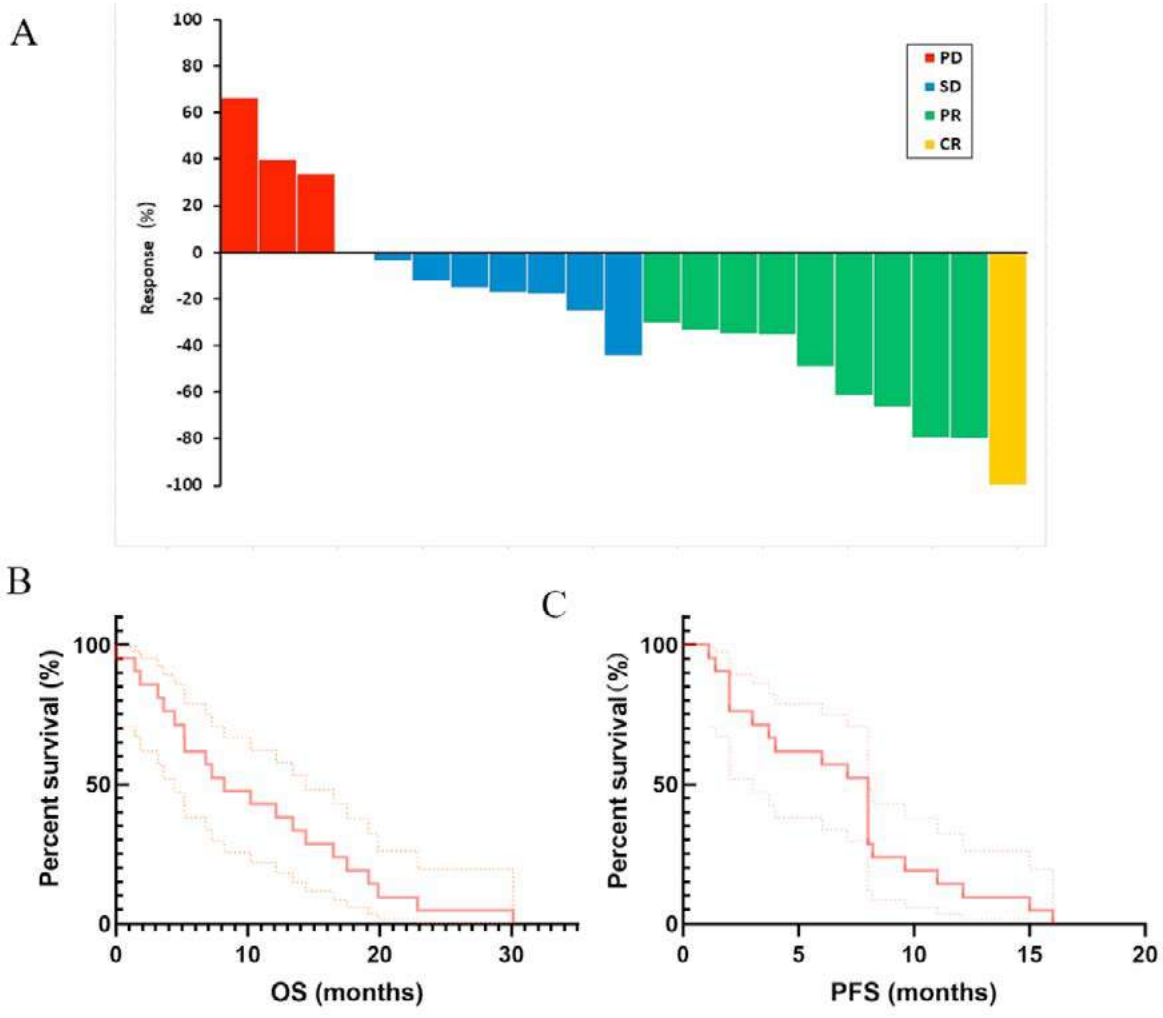
Introduction: Pulmonary sarcomatoid carcinoma (PSC) is a rare non-small cell lung cancer (NSCLC) subtype with a poor prognosis. The phase II trial aims to evaluate the efficacy and safety of tislelizumab in combination with anlotinib in patients with stage III and IV PSC.

Methods: This is a single-arm, prospective, open-phase II trial conducted at the second affiliated hospital of Nanchang University to assess the efficacy and safety of tislelizumab in combination with anlotinib in patients with stage III and IV PSC. All patients received first-line treatment with tirelizumab in combination with anlotinib. The primary endpoint was objective response rate (ORR), secondary endpoints included progression-free survival (PFS), overall survival (OS), and safety.

Results: Total 21 patients were enrolled from August 2021 to December 2023. In this study, the median age was 71 years (range 64.0-74.0), 76.2% were male, and 28.6% had a ECOG score of 2. The ORR was 85.7%, meeting the primary endpoint. Partial response (PR) and stable disease (SD) occurred in 10 (42.8%) and 8 (38.1%), respectively, and 1 (4.8%) achieving complete response (CR) (Fig.1A). The median PFS and OS were 8.0 months (95%CI: 0.38-0.82) and 13.4 months (95%CI: 0.29-0.78), respectively (Fig.1B-C). The main adverse events were immune-related toxicities associated with immunotherapy (irAEs), with an incidence rate of 52.4%. The incidence rate of treatment-related adverse events of grade 3 or higher (TRAE3) was 23.8% (5/21). No treatment-related deaths occurred.

Conclusions: Tislelizumab in combination with anlotinib as first-line treatment for PSC appears to be a safe and effective regimen. However, further confirmation through larger-sample studies is warranted. (ClinicalTrials.gov ID: NCT05375734).

Keywords: Pulmonary Sarcomatoid Carcinoma, Immunotherapy, Anlotinib



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P4.11D.09 Fianlimab-Based Combination Therapies in Patients with Advanced Non-Small Cell Lung Cancer: Trials in Progress Updates

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Introduction: Fianlimab (anti-lymphocyte activation gene 3) and cemiplimab (anti-programmed cell death-1) are high-affinity, fully human IgG4 monoclonal antibodies. Cemiplimab has shown promising clinical efficacy in patients with non-small cell lung cancer (NSCLC) and no actionable mutations, alone (programmed cell death ligand-1 [PD-L1] expression ≥50%) and in combination with chemotherapy (regardless of PD-L1 expression). However, many patients do not respond or only respond for a limited time. Although the standard of care for NSCLC continues to evolve, one approach to potentially improve outcomes is combination therapy with multiple checkpoint inhibitors with or without chemotherapy. In a previous Phase 1 study of fianlimab plus cemiplimab (NCT03005782), clinically meaningful activity and an acceptable risk-benefit profile were observed in patients with advanced melanoma.

Methods: Two parallel, randomized, multicenter, Phase 2/3 studies are ongoing. In Study 1 (NCT05785767), investigators are evaluating fianlimab + cemiplimab versus cemiplimab monotherapy as first-line treatment in patients with advanced NSCLC and tumors expressing PD-L1 ≥50%. In Study 2 (NCT05800015), investigators are evaluating fianlimab + cemiplimab + platinum-doublet chemotherapy versus cemiplimab + chemotherapy in patients with advanced NSCLC regardless of PD-L1 expression. Eligibility criteria for either study include: patients with histologically confirmed squamous/non-squamous stage IIIB/C (not candidates for surgical resection or definitive chemoradiation) or stage IV NSCLC (no prior systemic treatment for recurrent/metastatic NSCLC); ≥1 radiographically measurable lesion per Response Evaluation Criteria in Solid Tumors v1.1; Eastern Cooperative Oncology Group performance status ≤1; and adequate organ and bone marrow function.

In the Phase 2 part of Study 1, patients will be randomized 1:1:1 into three treatment arms (IV every 3 weeks [Q3W]): fianlimab high dose + cemiplimab 350 mg (Arm A); fianlimab low dose + cemiplimab 350 mg (Arm B); or cemiplimab 350 mg + saline/dextrose placebo (Arm C). Similarly, the Phase 2 part of Study 2 will be used to determine the fianlimab dose selected for the Phase 3 part. Patients will be randomized 1:1:1 to receive fianlimab high dose + cemiplimab 350 mg + chemotherapy (Arm A), fianlimab low dose + cemiplimab 350 mg + chemotherapy (Arm B), or cemiplimab 350 mg + chemotherapy + placebo (Arm C), IV Q3W. In the Phase 3 part of both studies, patients will be randomized 1:1 into either Arm A or B, or the comparator Arm C.

For both studies, the primary endpoint of the Phase 2 part is objective response rate (ORR) per blinded independent central review. In the Phase 3 part, the primary endpoint is overall survival (OS). Secondary endpoints for both studies include tolerability, safety, ORR per investigator assessment, disease control rate, time to tumor response, duration of response, progression-free survival, OS (Phase 2), patient-reported outcomes, pharmacokinetics, and immunogenicity.

Both studies are currently open for enrollment, along with a third Phase 2 study in which fianlimab + cemiplimab + chemotherapy versus cemiplimab + chemotherapy will be evaluated as perioperative therapy in patients with stage II/III NSCLC (NCT06161441).

Keywords: Fianlimab, Non-small cell lung cancer, Cemiplimab

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P4.11D.10 A Phase II Trial of Tiragolumab with Carboplatin, Pemetrexed, And Atezolizumab in Non-Squamous NSCLC and Brain Metastases

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Introduction: Registrational trials that have led to the approvals of immunotherapy alone or in combination with chemotherapy in patients with metastatic non-small cell lung cancer (NSCLC) have excluded patients with active brain metastases. There are encouraging phase II data supporting the antitumor activity of pembrolizumab monotherapy and the combination of carboplatin, pemetrexed and atezolizumab in patients with untreated NSCLC brain metastases. Tiragolumab, a monoclonal antibody that blocks TIGIT (T Cell Immunoreceptor with Ig and ITIM domains; an immune inhibitory receptor expressed on T cells and natural killer cells that interacts with CD155), can enhance anti-tumor activity when combined with immunotherapy and is currently being evaluated in combination with carboplatin, pemetrexed and atezolizumab in patients with newly diagnosed non-squamous NSCLC (SKYSCRAPER-06). We are conducting a phase II single arm investigator initiated clinical trial of this regimen in patients with newly diagnosed metastatic NSCLC and untreated brain metastases (NCT05746481).

Methods: Patients must have histologically or cytologically confirmed non-squamous NSCLC, with asymptomatic brain metastases with at least one untreated evaluable (modified RANO-BM) brain metastasis of 5 mm or more. Symptoms related to brain metastases requiring CNS radiation ≤ 2 weeks, steroids greater than prednisone 10 mg/d or equivalent or anti-epileptic therapy ≤ 2 weeks of treatment initiation are exclusionary. Patients must have adequate marrow function and an ECOG PS of 0 or 1. Tiragolumab 600mg IV is administered on day 1 of a 21-day cycle for 4 cycles in combination with atezolizumab plus carboplatin and pemetrexed, and then on day 1 of a 21-day cycle in combination with atezolizumab plus pemetrexed for up to 2 years as maintenance therapy until loss of clinical benefit, unacceptable toxicity, death or withdrawal of consent. MRI brain is performed at three weeks to assess safety and restaging MRI brain and CT will be done every nine weeks, thereafter. The primary end point is the proportion of patients that require salvage radiation therapy to the CNS within 18 weeks of study initiation. The proportion of participants requiring salvage therapy will be calculated with a 95% exact (Clopper-Pearson) confidence interval. Thirty-five patients will be enrolled with power in excess of 80% if the true P (salvage therapy) is less than or equal to 0.27. A stopping rule for excess toxicity, as measured by Grade 2 or worse CNS adverse events, will be employed after every five participants have received four cycles of treatment. Secondary endpoints include frequency of symptomatic CNS related adverse events, brain metastasis response rate (modified RANO-BM), ORR (RECIST v1.1), PFS, OS, PFS2 (PFS after salvage radiotherapy.) Accrual is ongoing.

Keywords: Tiragolumab, NSCLC, Metastases

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P4.11D.011 Evaluating the Impact of Performance Status on Outcomes in Advanced Lung Cancer: A Phase II Clinical Trial

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Introduction: The majority of metastatic non-small cell lung cancer (NSCLC) cases, lacking actionable tumor genetic alterations, are treated with immunotherapy with or without chemotherapy. Although NCCN guidelines include ECOG Performance Status (ECOG) 2 patients as candidates for systemic therapy, most registration trials for frontline therapy are limited to ECOG 0-1 patients. While ECOG performance status (PS) can be predictive for outcome, its value may be confounded by its subjectivity or by comorbidity (e.g., COPD). Additionally, PD-L1 is limited in predicting efficacy and is non-predictive for toxicity. Clinical trial data are needed to better define the first-line treatment approach for this large subgroup of patients and to develop better predictive assessments (e.g., patient-reported outcomes [PROs]) and circulating biomarkers). Our study objective is to test the use of standard first-line systemic regimens in patients with advanced NSCLC and compare outcomes between PS 0-1 versus PS 2 after three months of treatment. Exploratorily, we will longitudinally collect PROs and analyze key metabolomic factors in the transcriptional activity of peripheral blood mononuclear cells to compare patients with/without treatment response and high-grade immunotherapy toxicity, guided by prior studies.

Methods: The present study is a non-randomized phase II clinical trial (NCT04253964) that assigns advanced NSCLC patients to a standard first-line treatment regimen, stratifying outcomes per baseline ECOG PS: good (0-1) vs borderline (2). Eligibility criteria include: pathologically confirmed advanced NSCLC with no standard curative options, measurable disease, and no prior systemic therapy. Exclusion criteria include a high-level targetable tumor alteration, uncontrolled or autoimmune comorbidity, and pregnancy. Standard regimens are: pembrolizumab (PD-L1 ≥50%); carboplatin, pemetrexed, and pembrolizumab (PD-L1 <50%, non-squamous); or carboplatin, paclitaxel, and pembrolizumab (PD-L1 <50%, squamous). The primary outcome is progression-free survival (PFS) at three months, and we estimate our planned sample size of 105 patients will have 62% power to declare non-inferiority given no difference between two PS groups (90% CIs, margin -0.15, -0.05). Secondary outcomes include incidence of grade 3-5 treatment-related adverse events, change in quality of life by overall EORTC QLQ-C30 score, and deterioration of symptoms by ≥10 points on the QLQ-LC13 PRO measure. Exploratory outcomes will assess mitochondrial respiratory capacity of circulating mononuclear cells, mitochondrial function, plasma metabolomics, changes in COPD-specific PRO measures (i.e., COPD Assessment Test, mMRC dyspnea scale), and differences in PS assignment between treating physicians with an algorithmic assessment by the study team. Currently at 61% accrual (64/105), the study is anticipated to complete enrollment in 2025.

Keywords: NSCLC, Performance Status

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P4.11D.12 Phase 3 Trial of OSE2101 Versus Docetaxel in Patients with Non-Small Cell Lung Cancer & Secondary Resistance to Immunotherapy

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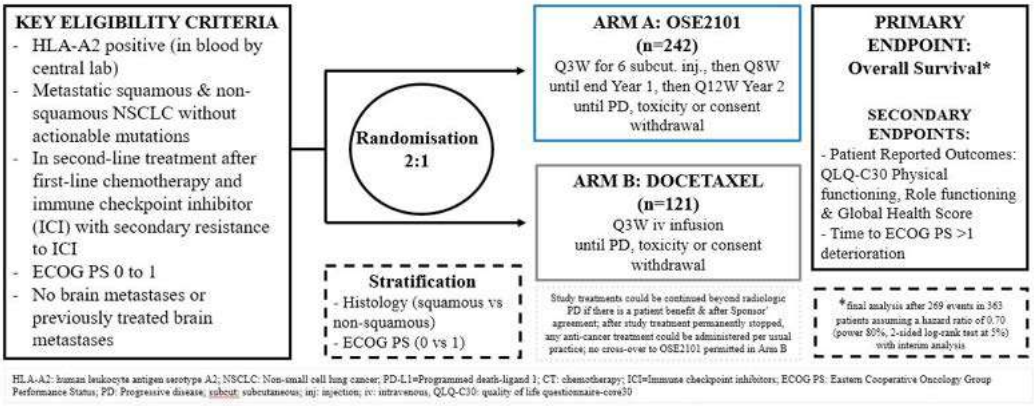
Introduction: OSE2101 is a therapeutic cancer vaccine composed of multiple peptides restricted to HLA-A2 phenotype targeting tumor-associated antigens (CEA, HER-2, MAGE-2, MAGE-3, P53) frequently expressed in non-small cell lung cancer (NSCLC). In a prior phase 2 study in heavily pretreated patients with NSCLC, OSE2101 strongly induced T cell immune responses, with higher immune responses associated with longer survival (OS). In the prior randomized ATALANTE-1 study, OSE2101 significantly improved OS with a better safety profile and quality of life (QoL) compared to third-line chemotherapy (CT) in patients with NSCLC with progressive disease (PD) after at least 12-weeks of second line anti-PD(L)1 monotherapy. The aim of the phase III ARTEMIA study is to confirm the benefit of OSE2101 versus CT in second-line treatment of patients with NSCLC and secondary resistance to immune checkpoint inhibitor (ICI) given in the first line setting.

Methods: HLA-A2 positive patients with metastatic NSCLC without known EGFR, ALK, ROS1 or other targetable mutations, no brain metastases, ECOG PS 0 or 1, who had a PD after 24 weeks or more of first line CT-ICI including at least 12 weeks of maintenance ICI without cytotoxic therapy, will be randomized 2:1 to receive either OSE2101 or docetaxel. Randomization will be stratified by histology (squamous vs non-squamous), and ECOG PS (0 or 1). Patients will receive subcutaneous OSE2101 every 3 weeks for 6 injections, then every 8 to 12 weeks up to end of year 2. In the control group, patients will receive docetaxel at 75mg/m2 per standard of care. Primary endpoint is OS defined as time from randomization to death of any cause. Secondary endpoints include QoL Physical, Role, and Global Health Score by EORTC QLQ-C30 questionnaire, and time to ECOG PS deterioration. For sample size calculation, assuming a hazard ratio of 0.70 with a power of 80% using a 2-sided log-rank test, 363 patients will be enrolled to reach 269 events. An interim analysis is planned.

Conclusions: The ARTEMIA phase 3 study aims to confirm the benefit on survival and quality of life of the therapeutic cancer vaccine OSE2101 compared to docetaxel in second-line treatment of HLA-A2 positive patients with NSCLC and secondary resistance to immune checkpoint inhibitor.

Keywords: Metastatic NSCLC, Therapeutic Cancer Vaccine, Resistance to Immune Checkpoint Inhibitor



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P4.11E.01 Real-World First-Line Maintenance Immunotherapy for Nonsquamous Advanced/Metastatic NSCLC without Targetable Mutations

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Introduction: Real-world data comparing first-line maintenance (1LM) immunotherapy (IO)±pemetrexed for patients with nonsquamous (NSQ) advanced/metastatic non-small cell lung cancer (a/mNSCLC) are lacking. This retrospective study compared effectiveness and safety of 1LM IO vs IO+pemetrexed for patients with NSQ a/mNSCLC.

Methods: Physician-provided data, collected via chart review, included patients from Canada, France, Germany, Italy, Spain, the UK, and the US who had NSQ (including mixed squamous/NSQ) a/mNSCLC without targetable mutations, completed 4-6 cycles of 1L chemotherapy (platinum-based chemotherapy+IO, ±pemetrexed) between January 2019 and March 2021, were ≥18 y, and had achieved stable disease or complete or partial response on completion of 1L therapy. Patients who received 1LM of either IO monotherapy or IO+pemetrexed were selected for the current analysis. Progression-free survival (PFS; time from 1LM initiation to progression, death, or second-line maintenance initiation), overall survival (OS; time from 1LM initiation to death), safety, and time to treatment discontinuation (TTD) were assessed.

Results: By selecting patients with NSQ a/mNSCLC receiving 1LM achieving stable disease or complete or partial response, 469 were eligible (median age 64.0 y, 70.1% male, 85.7% current/former smokers, 75.3% PD-L1 ≥1%), 283 received IO, most commonly pembrolizumab monotherapy, and 186 received IO+pemetrexed, most commonly pembrolizumab+pemetrexed. Patients receiving IO monotherapy vs IO+pemetrexed had longer median PFS and median OS (Table; similar efficacy results were seen for patients with PD-L1 ≥1%), had longer median TTD (20.0 vs 11.0 months, P<0.001), and were less likely to experience fatigue (28.3% vs 39.8%, P<0.05) and anemia (16.6% vs 31.2%, P<0.001) while on 1LM therapy.

Conclusions: Among the selected patients with NSQ a/mNSCLC who achieved stable disease or complete or partial response to 1L therapy, the addition of pemetrexed to IO for 1LM did not appear to confer additional clinical benefit.

Keywords: amNSCLC, non-squamous, maintenance immunotherapy

Table. Real-world PFS and OS stratified by IL maintenance therapy

1L maintenance therapy	IO n=283	IO + pemetrexed n=186	Hazard ratio (95% CI)[a]
Adjusted median PFS, mo	21.1	11.1	0.56 (0.37–0.76)
Adjusted median OS, mo	35.3	27.3	0.70 (0.41–0.98)

[a]The adjusted survival curve were estimated using standardized mortality ratio weighting method. 95% CIs were estimated using bootstrapping.
1L, first-line; IO, immunotherapy; OS, overall survival; PFS, progression-free survival.

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P4.11E.02 Efficacy of Pembrolizumab Plus Pemetrexed in Older Patients with Non-squamous NSCLC According to PD-L1 Status from the CJLSG1901 Study

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Introduction: Pembrolizumab combined with pemetrexed and carboplatin is the standard of care for patients with metastatic non-squamous non-small cell lung cancer (NSCLC); however, its efficacy and safety remain unclear in older patients with metastatic non-squamous NSCLC.The CJLSG1901 phase 2 study suggested pembrolizumab plus pemetrexed was a promising candidate as a novel first-line treatment strategy for patients aged ≥75 years with metastatic non-squamous NSCLC. Previous studies also revealed that pembrolizumab efficacy varied with PD-L1 status in advanced non-squamous NSCLC. Therefore, this study aimed to evaluate the efficacy and safety of pembrolizumab plus pemetrexed according to PD-L1 status in this patient population.

Methods: We investigated the efficacy and safety of pembrolizumab combined with pemetrexed in older patients with metastatic non-squamous NSCLC according to PD-L1 status (< 1% vs 1-49%) in the post-hoc subgroup analysis from CJLSG1901. The Clopper-Pearson method was used to estimate the 95% confidence interval (CI) of objective response rate (ORR). The Kaplan-Meier method was used to estimate survival functions, and the Brookmeyer-Crowley method was used to estimate the 95% CIs of median survival time.

Results: A total of 49 patients were enrolled between July 2020 and May 2022. The median age was 79 years (range, 75-91). The primary endpoint of ORR was 36.7% (95% CI: 23.4-51.7). The median progression-free survival (PFS) was 7.6 months (95% CI: 4.8-16.2), and the median overall survival (OS) was 19.4 months (95% CI: 11.8- not reached). Overall, 21 patients had PD-L1 < 1% and 28 patients had PD-L1 1-49%. Characteristics such as median age, sex, Eastern Clinical Oncology Group performance status, and stage were similar between the groups. ORR of the patients with PD-L1 < 1% and 1-49% was 23.8% (95% CI: 8.2-47.2), and 46.4% (95% CI: 27.5-66.1), respectively. The median PFS of patients with PD-L1 < 1% and 1-49% were 4.4 months (95% CI: 2.9-24.1) and 7.8 months (95% CI: 5.5-18.2), while the median OS was 19.4 months (95% CI: 6.4-not reached) and 19.1 months (95% CI: 11.8-not reached), respectively. All patients experienced adverse events (AEs) of any grade, regardless of PD-L1 status. AE severities were similar between groups. Serious treatment-related AEs were observed in five (25%) patients with PD-L1 < 1% and seven (25%) patients with PD-L1 1-49%.

Conclusions: The ORR and median PFS of patients with PD-L1 1-49% were numerically higher than those of patients with PD-L1 < 1%; however, OS were similar in both groups. AE proportions and severities were similar among all patients with PD-L1 <50%. Thus, pembrolizumab plus pemetrexed may be effective in older patients with non-squamous NSCLC with PD-L1 <1% and 1-49%.

Keywords: pembrolizumab plus pemetrexed, older patients, PD-L1

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P4.11E.03 Safety and Efficacy of AL2846 Combined with TQB2450 In NSCLC Patients with Previous PD-(L)1 Inhibitor Treated (NCT06116240)

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Introduction: For patients who have failed first-line treated by PD-1/PD-L1 inhibitors and platinum-containing chemotherapy, there is currently no higher-level evidence of more effective treatment options other than single-agent chemotherapy.

Methods: This open-label, multicenter study include two phases of dose-escalation and dose-expansion. In dose-expansion phase, patients with locally advanced or metastatic NSCLC were enrolled and previous treated with PD-(L)1 inhibitors, either singly or in combination with platinum-based chemotherapy. The primary endpoints were safety and objective response rate (ORR). Secondary endpoints included progression-free survival (PFS), disease control rate (DCR), duration of response (DOR) and overall survival (OS). Patients received a fixed dose of TQB2450 (PD-L1 inhibitor) 1200mg/Q3W, and AL2846 (multi-target tyrosine kinase receptor inhibitor) 120mg/QD, every 3 weeks in a treatment cycle, and imaging assessment every 6 weeks. Efficacy was evaluated according to RECIST 1.1/iRECIST evaluation criteria, mainly RECIST 1.1.

Results: As of January 31, 2024, 44 patients have been enrolled in the study, 39 patients can be evaluated for efficacy. The number of prior systemic lines of therapy was range1~3. In terms of histopathologic subtypes, most of them were squamous cell carcinoma. Preliminary efficacy results showed that ORR assessed by the investigators was 25.6% (10/39), the median PFS was 5.72 months (95% confidence interval [CI], 4.07~8.21), DCR was 94.9%(37/39), the median DOR was 5.54 months (95% CI, 3.52~NR), the median OS was 13.44 months (95% CI, 7.98~21.26). Most PR were achieved at the first time of efficacy evaluation. Among the best response was evaluated as SD, 22 patients had tumor shrinkage, of which 8 patients had tumor shrinkage to more than 20%. Regarding safety, Grade ≥3 treatment related adverse events (TRAEs) occurred in 59.1% (26/44) of patients, the most common events involved hypertension (22.7%, 10/44), diarrhea (4.5%, 2/44), palmar and plantar redness syndrome (2.3%, 1/44), proteinuria (2.3%, 1/44). 11.4%(5/44) of patients occurred dose reduction because of TRAEs, mainly were caused by hypertension, diarrhea, proteinuria.

Conclusions: AL2846 combined PD-L1 inhibitor showed promising clinical activity in patients with locally advanced or metastatic NSCLC who previous treated with PD-(L)1 inhibitors. Based on the good efficacy and safety results of this study, the phase III study is currently being recruited.

Keywords: NSCLC, PD-(L)1 inhibitor, multi-target tyrosine kinase receptor inhibitor

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P4.11E.05 A Phase II, Randomized Trial of Trilaciclib Plus Chemotherapy and Tislelizumab as First-Line Treatment for Advanced SqNSCLC

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Introduction: Immune checkpoint inhibitors (ICIs) combined with chemotherapy has been established as the standard first-line treatment for advanced squamous non-small cell lung cancer (sqNSCLC), regardless of PD-L1 expression levels. However, chemotherapy-induced myelosuppression (CIM), resulted in reduced neutrophils, platelets, and anemia, seriously affecting patients' quality of life and survival. Trilaciclib, a CDK4/6 inhibitor administered prior to chemotherapy for multilineage myeloprotection, has been commercialized in America and China as a myeloprotective agent for specific SCLC chemotherapy regimens. This study aimed to explore the myeloprotective effects of trilaciclib in patients with squamous NSCLC receiving a combination therapy of chemotherapy (carboplatin+paclitaxel) and ICI (tislelizumab).

Methods: This is a prospective, randomized, multi-center, phase II clinical study (NCT05900921). Eligible patients with advanced, untreated squamous non-small cell lung cancer, ECOG PS of 0-1 were randomly assigned 1:1 to two groups. The patients in the treatment group received trilaciclib (240 mg/m2) plus paclitaxel (175 mg/m2), carboplatin (AUC=5), and tislelizumab (200mg,Q3W) for 4-6 cycles (induction period), followed by maintenance treatment with trilaciclib plus tislelizumab (200mg,Q3W) until disease progression or unacceptable toxicity. The patients in the control group received the same chemotherapy plus ICI treatment without trilaciclib. The primary endpoint was the occurrence of grade ≥3 neutropenia during induction period. Secondary endpoints included other myeloprotective indicators, such as the incidence of thrombocytopenia and anemia, anti-tumor efficacy such as objective response rate, progression-free survival, and overall survival. If subsequent chemotherapy is indicated for patients after first-line progression, trilaciclib will be provided to observe the myeloprotective effect in second-line treatment.

Results: Between August 9, 2023 and March 31, 2024, 11 patients were randomized into 2 groups (treatment group, n=4; control group, n=7). 7 patients completed ≥1 cycle follow-up (3 in the experimental group and 4 in the control group). Baseline demographic characteristics were similar between the two groups. All the 7 patients were male, ECOG score 0-1, 49-70 years old, and stage IV squamous non-small cell lung cancer. In the treatment group: the reported CIM were neutropenia (1 patient had grade 2 and 1 patient had grade 3), thrombocytopenia (1 patient had grade 1), anemia (2 patient had grade 1,assessed according to CTCAE 5.0). One patient was administrated with granulocyte colony-stimulating factor (G-CSF) to treat grade 3 neutropenia. All 3 patients achieved partial responses. In the control group, The reported CIM in the 4 patients were neutropenia (1 patient had grade 3 and 2 patient had grade 4), thrombocytopenia (1 patient had grade 1), anemia (2 patient had grade 2, 1 patient had grade 1). All the 3 patients reported grade ≥3 neutropenia were treated with G-CSF. The anti-tumor efficacy of 3 patients was evaluable, 1 patient achieved partial responses and 2 patients achieved stable disease.

Conclusions: Preliminary results revealed that trilaciclib-based combination therapy demonstrated potential improvement of the tolerability of chemotherapy in patients with sqNSCLC. The study is currently recruiting.

Keywords: Squamous non-small cell lung cancer, Trilaciclib, Myeloprotection

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P4.11E.06 Envafolimab Combined with Recombinant Human Endostatin and Chemotherapy as First-Line Treatment for Advanced Squamous NSCLC

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Introduction: In recent years, immunotherapy combined with chemotherapy has been established as the standard first-line treatment for patients with advanced squamous NSCLC (sq-NSCLC). Antiangiogenic drugs can enhance the efficacy of immunotherapy and chemotherapy by normalizing blood vessels and improving the tumor microenvironment. However, antiangiogenic agents have a high risk of hemorrhage in the treatment of sq-NSCLC. Recombinant Human Endostatin (Rh-endostatin) has previously been proven to prolong survival in patients with sq-NSCLC without increasing the risk of hemorrhage, and is currently the only approved antiangiogenic agent for first-line treatment of sq-NSCLC. Envafolimab, the first approved single-domain anti-PD-L1 antibody, represents a potential advance because it can be conveniently administered subcutaneously. This study aimed to investigate the efficacy and safety of envafolimab plus Rh-endostatin and chemotherapy as first-line treatment for advanced sq-NSCLC.

Methods: This was a single-arm, multi-center, prospective, phase II clinical study (NCT05243355). Between December 2021 and January 2024, consecutive patients with histologically or cytologically confirmed sq-NSCLC were enrolled. Patients received envafolimab (300mg, subcutaneous, day 1,) and Rh-endostatin (210 mg, continuous intravenous infusion over 72 h, day 1-3) combined with platinum-based chemotherapy every 3 weeks for 4-6 cycles, followed by maintenance treatment with envafolimab until disease progression (PD), unacceptable toxicity, or patient refusal. The primary endpoint was the 1-year PFS rate, and secondary endpoints included objective response rate (ORR), disease control rate (DCR), progression-free survival (PFS), overall survival (OS), safety, and tolerability.

Results: Overall, 26 patients with previously untreated stage IIIB/IIIC or IV sq-NSCLC were screened in this study. As of January 29, 2024, 24 patients were included for safety evaluation with 21 patients for efficacy analysis. According to RECIST v1.1, the ORR was 81% (95% CI, 58.1-94.6), and the DCR was 100% (95% CI, 83.9-100). Survival data were not mature at present. Adverse events (AEs) of any grade were reported in 95.8% (23/24) patients, the most common AEs were myelosuppression, alopecia, nausea, which were more related to chemotherapy. 45.8% (11/24) patients experienced immune-related AEs (irAEs), the most common irAE was rash (7/24, 29.2%). Grade ≥ 3 irAEs occurred in four patients, which were mainly skin-related toxicities. There were no unexpected AEs identified in this study.

Conclusions: Envafolimab plus Rh-endostatin and chemotherapy resulted in a favorable clinical efficacy with tolerable safety profile in advanced sq-NSCLC, representing a promising treatment regimen for this population.

Keywords: Envafolimab, sq-NSCLC, First-line

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P4.11E.07 Envafolimab Combined with Recombinant Human Endostatin and Chemotherapy for NSCLC, C. Miao1, S. Yuan2, 2Provincial Hospital Affiliated to University of Science and Technology of China, Hefei/CN

Introduction: In recent years, the integrated treatment modality of immunotherapy combined with anti-angiogenesis has achievedgratifying therapeutic effects in the second-line treatment of lung cancer. Envafolimab is the first PD-L1 drug to be injected subcutaneously. This study aimed to investigate the efficacy and safety of the combined first-line treatment modality involving Envafolimab, a subcutaneously injected PD-L1 inhibitor, with Recombinant Human Endostatin (Rh-endostatin) and chemotherapy in patients with driver gene-negative advanced Non-Small Cell Lung Cancer (NSCLC).

Methods: This was a single-arm, single-center, prospective, phase II clinical study. Between April 2022 and August 2023, consecutive eligible patients with histologically or cytologically confirmed with untreated stage IV NSCLC (excluding driver mutations) were enrolled. Patients received 4-6 cycles of Envafolimab (300 mg, subcutaneous, Day 1, every 3 weeks) and Rh-endostatin (210 mg, continuous intravenous infusion over 72 h, every 3 weeks) combined with platinum-based dual-agent chemotherapy, followed by maintenance therapy with Envafolimab and Rh-endostatin until disease progression or intolerable toxicity. The primary endpoints were the objective response rate (ORR) and disease control rate (DCR), and secondary endpoints included progression-free survival (PFS), overall survival (OS), safety, and tolerability.

Results: As of December 1, 2023, the median follow-up was 11.8 months (95% CI, 9.4-12.6). Twenty-nine patients with advanced NSCLC were enrolled at Shandong First Medical University Affiliated Cancer Hospital. Of the 29 patients, 14/29 were squamous cell carcinoma, and 15/29 were non-squamous non-small cell lung cancer. The ORR was 72.4% (95% CI, 56.1%-88.7%), and the DCR was 93.1% (95% CI, 76.8%-109.4%), showing statistically significant differences compared with data from previous results. Median PFS and OS were not reached yet. Safety was manageable with no ≥ grade 3 treatment-related adverse events (TRAEs) or immune-related adverse events (irAEs).

Conclusions: Envafolimab in combination with Rh-endostatin and chemotherapy as a first-line treatment for lung cancer exhibits favorable therapeutic efficacy with a manageable safety profile, which might represent a promising treatment regimen and warrant further investigation.

Keywords: Envafolimab, Rh-endostatin, NSCLC

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P4.11E.08 Integrated PK/PD Modeling for Ulileldlimab, an Anti-CD73 Monoclonal Antibody, In Non-Small Cell Lung Cancer Patients

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Introduction: Ulileldlimab is a CD73 antagonistic monoclonal antibody designed to inhibit CD73 enzymatic activity leading to suppression of adenosine production. Adenosine has been shown to cause immunosuppression and PD-1/PD-L1 checkpoint inhibitor resistance. Complete inhibition of CD73 function across a wide range of expression and potentiation of PD-1/PD-L1 inhibitor activities in vivo supported Phase 1 clinical evaluation with combination therapies for non-small cell lung cancer (NSCLC) patients.

Methods: To evaluate the impact of ulileldlimab dosage after Phase 1 study, an integrated approach leveraging nonclinical and clinical results was applied, including target threshold estimation, PK/PD, population PK (popPK) modeling & simulation, and exposure-response (E-R) analyses. The target threshold in human serum was derived from functional activity inhibition and PK/PD analyses with consideration of tumor penetration rate. PK data from three previous clinical studies with ulileldlimab monotherapy or in combination with atezolizumab or toripalimab were used to construct the popPK model. The simulated exposure of ulileldlimab in humans was used to evaluate trough concentrations against the target threshold of different dosing regimens. Serum exposure, overall response rate (ORR), and progression free survival (PFS) data from the patients with treatment-naïve metastatic NSCLC who received ulileldlimab 20 and 30 mg/kg Q3W (in combination with toripalimab) were included in the E-R analyses.

Results: A target threshold of 80 μg/mL was derived from EC80 of the functional CD73 activity inhibition and the assumed tumor penetration rate. The 2-compartment popPK model with parallel linear and nonlinear eliminations captured adequately the ulileldlimab pharmacokinetics in human serum. It was observed that the 30 mg/kg Q3W dose was superior to the 20 mg/kg Q3W dose to provide ulileldlimab trough concentrations achieving and maintaining above 80 μg/mL after the third dose in the majority (95%) of the simulated population. The relationship between Ctrough after the first dose or at the steady state and the probability of ORR was explored. A clear trend of higher ORR probability was associated with higher trough concentration after the first dose or at the steady state. The Kaplan-Meier (K-M) curves of the longitudinal PFS stratified by a target threshold of 80 μg/mL after the first dose and at steady state reported a clear separation. The patients who achieved ulileldlimab exposure equal to or above 80 μg/mL showed a greater median PFS than those below. These PFS analyses by Ctrough further supported that the target threshold of 80 μg/mL may be clinically meaningful.

Conclusions: A population PK model was established and the integrated PK/PD analyses were performed. The E-R analysis showed a positive relationship between ulileldlimab concentration and the probability of ORR in patients with NSCLC. The K-M analysis indicated that the ulileldlimab Ctrough threshold of 80 μg/mL may be associated with PFS benefit and is likely clinically meaningful. The non-traditional integrated PK/PD coupled with modeling & simulation and exposure-response analyses and findings support and inform further ulileldlimab development in NSCLC patients.

Keywords: Ulileldlimab, PK/PD, NSCLC

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P4.11E.09 The Efficacy of PD-1/PD-L1 Inhibitors Combined with Chemotherapy and Anti-Angiogenesis Therapy in Driver Gene-Negative NSCLC Brain Metastases

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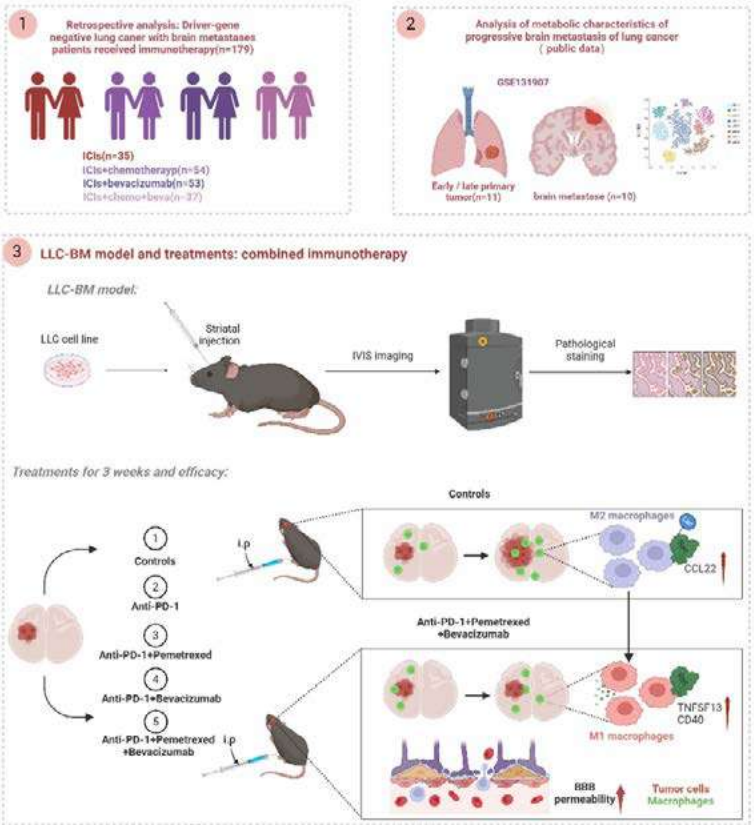
Introduction: The IMpower150 study suggest that immune checkpoint inhibition combined with chemotherapy and anti-angiogenic therapy may delay the onset of brain metastases, highlighting the urgent need for further clincial and preclinical investigations to explore optimal treatment modalities for driver-gene negative lung adenocarcinoma brain metastases. Theoretically, anti-angiogenic agents hold the potential to promote the normalization of tumor vasculature structure and function, correcting the immune-suppressive microenvironment, restoring drug penetration in the tumor core, and sensitizing to combined therapies. This study combined clinical restrospective analysis and precilinical experiments to elucidate the potential mechanisms underlying the therapeutic effects of PD-1 inhibitor combined with chemotherapy and anti-angiogenic treatment on driver gene-negative lung adenocarcinoma brain metastasis, focusing on alterations in the immune microenvironment and vascular normalization.

Methods: Clinical data of patients with driver gene negative lung cancer brain metastases who received PD-1/PD-L1 inhibitors at the Second Affiliated Hospital of Nanchang University between May 2020 and July 2022 were collected. Univariate and multivariate analyses were performed to identify independent prognostic factors. Overall survival (OS) and intracranial progression-free survival (iPFS) was analyzed. Animal model of driver gene negative lung adenocarcinoma brain metastases (LLC-BM) was established. The anti-tumor effect, blood-brain barrier permeability and immune microenvironment of mice treated with immunotherapy were detected by in vivo imaging, immunohistochemistry and EB/FITC staining.

Results: 179 patients were included. PD-1/PD-L1 inhibitors combined with chemotherapy and antiangiogenic therapy (n=37) versus PD-1/PD-L1 inhibitors combined with chemotherapy (n=54), PD-1/PD-L1 inhibitors combined with anti-angiogenic therapy (n=53), and PD-1/PD-L1 inhibitors alone (n=35) showed median OS of 21.20 vs 16.00 vs 16.53 vs 9.30 months (P=0.013) and median iPFS of 15.20 vs 11.30 vs 9.03 vs 8.10 months (P=0.118), respectively. In the LLC-BM animal model, the mice in the PD-1 inhibitor combined with bevacizumab and pemetrexed group exhibited the lowest tumor fluorescence intensity, sustained tumor area reduction, and the longest average survival time, suggesting the best inhibitory effect of PD-1/PD-L1 inhibitors combined with chemotherapy and antiangiogenic therapy, which reduced infiltration of M2 macrophages and increased PD-L1 expression, normalized vascular morphology (linear, less bending) and increased CD8+ T cell infiltration, improved tumor hypoxia, enhanced blood-brain barrier permeability and increased perivascular coverage.

Conclusions: PD-1/PD-L1 inhibitors combined with chemotherapy and antiangiogenic therapy may represent the optimal combination regimen for driver gene negative lung adenocarcinoma brain metastases. PD-1 inhibitor combined therapy with chemotherapy and anti-angiogenic treatment activates the immune microenvironment, ameliorate hypoxia, enhance blood-brain barrier permeability and promote vascular normalization.

Keywords: Lung adenocarcinoma, brain metastases, immunotherapy



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P4.11E.10 Safety and Efficacy of Sintilimab Combined with Anlotinib in Patients with KRAS-Mutant Advanced Non-Small Cell Lung Cancer

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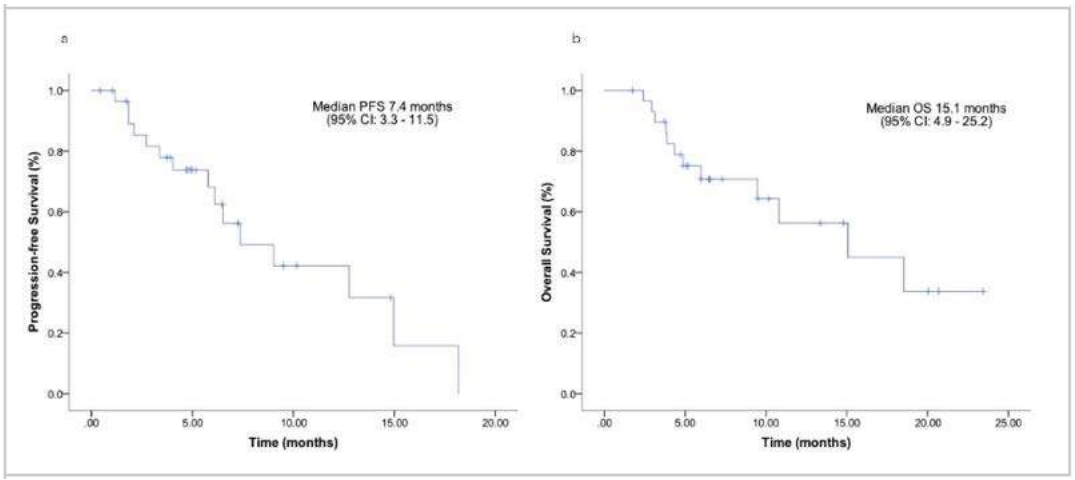
Introduction: The KRAS mutation is prevalent in non-small cell lung cancer (NSCLC), emphasizing the urgency for effective treatments. Specific KRAS G12C inhibitors are in development, with their clinical efficacy eagerly anticipated. Immune checkpoint inhibitors (ICIs), either alone or in combination with chemotherapy, represent the current standard of care for the treatment of advanced NSCLC lacking targetable oncogenic mutations, including those with KRAS mutations. Anti-angiogenesis agents have shown potential to enhance the efficacy of immunotherapy. This study aims to evaluate the efficacy and safety of the combination of sintilimab with anlotinib in previously treated patients with advanced KRAS-mutant NSCLC.

Methods: Patients who had disease progression on at least one line of systemic therapy were included. Participants received sintilimab (200 mg intravenously on day 1) and anlotinib (12 mg orally from day 1 to day 14) once every three weeks. The primary endpoint was progression-free survival (PFS). The secondary endpoints included overall survival (OS), objective response rate (ORR), disease control rate (DCR) and safety. Subset with KRAS G12C mutations and non-G12C subtypes were identified. This study is registered with the Chinese Clinical Trial Registry (ChiCTR2000032266).

Results: Thirty eligible patients were enrolled from April 2019 to June 2022 at Peking University Shenzhen Hospital. Most had stage IV (76.7%) adenocarcinoma (93.3%), with 53.3% having non-G12C mutations. Frontline treatment included anti-angiogenesis (20.0%), anti-PD-(L)1 (63.3%), and chemotherapy (90.0%). The ORR and DCR were 23.3% and 76.7%, respectively. The median PFS was 7.4 months (95% CI: 3.3 - 11.5), while the median OS was 15.1 months (95% CI: 4.9 - 25.2). Both G12C and non-G12C subtypes demonstrated comparable outcomes (PFS, 9.0 vs. 7.4 months, P = 0.80; OS, 15.1 vs. 10.8 months, P = 0.64, respectively). Patients who did not receive prior anti-angiogenesis therapy exhibited longer PFS (12.8 vs. 2.7 months, P < 0.001) and OS (18.5 vs. 4.3 months; P = 0.008) compared to those who did. Treatment-related adverse events (TRAEs) occurred in 93.3% of patients, with 23.3% classified as grade 3 - 4. The most common grade 3 - 4 TRAEs included hypertension (10.0%), hand and foot skin syndrome (6.7%), rash (3.3%), elevated alanine aminotransferase (ALT) levels (3.3%), and proteinuria (3.3%). No deaths were attributed to TRAEs.

Conclusions: The combination of sintilimab with anlotinib shows promising efficacy and manageable toxicities in previously treated patients with advanced KRAS-mutant NSCLC. Further study in phase 3 trials is warranted.

Keywords: KRAS mutant non-small cell lung cancer, immune checkpoint inhibitor, anti-angiogenesis



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P4.11E.11 Dosing Regimen for Acasunlimab (DuoBody-PD-L1x4-1BB) In Combination with Pembrolizumab

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Introduction: Acasunlimab (DuoBody®-PD-L1x4-1BB) is an investigational bispecific antibody immunotherapy designed to elicit an antitumor response via conditional 4-1BB activation that is strictly dependent on simultaneous PD-L1 binding. The PD-L1 arm of acasunlimab also functions as an immune checkpoint inhibitor (CPI) by blocking the PD-1/PD-L1 axis. A semi-mechanistic pharmacokinetics/pharmacodynamics (PK/PD) model was used to determine acasunlimab 100 mg Q3W as the expansion dose, allowing optimum trimer (PD-L1:acasunlimab:4-1BB) formation and 4-1BB activation, with partial PD-L1 blockade. Acasunlimab is currently being evaluated in a randomized phase 2 trial (NCT05117242) in patients with CPI-experienced PD-L1+ metastatic non-small cell lung cancer as monotherapy (100 mg Q3W x2 cycles, then 500 mg Q6W), or combination (100 mg + pembrolizumab 200 mg Q3W or 100 mg + pembrolizumab 400 mg Q6W), allowing maximum blockade of the PD-1 pathway. Initial results indicate acasunlimab combination with pembrolizumab shows promising efficacy with durable disease control in patients treated Q6W (Aerts J et al. ASCO 2024). Here we describe PK/PD, exposure-response (E-R), and peripheral PD analyses used for dose-optimization of acasunlimab plus pembrolizumab.

Methods: Acasunlimab exposures (average concentration over first dosing cycle) predicted from population PK model were used in the E-R analyses of efficacy (objective response rate [ORR]), safety (standardized MedDRA query [SMQ]-hepatic events) or PK/PD model describing soluble 4-1BB (s4-1BB) levels. Additionally, a quantitative systems pharmacology (QSP) model was developed to predict conditional 4-1BB engagement and PD-1/PD-L1 complex disruption, by combining a physiologically based PK model for acasunlimab distribution and relevant immune system components. Baseline and on-treatment peripheral blood analyses determining serum s4-1BB and cytokine levels by immunoassays and assessing T-cell proliferation and functionality by flow cytometry were utilized to support dose selection.

Results: Model predictions showed that while acasunlimab 500 mg Q6W resulted in >90% PD-L1 receptor occupancy, trimer engagement was approximately 50% compared with 100 mg Q3W. In combination with pembrolizumab, E-R analyses showed no apparent trend for probability of ORR (efficacy) and SMQ-hepatic events (safety) at range of acasunlimab exposures evaluated at 100 mg Q3W or Q6W, indicating less-frequent administration leading to lower average exposure may be sufficient. Peripheral s4-1BB, a surrogate for target engagement, showed intermittent on-treatment induction in patients treated with combination Q6W compared with sustained induction with Q3W. Further PD analyses showed a more intermittent T-cell proliferation (as predicted in the QSP model) and cytokine modulation in patients treated with combination Q6W compared with Q3W. Reduced on-treatment induction of the coinhibitory marker TIM-3 was observed on CD8 T-cell subsets in patients treated with combination Q6W, with retained T-cell proliferation/activation observed in later cycles in patients with long-term treatment benefit.

Conclusions: Less-frequent acasunlimab dosing (Q6W) in combination with pembrolizumab leading to intermittent engagement of 4-1BB showed more durable clinical activity and peripheral immunomodulation in patients. PD results support the hypothesis that intermittent 4-1BB engagement reduces chronic T-cell stimulation, potentially mitigating T-cell dysfunction by allowing a resting interval and resetting of T-cell function. This may improve the magnitude and quality of antitumor immune responses and result in improved durability in the clinical setting.

Keywords: bispecific, pharmacokinetics, pharmacodynamics

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P4.11E.12 First Line Camrelizumab for Brain Metastases of NSCLC (CTONG 2003): A Randomized Controlled Trial

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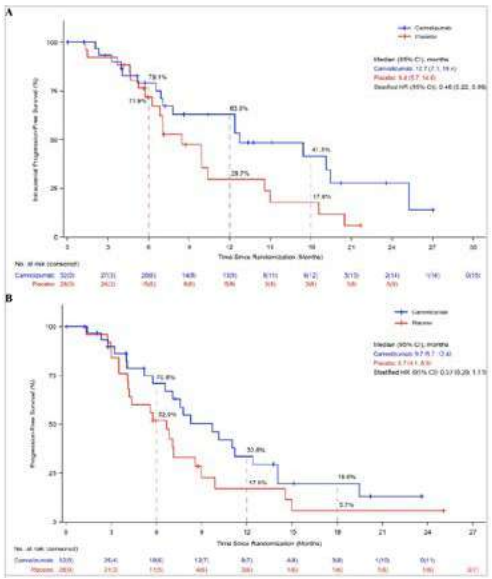
Introduction: Several retrospective studies showed preliminary effectiveness of immunotherapy plus radiotherapy in brain metastases (BM) of NSCLC. However, prospective RCTs remain lacking for further validation. CTONG 2003 is the first RCT to compare first-line camrelizumab with placebo for BM.

Methods: CTONG 2003 was a multicenter, randomized, double-blind, placebo-controlled trial conducted at 15 sites in China. Adult treatment-naïve NSCLC patients with BM and no EGFR/ALK alterations were randomized at 1:1 to receive camrelizumab (200mg) or placebo, plus platinum-doublet chemotherapy on day 1 of each 3-week cycle for 4-6 cycles, followed by maintenance camrelizumab or placebo ± pemetrexed (500mg/m^2) for up to 31 cycles. SRT or WBRT, if performed, was administered for BM within 42 days of the first dose. Randomization was stratified by histology (squamous versus non-squamous), number of BM lesions (1-5 versus ≥6) and radiotherapy (yes versus no). The co-primary endpoints were intracranial PFS (iPFS) and PFS. Totally 200 cases were needed but recruitment was prematurely terminated owing to therapeutic paradigm shifts rendering placebo inapplicable.

Results: Between May 28, 2021, and July 21, 2023, 60 eligible patients were assigned: 32 to the camrelizumab group and 28 to the placebo group. Twenty-one (65.6%) patients in the camrelizumab group and 23 (82.1%) in the placebo group received radiotherapy. As of February 20, 2024, median follow-up duration was 17.4 months (95%CI:12.9-20.5). As shown in Figure below, median iPFS was 12.7 months (95%CI: 7.1-19.4) in the camrelizumab group versus 8.4 months (95% CI:5.7-14.6) in the placebo group (HR:0.46, 95%CI:0.22-0.99), and median PFS in the respective group was 9.7 months (95%CI:5.7-12.4) versus 6.7 months (95%CI:4.1-8.6; HR:0.57 [95%CI:0.29-1.11]). A similar improved trend was also observed in OS (HR:0.51, 95%CI:0.21-1.24). The 12- and 18- month OS rates were 79.6% versus 57.2% and 61.3% versus 52.0%, respectively. The confirmed iORR was 56.3% in the camrelizumab group versus 42.9% in the placebo group, with median iDoR of 16.2 months (95%CI:5.3-21.2) versus 5.7 months (95%CI:3.9-15.9). The corresponding ORR and median DoR were 65.6% versus 32.1% and 8.5 months (95%CI:5.7-11.4) versus 4.4 months (95%CI:2.8-7.1), respectively. Grade ≥3 TEAEs occurred in 22 (68.8%) patients in the camrelizumab group and 17 (60.7%) in the placebo group, mainly anemia (34.4% versus 21.4%) and neutropenia (34.4% versus 28.6%). One patient in the camrelizumab group experienced a Grade 5 TRAE.

Conclusions: Although this trial closed early, camrelizumab trended toward improved iPFS and PFS for BM of NSCLC. The toxicity profile was generally manageable.

Keywords: Brain metastases, Non-small-cell lung cancer, Camrelizumab



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P4.11E.13 Real-World Treatment Patterns, Healthcare Cost and Resource Utilization in First-Line Treatment of Metastatic NSCLC in the US

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Introduction: Few studies have reported data on the current treatment landscape and real-world outcomes in the first-line treatment of non-small cell lung cancer (NSCLC). Such information is important to understand the burden of disease in the real-world setting, which is particularly relevant to stakeholders transitioning towards value-based care models. The objective of the current study was to assess real-world treatment patterns, healthcare cost, and healthcare resource utilization (HCRU) associated with the non-targeted first-line treatment of metastatic NSCLC in the US.

Methods: This retrospective observational study used data from the US Optum Clinformatics Data Mart® administrative claims database. Eligible patients were adults (≥18 years) who started non-targeted first-line treatment for metastatic NSCLC between January 01, 2020 and March 31, 2023. Patients were also required to be continuously enrolled in medical and pharmacy benefits for at least 6 months before the NSCLC diagnosis until at least 30 days after starting first-line therapy.

Results: A total of 15,659 patients with metastatic NSCLC met the inclusion criteria. The median age at the start of first-line treatment was 72 years (Interquartile range [IQR]: 67-78 years) and 48% were women; 86% were covered by Medicare Advantage. The median National Cancer Index adapted Charlson Comorbidity index was 2.0 (IQR: 1.0-3.0). The median duration of first-line treatment was 4.2 months, over an average follow-up of 11.2 (Standard deviation [SD]: 9.2) months. The most common treatments administered as first-line were immunotherapy (IO) plus chemotherapy (CT) (48.1%), mono or dual platinum-based CT (PBCT) (26.4%), and mono or dual IO (19.7%). All-cause HCRU during first-line treatment was mainly attributed to outpatient visits (6.6 [SD: 8.9] per patient per month [PPPM]). Inpatient and emergency department (ED) accounted for an average of 0.12 (SD: 0.59) and 0.11 (SD: 0.63) visits PPPM. Mean all-cause total healthcare costs were $32,215 (SD: 44,597) PPPM, incurred mostly in outpatient settings ($28,045 [SD: 37,735]). Healthcare costs were highest for patients receiving IO + chemo ($34,808 PPPM). Among them, IO + non-PBCT (n=176) costs were $38,454 PPPM and $34,721 PPPM for IO + PBCT (n=7,359). Patients receiving IO + non-PBCT also had the highest average outpatient and ED costs ($32,913 and $282, PPPM, respectively), followed by those receiving IO + PBCT ($30,888 and $114, PPPM, respectively).

Conclusions: Despite improvements in the treatment landscape of NSCLC in recent years, non-targeted first-line treatments; particularly IO + chemotherapy continues to be associated with substantial healthcare costs and resource burden. This highlights an unmet need for advancing first-line treatments to reduce the burden of disease in patients with metastatic NSCLC.

Keywords: Non-small cell lung cancer, First-line, Real-world outcomes

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P4.11E.14 Anlotinib Plus Penpulimab in Advanced Non-Small-Cell Lung Cancer Previously Treated with PD-1/PD-L1 Inhibitors

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Introduction: Immunotherapy monotherapy or combination therapy, represented by PD-1/PD-L1 inhibitors, has become the first-line standard treatment for driver gene-negative advanced non-small cell lung cancer (NSCLC). However, disease progression is inevitable in most patients, posing challenges for subsequent lines of treatment. Regarding patients with advanced NSCLC who have failed previous PD-1/PD-L1 inhibitor treatment, the question remains whether immunotherapy rechallenge can bring further survival benefits. This study aims to evaluate the efficacy and safety of combining anlotinib hydrochloride with pazopanib monotherapy in the treatment of patients with advanced NSCLC who have previously failed PD-1/PD-L1 inhibitor treatment.

Methods: This open-label, single-arm, multicenter, exploratory study (NCT05460481) enrolled patients with histologically confirmed driver gene-negative advanced NSCLC who had previously failed PD-1/PD-L1 inhibitor treatment. Participants were given 200mg of penpulimab every three weeks and 12mg of anlotinib daily, with a two-week on and one-week off schedule, until disease progression, unacceptable toxicity, or study discontinuation. The primary objective of the study was to evaluate the antitumor activity of the combination therapy using the objective response rate (ORR) as measured by RECIST v1.1. Secondary objectives included evaluating the disease control rate (DCR), progression-free survival (PFS), and overall survival (OS), and the safety and tolerability of the combination therapy.

Results: From September 2022 to present, 13pts aged 38-69 years (median age 60 years) were enrolled. 12 pts (92.3%) were men, 13 pts (100%) ECOG PS=0-1, and 3 pts (23.1%) had brain metastases. Of these, 13 patients were evaluable for RECIST and had an ORR of 23.08% (3/13) and a DCR of 92.31% (12/13). The median PFS was7.54 months, and the median OS were not mature.Two of the 13 patients(15%) experienced grade 3 or higher adverse events. The most common adverse reactions related to anlotinib hydrochloride included hepatic injury, general fatigue, and hand-foot syndrome.

Conclusions: Anlotinib Plus Penpulimab as second-line therapy showed a promising efficacy with a favorable toxicity profile for patients with advanced non-small cell lung cancer. We will report more data in the future.

Keywords: NSCLC, Anlotinib Plus Penpulimab, Previously Treated With PD-1/PD-L1 Inhibitors

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P4.11E.15 Risk Factors for Ir-AEs in Patients with NSCLC Receiving Chemotherapy Combined with a PD-1/PD-L1 Inhibitor or Nivolumab and Ipilimumab

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Introduction: Chemotherapy combined with PD-1/PD-L1 inhibitors is the standard first-line treatment for non-small-cell lung cancer (NSCLC), and chemotherapy combined with nivolumab and ipilimumab is considered effective in patients with low PD-L1 expression. Both regimens are associated with an increased incidence of immune-related adverse events (ir-AEs). Several studies have identified risk factors for ir-AEs and prognostic factors associated with PD-1/PD-L1 inhibitor treatment. To date, prognostic factors associated with chemotherapy combined with ipilimumab immunotherapy remain unclear.This study was performed to identify risk factors for grade 3 or higher ir-AEs and prognostic factors associated with combined immunotherapy with or without ipilimumab in a real-world setting.

Methods: Patients with NSCLC who received combined immunotherapy with or without ipilimumab (IPI or non-IPI groups) between March 2019 and April 2022 were enrolled. Potential risk factors for grade 3 or higher ir-AEs and prognostic factors for combined immunotherapy with or without ipilimumab were retrospectively assessed.

Results: The IPI and non-IPI groups included 66 and 264 participants, respectively. The proportion of patients with low PD-L1 expression in the IPI group was significantly higher than that in the non-IPI group ($p<0.01$). No differences in other patient characteristics were observed between the two groups. The respective incidences of grade 3 or higher ir-AEs in the IPI and non-IPI groups were 46.9% and 21.2% ($p<0.01$). Multivariate logistic regression analysis showed that NLR<5 and CRP≥1 were independent risk factors for severe ir-AEs in the IPI group and the non-IPI group, respectively. Kaplan-Meier analysis showed that overall survival (OS) was not significantly different between patients with NLR<5 and NLR<5 in the IPI group (13.4 months vs. not reached, $p=0.31$). In contrast, OS in patients with CRP-1 was significantly shorter than that in patients with CRP<1 in the non-IPI group ($p<0.01$).

Conclusions: We should be alert for the occurrence of ir-AEs in patients with NLR<5 during combined immunotherapy using ipilimumab. In addition, patients with CR-1 are not expected to benefit from combining chemotherapy with PD-1/PD-L1 inhibitor treatment. The findings of this study will be useful for guiding appropriate treatment choices for clinicians in practice.

Keywords: Risk factors, Chemotherapycombined with ICI, Ipilimumab

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P4.11E.16 Clinical Outcome of HER2-mut NSCLC Treated with First-Line Immunotherapy-Based Regimens versus Chemotherapy/HER2-TKIs

K. Yin, L-P. Chen, S-Y.M. Liu, Q. Zhou, Y-L. Sun, E-E. Ke, Y-S. Li, M-M. Zheng, C-R. Xu, J-X. Lin, X-Y. Bai, Z. Wang, H-H. Yan, J-J. Yang, H-J. Chen, B-C. Wang, H-Z. Hong, W-Z. Zhong, Y-L. Wu, H-Y. Tu, Guangdong Lung Cancer Institute, Guangdong Provincial People's Hospital (Guangdong Academy of Medical Sciences), Guangzhou/CN

Introduction: The current standard treatment regimen for advanced non-small-cell lung cancer (NSCLC) with HER2 mutations remains the same as for patients without driver genes, due to the absence of approved first-line targeted treatment. However, there is a discrepancy on whether priority should be given to immunotherapy-based regimen over conventional chemotherapy.

Methods: We retrospectively collected patients with primary HER2-mutated locally advanced or advanced NSCLC who received first-line treatment between January 1, 2016 and December 31, 2023 in Guangdong Provincial People's Hospital. Patients with known other oncogenic genes including sensitizing EGFR mutations, BRAF V600E mutation, KRAS G12C mutation, ALK/ NTRK/RET/ROS1 fusion, and MET exon 14 skipping were excluded. Patients were divided into three cohorts based on the first-line treatment regimen: immunotherapy ± chemotherapy (Group I), anti-angiogenic treatment ± chemotherapy (Group C), and targeted treatment (pyrotinib or afatinib) group (Group T). A comparison was made between the median progression-free survival (mPFS) and median overall survival (mOS) of Group I and those of either Group C or Group T.

Results: This study included 160 primary HER2-mutated patients with locally advanced or advanced NSCLC (median age, 57 years; 56% female; 90% stage IV; 24% with brain metastasis). The median follow-up time was 37.1 months (95% CI, 32.2-42.0). In group I (n=55), the majority of patients were treated with a combination of immune-chemotherapy regimens, and only 5 patients used immune monotherapy. The mPFS and mOS were 8.8 months (95% CI, 5.2 to 12.4) and 40.0 months (95% CI, 22.0 to 62.6), respectively. The mPFS of Group I significantly exceeded that of Group C (n=52) (8.8 vs 6.0, p=0.014) and Group T (n=53) (8.8 vs 4.9, p=0.016). The mOS of Group I was significantly longer compared to both Group C (40.0 vs 29.3, p=0.007) and Group T (40.0 vs 26.3, p=0.001).

Conclusions: The first-line immunotherapy-based treatment showed potential improvement for the clinical outcome of HER2 mutated NSCLC patients compared with chemotherapy and existing targeted treatment. Clinical trials comparing first-line novel targeted treatment with immunotherapy and chemotherapy are underway.

Keywords: HER2 mutation, Non-small-cell lung cancer, immunotherapy

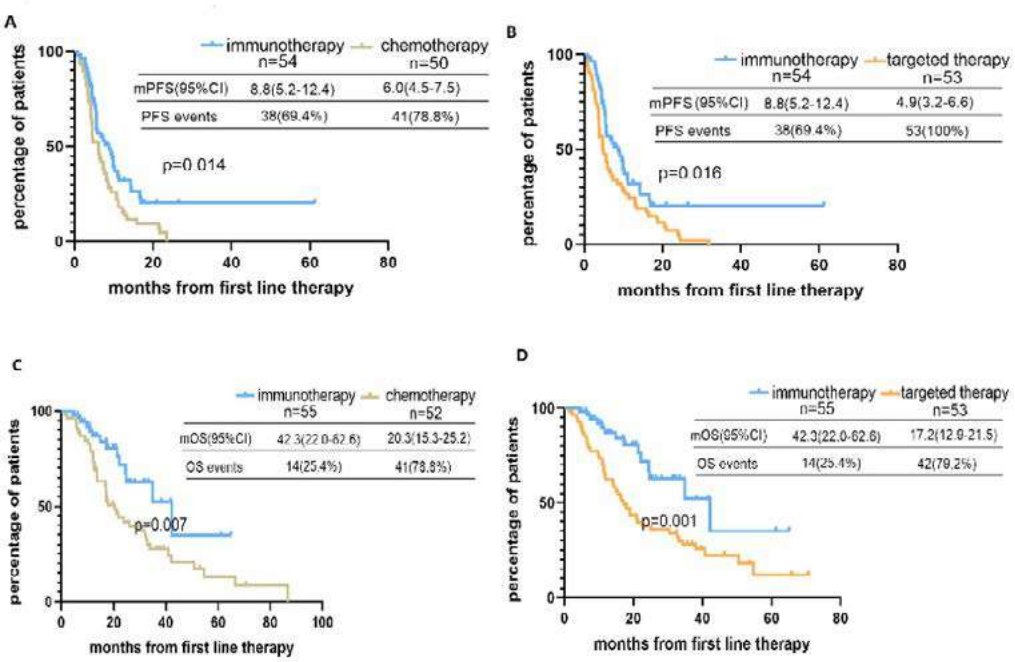

Figure 1: mPFS and mOS of HER2-mutated locally advanced or advanced NSCLC patients treated with different first-line regimens. Group I (Immunotherapy) received ICI-based therapy, Group C (Chemotherapy) received Chemotherapy ± anti-angiogenic treatment and Group T (targeted therapy) received pyrotinib or afatinib as first-line treatment.

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P4.11E.17 Clinical Outcomes and Immunotherapy Retreatment in Patients with Metastatic NSCLC Who Complete at Least Two Years of Immune Checkpoint Blockade

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Introduction: Immune checkpoint inhibition (ICI) has extended survival in patients with metastatic non-small cell lung cancer (NSCLC). While ICI duration is commonly limited to two years, the optimal duration of ICI, and post-progression treatment outcomes in patients who received at least two years of ICI are unknown.

Methods: We conducted a global, multi-center study of patients with metastatic NSCLC treated with ICI for at least two years to characterize clinical outcomes and post-progression treatment patterns. Log-rank tests were used to test for differences in event-time distributions, and Cox proportional hazards models were used to estimate hazard ratios.

Results: We identified 421 patients with metastatic NSCLC treated with ICI alone (N=320, 76%) or ICI + chemotherapy (N=101, 24%) for least two years. The median age was 63.2, 43.2% were women, 91% had history of tobacco use, 78.9% had adenocarcinoma histology, 48% had a PD-L1 TPS ≥50%. From the start of ICI, the median time to progression (mTTP) was 7.0 years (95%CI 5.6-NR) and the median overall survival (mOS) was 9.5 years (95%CI 8.1-NR).

Patients who achieved a complete response to ICI (N=77) had a significantly longer mTTP compared to those with a partial response (N=242) (HR 0.45, P<0.01) and stable disease (N=93) (HR 0.30, P<0.01). Patients with high PD-L1 ≥50% (HR 0.30, P=0.04 vs PD-L1 <50%), very high tumor mutational burden (TMB) ≥20 mut/Mb (HR 0.70, P=0.03, vs <20 mut/Mb) and ever smoking status (HR 0.52, P=0.03, vs never smokers) had also significantly longer mTTP. Sex, ECOG PS, and number of metastatic sites at baseline were not associated with mTTP. There was no difference in mTTP (HR: 1.19, P=0.28) between patients who stopped ICI after 2 years vs those who continued indefinitely, although mOS was shorter among patients who stopped ICI at 2 years (HR 0.52, P=0.01). Among 158 patients who progressed after ICI, 32.9% (N=52) received local ablative therapies (surgery or radiation), 9.4% (N=15) patients received systemic chemotherapy and 29.1% (N=46) patients received ICI retreatment. Among those retreated with ICI, the response rate was 61.2%, mTTP and mOS from the date of start of ICI retreatment were 22.7 (95%CI 11.2-NR), and 41.7 months (19.3-NR), respectively. Clinico-genomic predictors of response to ICI retreatment included higher TMB at baseline (16.2 vs 7.4 mut/Mb, P<0.001), adenocarcinoma histology (94.4% vs 50.0%, P=0.01), and longer ICI treatment duration prior to retreatment (34.2 vs 24.5 months, P=0.02).

Conclusions: Patients who received a minimum of two years of treatment with ICI experienced unprecedented long-term survival. After completing two years of initial ICI therapy, a large fraction of patients who subsequently experience disease progression and are retreated with ICI experience an objective response, particularly those with longer duration of prior ICI treatment, higher TMB, and adenocarcinoma histology.

Keywords: PD-(L)1 blockade, Long term survival, Biomarkers

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P4.11E.18 Impact of Prophylactic use of PEG-rhG-CSF on First-Line Immunochemotherapy in Advanced Non-Small Cell Lung Cancer: A Cohort Study

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Introduction: PEG-rhG-CSF is commonly used as a supportive therapy to prevent neutropenia in patients with malignant tumors undergoing chemotherapy; however, its impact on current immunochemotherapy remains unclear. This study aimed to evaluate the impact of the prophylactic use of PEG-rhG-CSF on the efficacy and safety of first-line immunochemotherapy in patients with advanced non-small cell lung cancer (NSCLC).

Methods: A cohort of patients with advanced NSCLC who received first-line immunochemotherapy (PD-1 inhibitor plus chemotherapy) at Shengjing Hospital of China Medical University between January 2019 and August 2023 were selected for inclusion in this study and divided into two groups: the treatment group, which received prophylactic PEG-rhG-CSF (≥1 cycle) 48 hours after immunochemotherapy, and a control group that did not receive PEG-rhG-CSF. The primary endpoints assessed were PFS, OS, ORR, and safety. A propensity score-matched analysis was performed to reduce potential confounders. The study was approved by the Ethics Committee of Shengjing Hospital (Ethics Approval Number: 2022PS013T).

Results: A total of 127 patients were enrolled in the study, with 48 patients in the treatment group and 79 in the control group. The median duration of follow-up was 14.3 months (range, 3.1-40.9 months). In the unmatched population, the median PFS was 12.7 months (95% CI: 4.9-20.5) for the treatment group and 12.2 months (95% CI: 2.9-21.5) for the control group (HR=0.88, p=0.85). The median OS was not reached (NR) and 33.2 months (HR=0.72, p=0.36). The ORR was 64.6% and 60.8% in the treatment and control groups, respectively (p=0.67), and the DCR was 97.5% and 97.9% (p=0.87), respectively. Following a propensity score-matched analysis (each group contained 34 patients), the median PFS was 9.5 months (95% CI: 3.6-15.4) for the treatment group and 10.8 months (95% CI: 7.7-13.9) for the control group (HR=0.95, p=0.89), and the median OS was NR and 24.9 months (HR=0.71, p=0.47), respectively. Multivariate Cox regression analyses across all 127 patients showed that the lack of antibiotic use (NR vs. 13.0 months; HR=0.43, 95%CI: 0.22-0.86; p=0.016) and a decrease in neutrophil-to-lymphocyte ratio (HR=0.47, 95%CI: 0.24-0.96; p=0.037) were significantly associated with longer OS. Antibiotic usage was less frequent in the treatment group (14.60%) than in the control group (22.80%), and the treatment group experienced a reduced incidence of severe leukopenia and granulocytopenia, without an increase in immune-related adverse events.

Conclusions: The prophylactic use of PEG-rhG-CSF did not adversely affect the efficacy and safety of first-line immunochemotherapy in patients with advanced NSCLC.

Keywords: PEG-rhG-CSF, immunochemotherapy, non-small cell lung cancer

Endpoints	Treatment group (n=48)	Control group (n=79)	HR or chi-square value	P value
Median PFS, unmatched (95%CI), months	12.7 (4.9-20.5)	12.2 (2.9-21.5)	0.88 (0.44-1.78)	0.85
Median PFS, matched (95%CI), months	9.5 (3.6-15.4)	10.8 (7.7-13.9)	0.95 (0.45-2.00)	0.89
Median OS, unmatched (95%CI), months	NR	33.3 (NR-NR)	0.72 (0.36-1.45)	0.36
Median OS, matched (95%CI), months	NR	24.9 (NR-NR)	0.71 (0.29-1.77)	0.47
ORR (%, n/N)	64.6% (31/48)	60.8% (48/79)	0.19	0.67
DCR (%, n/N)	97.5% (47/48)	97.9% (77/79)	0.03	0.87
Antibiotic use rate (%, n/N)	14.6% (7/48)	22.8% (18/79)	1.27	0.19
TRAE (%, n/N)	100% (48/48)	98.7% (78/79)	0.63	0.43
Grade ≥3 TRAE (%, n/N)	25.0% (12/48)	44.3% (35/79)	5.36	0.02
AE leading to dose interruption of immunochemotherapy (%, n/N)	2.1% (1/48)	8.9% (7/79)	2.45	0.12
AE leading to dose reduction of immunochemotherapy (%, n/N)	2.1% (1/48)	8.9% (7/79)	2.45	0.12
AE leading to withdrawal from immunochemotherapy (%, n/N)	2.1% (1/48)	5.1% (4/79)	0.76	0.38
AE caused by immunotherapy (%, n/N)	39.6% (19/48)	38.0% (30/79)	0.01	0.97

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P4.11E.19 The Effect of COVID-19 On Treatment Outcomes in Non-Small Cell Lung Cancer Patients: A Propensity Score Matched Analysis

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Introduction: Patients with cancer, particularly those with non-small cell lung cancer (NSCLC), face higher morbidity and mortality from severe COVID-19 infections than the general population. Despite extensive research focusing on outcomes of COVID-19 infection among cancer patients, outcomes related specifically to NSCLC treatment in the context of COVID-19 have not been explored. COVID-19 induced inflammation is hypothesized to adversely impact the tumor microenvironment (TME), with in vitro studies noting T-cell exhaustion with increased expression of PD-1 and PD-L1 in COVID-19 patients, suggesting a tumor-favorable microenvironment. Additionally, inflammatory response associated with COVID-19 infection may enhance T-cell activation and cytokine release, increasing the risk of irAEs. This study seeks to examine the effect of COVID-19 infection on overall survival and treatment outcomes in patients with NSCLC.

Methods: We conducted a propensity-matched, retrospective cohort study utilizing data from the TriNetX database and the US Collaborative Network, encompassing 60 healthcare organizations. The study population comprised patients diagnosed with NSCLC after January 1, 2019. We performed propensity score matching based on stage, age, race, gender, and existing comorbidities to create comparable groups of NSCLC with and without COVID-19 infection. The primary outcome was overall survival at 1 year and 3 years. Secondary outcomes include adverse events from chemoimmunotherapy.

Results: We identified a total of 553 NSCLC patients receiving chemotherapy or immunotherapy who had a positive COVID test, and 3025 similar patients who had a negative COVID test without history of COVID infection. Cohorts had 534 propensity-matched patients. At one year follow-up, overall survival of COVID-19 negative NSCLC cohort was 69.2% compared to 65.6% in COVID-19 positive cohort. There was no significant difference in overall survival at 1 year (HR 0.90, 95% CI 0.75-1.07) and 3 years (HR 1.11, 95% CI 0.97-1.27). There was also no significant difference in incidence of adverse events associated with chemoimmunotherapy (RR 1.09, 95% CI 0.88-1.36) between the matched cohorts.

Conclusions: Our results indicate no significant impact of COVID-19 infection on overall survival or treatment outcomes, contrary to the hypothesis that COVID-19-induced inflammation might exacerbate disease progression and treatment related adverse events. A noteworthy consideration and limitation in our work is the role of widespread implementation of vaccination, which may mitigate the potential negative effects of COVID-19, highlighting the importance of vaccination in maintaining effective cancer treatment outcomes. Future studies are needed to explore the interaction between COVID-19 vaccination status and cancer treatment outcomes.

Keywords: COVID-19, NSCLC, Immune checkpoint inhibitor

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P4.11E.20 Immune Checkpoint Inhibitors Plus Chemotherapy as First-Line Treatment in Patients with Advanced Pulmonary Sarcomatoid Carcinoma

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Introduction: Immune checkpoint inhibitors (ICIs) have demonstrated promising efficacy in patients with pulmonary sarcomatoid carcinoma (PSC) in retrospective studies. Here, we report a phase II study investigating efficacy and safety of immunotherapy combined with chemotherapy in patients with advanced PSC.

Methods: This was an open-label, single-arm phase II clinical trial (ChiCTR2000031478). Patients diagnosed with advanced PSC received first line anti-PD1 inhibitors plus chemotherapy until progression, unacceptable toxicity, withdrawal, or death. The primary endpoint was the objective response rate. The secondary endpoints included disease control rate, progression-free survival, overall survival, and side effects.

Results: Between October 2020 and January 2024, 38 patients diagnosed with advanced PSC were enrolled. Among them, 3 (7.9%) patients had Met exon14 skipping, 12(31.6%) patients had KRAS mutations and 1 (2.6%) patient had RET fusion. PD-L1 high expression (≥50%) was identified in 45.2% (14/31) patients. Thirty-five patients were available for response evaluation; the objective response rate and disease control rate were 65.7% and 82.8%, respectively. The median progression free survival was 10.5 months (95% confidence interval [CI], 3.5-17.2 months). The median overall survival was not reached and 1-year survival rate was 62.7 %. The most common side effects were chemotherapy associated. The irAEs of any grade were found in 29 (76.3%) patients, and those of grade 3 or worse were found in 8 (21.0%) patients.

Conclusions: Immunotherapy plus chemotherapy showed promising effects in patient with advanced or metastatic PSC.

Keywords: pulmonary sarcomatoid carcinoma, immunotherapy, PD-1 inhibitors

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P4.11E.21 Predictive Value of Longitudinal Systemic Inflammatory Markers for Pathologic Response to Neoadjuvant PD-1 Blockade in Resectable NSCLC

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Introduction: Identifying biomarkers to predict responses for neoadjuvant immunotherapy in resectable non-small cell lung cancer (NSCLC) has become an area of intensive researches. Based on a hypothesis that circulating and imaging inflammatory markers could serve as indicators of anti-tumor immune responses, we conducted an exploratory study to reveal the additional benefit of combining longitudinal systemic inflammatory markers, derived from 18F-fluorodeoxyglucose positron emission tomography-computed tomography (18F-FDG PET/CT) scans and peripheral blood tests, in stratifying the pathologic response to neoadjuvant sintilimab in resectable NSCLC. We also explored the association of tumor-infiltrating immune cells in the microenvironment with systemic inflammatory markers and primary tumor metabolism.

Methods: We retrospectively reviewed 36 patients (29 male and seven female) with NSCLC (stage IA-IIIB) who underwent pre- and post-treatment peripheral blood tests and 18F-FDG PET/CT scans before and after two cycles of neoadjuvant sintilimab. The neutrophil-to-lymphocyte ratio (NLR), immune-related adverse events on PET/CT, and lymphoid organ metabolism (spleen-to-liver SUVmean ratio [SLR] and bone marrow-to-liver SUVmean ratio) were evaluated to examine their predictive value in major pathologic response (MPR) and pathologic regression. Significant variables (ΔNLR% and pre-treatment SLR) were used to classify patients into low, intermediate, and high inflammatory burden groups for stratifying pathologic response and tumor-infiltrating immune cells abundance. Spearman's correlation analysis was performed to explore the correlation between systemic inflammatory markers, primary tumor metabolism, and tumor-infiltrating immune cells abundance at various time points.

Results: Of the 36 patients, 13 (36.1%) exhibited MPR. ΔNLR% was a significant negative predictor of MPR (p=0.047) and pathologic regression (p=0.045). Pre- and post-treatment SLRs were potential negative predictors of MPR (p=0.065; p=0.055) and pathologic regression (p=0.074; p=0.064). The ΔNLR% and pre- and post-treatment SLRs had the best discriminatory ability for MPR, with areas under the receiver operating characteristic curve of 0.702, 0.689, and 0.694, respectively. The high inflammatory burden group (pre-treatment SLR>0.83 and ΔNLR%>-17%) had the lowest pathologic regression (p=0.012) and the highest infiltration abundance of pre-treatment tumor-infiltrating CD68+ macrophage (p<0.05). The emergence of immune-related adverse events on PET/CT did not have significant effects on pathologic response in the overall and per-organ analyses.

Conclusions: The combination of pre-treatment SLR and ΔNLR% demonstrates promising predictive value in stratifying the pathologic response to neoadjuvant sintilimab in resectable NSCLC. The high inflammatory burden group showed the lowest pathologic regression and a pre-treatment immunosuppressive microenvironment with CD68+ macrophage enrichment.

Keywords: neoadjuvant immunotherapy, systemic inflammatory markers, tumor immune microenvironment

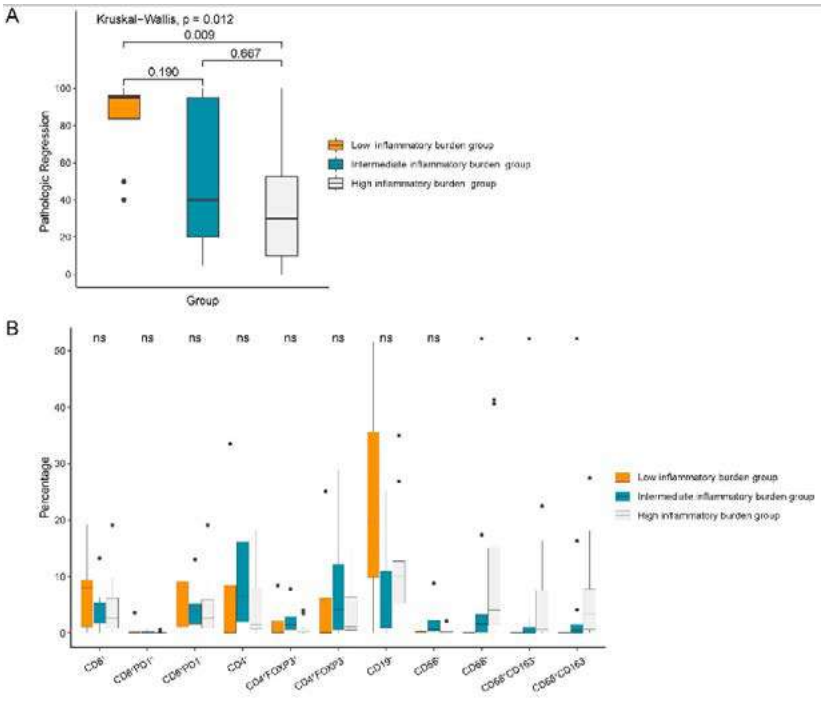

Figure Comparison of pathologic regression and pre-treatment tumor-infiltrating immune cells abundance among the low, intermediate, and high inflammatory burden groups.
(A) Comparison of pathologic regression to neoadjuvant immunotherapy among three groups.
(B) Comparison of pre-treatment tumor-infiltrating immune cells abundance among three groups.
In the boxplots, the center line represents the median value, the bounds of the box represent the interquartile range, and the whiskers extend to 1.5× the interquartile range on either side of the median (*, p<0.05; ns, not significant).

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P4.11E.22 Treatment-Free Survival in Advanced NSCLC Patients who Terminated Immune-Checkpoint Inhibitors.

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Introduction: Immune checkpoint inhibitors (ICI) are widely used in patients with advanced non-small cell lung cancer (NSCLC) without driver alterations. Although patients sometimes terminate ICI due to various reasons, it remains unclear how long the efficacy of ICI is sustained after termination.

Methods: In this single-centered retrospective study, we reviewed the medical records of patients who received ICI-containing treatment for advanced NSCLC between January 2016 and December 2020 at Wakayama Medical University Hospital and identified those who terminated ICI for reasons other than progressive disease. Patients who received ≥2 years of ICI were defined as the completion group, and patients who discontinued ICI within 2 years were defined as the non-completion group. The primary outcome of this study was treatment-free survival (TFS), defined as the time from the last dose of ICI administration to disease progression or death from any cause.

Results: Sixty-five of 233 patients (28%) met the criteria (median [range] age, 71 [41-91], 58 males [89%]). Of those, 15 patients were in the completion group, and 50 were in the non-completion group. In both groups, about 40% had PD-L1 expression level ≥50%, and almost half received ICI monotherapy. Fifty-two patients (80%) were treated with anti-PD-1 antibody and 13 (20%) with anti-PD-L1 antibody. The median duration of ICI-containing treatment was 3.9 months (range, 0-22) in the non-completion group. The most common reason for ICI termination was irAE (68%).The median follow-up period of TFS was 36.0 months (range, 1.7-93). The median TFS of the entire population was 11.5 months (95%CI, 7.2-20.7 months), and the annual TFS rates were 48% at 1 year, 38% at 2 years, 36% at 3 years, and 29% at 4 and 5 years, respectively: the Kaplan-Meier curve of TFS dropped in the first year and almost plateaued thereafter. Fourteen patients (26%) demonstrated TFS at 3 years. Nine of them discontinued ICI due to irAE, and all had PR as their best response. Univariate analysis showed that tumor shrinkage (CR/PR vs. SD) is the only predictor of TFS at 3 years. Median TFS was not reached in the completion group, while that was 9.4 months in the non-completion group. The TFS rates at each year were better in the completion group compared with those in the non-completion group (80% vs. 38% at 1 year, 64% vs. 30% at 2 years, 64% vs. 27% at 3 years, and 64% vs. 22% at 4 and 5 years, respectively). In both groups, the Kaplan-Meier curve reached at a plateau 1 year after termination.

Conclusions: Our findings showed that 36% of advanced NSCLC patients who terminated ICI had disease-free and treatment-free periods of more than 3 years, and even among patients who did not complete ICI, 27% achieved 3-year TFS. Our study also suggested that the imaging interval can be loosened after 1 year of ICI termination.

Keywords: immune-checkpoint inhibitors, treatment-free survival, NSCLC

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P4.11E.23 Real-World Data (RWD) Of First-Line Cemiplimab Single Agent for Advanced PD-L1 High Expression, Non-Small Cell Lung Cancer (NSCLC)

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Introduction: Cemiplimab, an anti-PD-1 antibody, has been approved for first-line treatment of NSCLC patients. In this scenario, single-agent cemiplimab demonstrated significant survival benefits over chemotherapy for NSCLC patients with high PD-L1 tumor proportion score (TPS) (≥ 50%) in a randomized phase III trial. However, there is limited RWD available on this compound. The aim of this study was to assess the real-world outcomes of NSCLC patients receiving cemiplimab as first-line therapy.

Methods: This multicenter retrospective study was conducted in 16 Spanish institutions and enrolled patients with confirmed advanced NSCLC PD-L1 TPS ≥ 50% who were treated with cemiplimab alone as first-line. Real-world safety, progression-free survival (PFS), overall survival (OS) and their correlation with clinical characteristics were examined. Log-rank tests were used to analyze differences in event-time distributions, and Cox proportional hazards models were used to estimate HR.

Results: A total of 102 patients were included in the study between 05/01/2022 and 07/31/2023. The median age was 70 years, 19.6% were women, 93% had history of tobacco use, 80.4% had a ECOG performance status (ECOG-PS) of 0-1, 69.7 % had a non-squamous histology, 40.2% had single metastatic location, 64.7% had extrathoracic disease and 26.5% had ≥3 metastases. Steroids were administered (>10 mg prednisone) in 24.5%. Hypoalbuminemia was detected in 28.9% of patients at baseline, and a poor lung immune prognostic index (LIPI) was found in 12.5%. Over half of the patients (53.1%) exhibited radiological response, including a 5.1% complete response rate. Immune-related adverse events (irAEs) occurred in 28.7 % of patients (44.8% grade 1-2), and 15.7% of patients discontinued cemiplimab due to immune-related toxicity. With a median follow-up of 9.8 months the median PFS was 8.1 months (95% CI, 3.9-12.2), while the median OS was not reached. Regarding PFS, extrathoracic disease (HR 3.2, p<0.000), poor ECOG-PS (HR 2.3, p<0.000), ≥3 metastatic sites (HR 2.2, p=0.005), hypoalbuminemia (HR 1.8, p=0.046) and specific metastatic allocations including liver (HR 2.1, p=0.026), and adrenal glands (HR 1.9, p=0.041) were significantly correlated with a worse PFS. Conversely, single-site metastasis (HR 0.4, p=0.001), irAEs onset (HR 0.5, p=0.047), as well as treatment discontinuation due to irAEs (HR 0.2, p=0.035) exhibited an increased PFS. On the other hand, a shorter OS was significantly associated with poor ECOG-PS (HR 3.1, p<0.000), extrathoracic disease (HR 3.9, p<0.000), bone metastases (HR 2.1, p=0.019), hypoalbuminemia (HR 2.0, p=0.027), poor LIPI score (HR 1.9, p=0.008), and steroids at the onset of cemiplimab (HR 2.6, p=0.001). Single-site metastasis (HR 0.2, p<0.000) and irAEs occurrence (HR 0.3, p=0.009) were linked to a longer OS. Poor ECOG-PS and extrathoracic disease remained significant for both survival outcomes in multivariate regression analysis: PFS (HR 2.7, p=0.012 and HR 3.7, p=0.001, respectively) and OS (HR 2.8, p=0.015 and HR 4.8, p=0.001, respectively).

Conclusions: The RWD of cemiplimab demonstrated a favorable safety profile and efficacy outcomes consistent with pivotal trial and other RWD of anti PD-1/PD-L1 agents developed in this context. Extrathoracic disease and ECOG-PS emerged as significant factors associated with clinical outcomes in multivariate analysis.

Keywords: real-world data, immunotherapy, first-line

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P4.11E.24 Clinical Features of Long-Term Response (LTR) to Immune Checkpoint Inhibitors (ICIs) in Patients with Advanced or Recurrent NSCLC

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Introduction: Long-term follow-up data from multiple phase III trials of ICIs demonstrate a 5-year overall survival (OS) rate of approximately 15-30% in pts with non-small-cell lung cancer (NSCLC). While biomarkers predicting the initial response to ICIs, such as tumor mutation burden, PD-L1 expression, and microsatellite instability, have been reported, there is currently limited data on the characteristics of pts who experience LTR to ICIs in advanced or recurrent NSCLC.

Methods: This is a retrospective study in which included pts with advanced or recurrent NSCLC who received any ICIs with or without chemotherapy at Kindai University Hospital from 2015 to 2021. LTR was defined as a progression-free survival (PFS) of more than two years on ICI treatment, and the clinical and genetic data were collected.

Results: Among the 388 pts, 57 (14.6%) were identified as patients who achieved LTR. The median age was 70 years (range: 37-86), with males constituting 42 pts (73.7%). Driver gene mutations were observed in 13 pts (22.8%) with the breakdown as follows: KRAS; 5, EGFR; 3, BRAF; 2, and ALK/RET/ROS1; 1 pt each. Clinical characteristics of patients who achieved LTR included non-squamous histology, PD-L1 TPS over 50%, and treatment regimen with PD-1 antibody monotherapy. Among the total of 57 patients, the median PFS was 84.6 months (95% CI: 42.3-not reached), with 5-year PFS rate of 59.4%. The median OS was not reached (95% CI: 69.5-not reached), with 5-year OS rate of 91.3%. Immune-related adverse events (irAEs) were observed in 28 pts (49.1%), with endocrine disorders being the most common, affecting 13 pts (46.4%). Based on the clinical course, they were classified into 3 patterns; continuous administration of ICI for more than two years, which constituted most of the long-term responders (39 pts, 68.4%), early discontinuation of ICI due to irAEs (9 pts, 15.8%), and completion of two years of ICI treatment followed by observation without treatment (9 pts, 15.8%). The median duration of treatment with ICIs was 41.4 months (range: 24.2-91.1), 12.7 months (range: 1.0-20.0), and 23.9 months (range: 22.1-26.5), respectively. The incidence of irAEs according to this classification was observed in 20 (51.3%), 9 (100%), and 3 (33.3%), respectively.

Conclusions: Among patients with advanced or recurrent NSCLC treated with ICI therapy, 14.6% achieved LTR, and those patients demonstrated a markedly favorable prognosis. Non-squamous histology, high PD-L1 expression, and treatment regimen with PD-1 monotherapy were enriched among these LTR patients. Furthermore, LTR patients were shown to be classified into 3 patterns of clinical courses.

Keywords: NSCLC, Immune checkpoint inhibitor, long-term responder

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P4.11E.25 NSCLC Immune Hemogram Index (NIHX) A Predictive Score for Immunotherapy Response in PD-L1 Negative Advanced NSCLC

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Introduction: The expression of PD-L1 serves as the main biomarker for response to immune checkpoint inhibitors (ICI) in NSCLC. However, approximately 30% of patients do not exhibit PD-L1 expression. This observation emphasizes the necessity to explore complementary biomarkers, particularly within the subgroup of NSCLC patients. The role of the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) relationship has been evaluated as markers of host inflammation, correlating with poorer response to ICI and overall survival in NSCLC. Therefore, this study aims to assess the predictive role of these two biomarkers together as a score, referred to as NSCLC Immune Hemogram Index (NIHX), in a retrospective cohort of PD-L1 negative patients (REAL-IMPACT).

Methods: Multicenter retrospective study including patients with advanced NSCLC PD-L1 negative (<1% by IHC), without driver mutations (negative test for EGFR and ALK), treated with ICI from 2017 to December 2023 from 21 Argentinian centers. Complete blood cell counts were measured before ICI treatment. NIHX based on NLR greater than 3 and PLR greater than 180 was developed, characterizing 3 groups (good, 0 factors; intermediate,1 factor; poor, 2 factors). The primary endpoint was Progression-free survival (PFS). Secondary endpoints were overall response rate (ORR) and overall survival (OS).

Results: 121 patients were analyzed. Median age at first line was 65 (range 59-73), male gender 88 (58%), previous or active tobacco use 134 (88%), adenocarcinomas 126 (83%). IO schemes: CT + Pembrolizumab 125 (82%), Ipilimumab + Nivolumab 12 (7.9%), CT + Ipilimumab + Nivolumab 11 (7.3%), CT + Atezolizumab + Bevacizumab 3 (2%). Based on the NIXH score, 45 (29%), 34 (22.5%), and 42 (27.8%) patients were categorized as having good, intermediate, and poor prognosis, respectively.Median PFS for good, intermediate and poor NIHX was 14.1 months (95% CI, 8.1 to 20.1 months), 11.3 months (95% CI, 4.6 to 17.9 months) and 6.5 months (95% CI, 2.1 to 10.8 months) and ORR with 66%, 47% and 33% partial responses, in that order (both p<0.004). Median OS was 20.8 months (95% IC, 12 to 28 months), 24.1 months (95% IC, 18.2 to 30 months) and 18 (95% IC 7.7 to 28 months), respectively (p=0.42).

Conclusions: Our study demonstrates that pretreatment NIHX, based on NLR and PLR, serves as a promising predictive tool for treatment response in PD-L1 negative advanced NSCLC patients. NIHX stratification into good, intermediate, and poor groups correlates with PFS and RR, highlighting its potential utility in guiding ICI therapy selection for this patient population.

Keywords: NSCLC, Immunotherapy, biomarkers

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P4.11E.26 A Multicenter Retrospective Study Reveals High MET Expression Associated with Superior Benefit from Immunotherapy in Advanced NSCLC Patients

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Introduction: MET has been recently scrutinized due to its association with resistance to chemotherapy and targeted therapy. However, the correlation between MET alterations and the efficacy of immune checkpoint inhibitors (ICIs) remains under explored. We sought to examine the clinicopathologic characteristics associated with high MET expression by immunohistochemistry (IHC) and explore the potential association between MET expression and ICI therapeutic benefits in advanced non-small cell lung cancer (NSCLC) patients.

Methods: We curated a multicenter dataset, encompassing 428 stage IV NSCLC patients who underwent MET IHC testing from MD Anderson Cancer Center (USA), Hospital del Mar (Spain), and Zhejiang Cancer Hospital (China). Among these patients, 382 received ICI treatment between October 2014 and October 2023, while the remaining 46 patients received chemotherapy alone. Experienced thoracic pathologists graded MET IHC results on a scale from 0 to 3+, defining high expression as a staining intensity of 2+ or 3+. The clinicopathological features associated with MET expression were assessed by logistic regression analysis. Kaplan-Meier analysis was conducted to investigate the correlation between MET expression and overall survival (OS) and progression-free survival (PFS) in ICI cohort and chemotherapy-alone cohort. Cox proportional hazards model was utilized for multivariate analysis.

Results: In the ICI cohort, 249 of 382 patients (65.2%) had high MET expression. High MET expression significantly correlated with female gender (P < 0.001), adenocarcinoma histology (P < 0.001), de novo stage IV diagnosis (vs. recurrent stage IV, P < 0.001), biopsy after ICI treatment (P = 0.022), and high PD-L1 expression (P < 0.001), while no significant correlations were observed with age and smoking history. In multivariate analysis, female gender (P = 0.001), adenocarcinoma histology (P = 0.007), de novo stage IV diagnosis (P < 0.001), and biopsy after ICI treatment (P = 0.027) remained significantly associated with high MET expression. Survival analysis revealed that high MET expression was associated with significantly improved OS (HR=0.740, 95% CI [0.556-0.984], p = 0.038), while PFS showed a trend towards improvement (HR=0.867, 95% CI [0.674-1.116], p = 0.269). To mitigate the impact of ICI treatment on MET expression, we conducted Cox regression analysis exclusively in patients who underwent biopsy before ICI treatment, revealing that high MET expression (P = 0.049) was associated with better OS, independent of PD-L1 expression. Additionally, age over 65 (P = 0.006), squamous cell carcinoma histology (P = 0.045), de novo stage IV (P = 0.003), and brain metastases (P = 0.002) were associated with inferior OS. Regarding PFS, only histology and PD-L1 expression were identified as independent factors, while MET expression was not significant (P = 0.538). In the chemotherapy-alone cohort, MET expression showed no correlation with either OS (P = 0.629) or PFS (P = 0.217).

Conclusions: In this real-world multicenter study, our findings indicated that high MET expression, assessed by IHC, was associated with improved OS in advanced NSCLC patients receiving ICI treatment, independent of PD-L1 levels. These results suggest that high MET expression may serve as an independent marker for predicting response to ICIs in advanced NSCLC patients.

Keywords: MET, Immunotherapy, Advanced NSCLC

P4.11E METASTATIC NON-SMALL CELL LUNG CANCER - IMMUNOTHERAPY - IMMUNOTHERAPY UTILIZATION
MONDAY, SEPTEMBER 9, 2024 - 18:30 - 20:00

P4.11E.27 Comparison of Immunotherapy for Metastatic Non-Small Cell Lung Cancer in Real-World Practice: A Japanese Registry Study

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Introduction: For metastatic non-small cell lung cancer (NSCLC) without driver alterations, several treatment options are available including immune-mono therapy, immune-chemo therapy and immune-combo therapy. The relative effectiveness of these approaches has yet to be determined through direct, prospective comparisons. This study employs real-world data to further investigate these treatment strategies.

Methods: This was a multi-center retrospective cohort study. We used anonymized records in hospital-based cancer registry data from 68 designated cancer care hospitals across Osaka Prefecture, Japan. Patients diagnosed with Stage IV NSCLC and treated with first-line therapy including immunotherapy between 2019 and 2021 were extracted and analyzed. The endpoint of this study was overall survival (OS) and time to treatment failure (TTF).

Results: From the cancer registry data, 2101 patients who were diagnosed with a StageIV NSCLC and treated with first-line therapy including immunotherapy. The distribution of regimens for the 2101 patients was 1173 for Pembro-chemo, 446 for Pembro, 272 for ATZ-chemo, 119 for NIV+IPI-chemo, 85 for NIV+IPI, and 6 for ATZ. First, we compared the immune-mono therapy group and the immune-chemo therapy group. TTF was 248 days (95% CI, 207 to 317 days) for the immune-mono therapy group and 252 days (95% CI, 237 to 275 days) for the immune-chemo therapy group (HR, 0.93 [95% CI, 0.81-1.07]) (P-value=0.33). OS was 492 days (95% CI, 365 days to NA) for the immune-mono therapy group and 829 days (95% CI, 805 days to NA) for the immune-chemo therapy group (HR, 0.62 [95% CI, 0.52-0.73]) (P-value=<0.05). Similar results were observed in the propensity score analysis. Second, we compared the Pembro-chemo therapy group and the ATZ-chemo therapy group. TTF was 267 days (95% CI, 245 days to 288) for the Pembro-chemo therapy group and 211 days (95% CI, 183 days to 245) for the ATZ-chemo therapy group (HR, 0.75 [95% CI, 0.63-0.89]) (P-value=<0.05). OS was NA (95% CI, 805 days to NA) for the Pembro-chemo therapy group and 609 days (95% CI, 437 days to NA) for the ATZ-chemo therapy group (HR, 0.75 [95% CI, 0.60-0.95]) (P-value=0.02). Similar results were observed in the propensity score analysis. Third, we compared the Pembro-chemo therapy group and the NIV+IPI-chemo therapy group. TTF was 267 days (95% CI, 245 to 288 days) for the Pembro-chemo therapy group and 217 days (95% CI, 176 to 322 days) for the NIV+IPI-chemo therapy group (HR, 0.85 [95% CI, 0.65-1.10]) (P-value=0.22). OS was NA (95% CI, 805 days to NA) for the Pembro-chemo therapy group and NA (95% CI, 454 days to NA) for the NIV+IPI-chemo therapy group (HR, 0.93 [95% CI, 0.64-1.36]) (P-value=0.72).

Conclusions: Our findings suggest that immune-chemo therapy, particularly pembrolizumab combined with chemotherapy, significantly enhances OS in stage IV NSCLC patients without driver alterations who are eligible for chemotherapy. This advantage was not observed with the combination of nivolumab and ipilimumab with chemotherapy, highlighting the importance of regimen selection in this patient population.

Keywords: Non-small cell lung cancer, Immunotherapy, Real world data

P4.11E METASTATIC NON-SMALL CELL LUNG CANCER - IMMUNOTHERAPY - IMMUNOTHERAPY UTILIZATION
MONDAY, SEPTEMBER 9, 2024 - 18:30 - 20:00

P4.11E.28 Pharmacological Comparison of Dostarlimab and Pembrolizumab in Metastatic Non-Small Cell Lung Cancer in PERLA

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Introduction: PERLA (NCT04581824) is a randomized phase II trial of dostarlimab + chemotherapy vs pembrolizumab + chemotherapy in non-squamous metastatic non-small cell lung cancer. At median 21 months follow-up, a numerical trend in overall survival (OS) favoring dostarlimab + chemotherapy vs pembrolizumab + chemotherapy was observed (hazard ratio = 0.75 [95% confidence interval (CI): 0.53-1.05]) [1]. Post-hoc analyses were conducted to elucidate the difference in OS based on pharmacokinetics (PK), functional receptor occupancy (fRO), structural binding, and longitudinal tumor response using tumor size-overall survival (TS-OS) modeling.

Methods: PERLA PK for dostarlimab and pembrolizumab was compared with historical data, and fRO was compared between dostarlimab and pembrolizumab. Dostarlimab and pembrolizumab antibody X-ray complexes within the Research Collaboratory for Structural Bioinformatics (RCSB) protein databank were compared and visualized using standard molecular modelling software. A joint mixed-effects TS-OS model was developed from multiple immuno-oncology studies and applied to PERLA data [2]. Individual TS profiles were modelled longitudinally; corresponding TS parameters and baseline patient factors were linked to OS using a log-normal survival model [2]. The TS-OS model was well qualified across multiple studies.

Results: Steady-state PK concentrations observed for PERLA were similar to prior PK data for both dostarlimab and pembrolizumab. fRO was similar between dostarlimab and pembrolizumab, with a slight trend favoring dostarlimab. High-resolution crystal structures show dostarlimab binds to programmed cell death protein 1 at a distinct binding site compared to pembrolizumab. Based on arm-specific population estimates for TS parameters, the TS-OS model predicted a differential TS response for dostarlimab + chemotherapy vs pembrolizumab + chemotherapy: median (95% CI) maximal reduction from baseline was 37.0% (45.8-27.1) vs 27.1% (36.8-17.6) and median (95% CI) time to tumor growth was 8.9 (7.2-10.6) vs 6.6 (5.2-8.2) months, respectively (Figure 1).

Conclusions: The difference in OS between the pembrolizumab + chemotherapy and dostarlimab + chemotherapy arms was not readily explained by PK or fRO. The clinical impact of the dostarlimab distinct binding mode is still unknown. The TS-OS model demonstrated that the numerically deeper/longer response for dostarlimab + chemotherapy vs pembrolizumab + chemotherapy is consistent with the difference in OS.

Keywords: mNSCLC, Tumor Size-Overall Survival Modeling, Clinical Pharmacology

P4.14C MESOTHELIOMA, THYMOMA, AND OTHER THORACIC TUMORS - MESOTHELIOMA
MONDAY, SEPTEMBER 9, 2024 - 18:30 - 20:00

P4.14C.01 Trends of Asbestos Lung Content in the General Population

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Introduction: Malignant Mesothelioma (MM) is well-known to be related to previous occupational or non-occupational exposure to asbestos. The existence of a "threshold dose" above which the risk of developing the MM is significantly increased is still under debate. As asbestos and asbestos-like minerals are ubiquitously diffused in urban and natural environments, everyone is potentially exposed during life and, as a consequence, may have asbestos in their lungs. However, there is lack of data about the quantification of this "background exposure", which some scientists (Carbone et al.) considered to be below 500 000 ff/gdw in the lung. Another issue of great interest is represented by the chronological trends of asbestos exposure. Roggli et al. observed a progressive decrease of asbestos lung content in people with MM during the past four decades. Our group reported similar trends in a recent paper. However, there is no data about these trends in the general population. The objective of this study is to quantify asbestos in lung tissue of healthy individuals from the general population and to understand if asbestos exposure changed over the past decades.

Methods: This study was carried out on formalin-fixed lung samples taken during autopsy from 50 healthy individuals deceased between 2001 and 2023 from traumatic causes, according to the following criteria: age above 40 years; no medical history or pathologic evidence of neoplastic or respiratory disease; negative known history for occupational, household or environmental asbestos exposure. Concentration of asbestos uncovered fibers (AF), of asbestos bodies (AB) and of each type of asbestos, as well as the length and width of each detected fiber, were determined using a scanning electron microscope equipped with energy dispersion spectroscopy (SEM-EDS).

Results: AF was detected in 28% of them, while AB in 22%. The mean concentration of AF and AB were, respectively, 3190 ff/gdw (SD=7580) and 2010 ABs/gdw (SD=5630). The maximum concentration of AF was 39000 ff/gdw. Chrysotile was detected in 3 cases (6%), tremolite/actinolite in 12 cases (24%); amosite and anthophyllite were detected in only one case each, crocidolite was never detected. We studied the chronological trends of asbestos lung content comparing subjects born before (n=11) and after (n=14) 1940, frequency matched the on age at death. We found that both AF (5909 vs 1197 ff/gdw) and AB concentrations were significantly lower in people born after 1940, and AF were significantly shorter in people born after 1940 (10.1+4.9 vs 23.2+17.1). Moreover, in people born before 1940 both chrysotile and non-commercial amphiboles tremolite/actinolite were detected, whereas in those born after 1940 we observed only non-commercial amphiboles and, in two cases, commercial amphiboles (amosite and anthophyllite).

Conclusions: In this work we observed a significant decrease in asbestos lung content during the past decades, suggesting that the ban of asbestos mining and use in most western countries led to a considerable decrease of asbestos exposure in the general population.

Keywords: asbestos, time trends, exposure

P4.14C MESOTHELIOMA, THYMOMA, AND OTHER THORACIC TUMORS - MESOTHELIOMA
MONDAY, SEPTEMBER 9, 2024 - 18:30 - 20:00

P4.14C.02 Analysis of Pleiotropic Effects of Nivolumab in Patients with Relapsed Pleural Mesothelioma: A Single Center Retrospective Study

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Introduction: Nivolumab, an immune checkpoint inhibitor (ICI), became the first therapy approved worldwide by the regulatory authority (Japanese PMDA - Pharmaceuticals and Medical Devices Agency) for previously treated unresectable progressive/recurrent Pleural Mesothelioma (PM), filling a therapeutic gap that previously existed. However, the vulnerability of evidence obtained from the non-blinded single-arm Phase II trial of 34 cases, known as the "MERIT (Multicenter, Open-label, Single-arm, Japanese Phase II study in Malignant Pleural Mesothelioma) Trial," was strongly emphasized.

Methods: At our institution, we aimed to retrospectively confirm the effectiveness and safety of Nivolumab in real-world clinical settings for patients with previously treated unresectable progressive/recurrent PM, while simultaneously analyzing their clinical background.We targeted 83 cases of histologically diagnosed previously treated unresectable progressive/recurrent malignant pleural mesothelioma who received Nivolumab at our institution from August 2018 to May 2022. Effectiveness was assessed based on modified RECIST criteria, and safety was evaluated using CTCAE version 5.0 to assess treatment-related adverse events (TRAE).

Results: Patient demographics were as follows: median age, 73 (range 45-88) years; male/female, 64/19 cases; performance status (PS) 0-1/2 or more, 73/10 cases; smoking history, yes/no, 61/22 cases; asbestos exposure, yes/no, 55/24 cases; stage I/II/III/IV, 47/36 cases; histological subtype, epithelioid/sarcomatoid/biphasic/unknown, 60/15/6/2 cases; treatment line, 2nd/3rd/4th or later, 62/13/8 cases. The effectiveness outcomes were as follows: best treatment response, complete response/partial response/stable disease/progressive disease/not evaluable, 0/16/30/29 cases; overall response rate (ORR), 19.28%; disease control rate (DCR), 55.42%. The median PFS was 5.13 months (95% CI: 3.50-6.27), and the median OS was 12.40 months (95% CI: 8.50-16.37). Regarding safety, treatment-related adverse events (TRAE) occurred in 45 cases (54.22%) of all grades, with 6 cases (7.23%) being grade 3 or higher, and there was 1 case (1.20%) of death.

Multivariate analysis revealed that significant correlations with PFS were male gender, TRAE positivity, and good PS (PS: 0-1), while significant correlation with OS was observed only with good PS (PS: 0-1). Significant correlations with both PFS and OS were observed only with good PS (PS: 0-1).

Conclusions: The effectiveness of Nivolumab administration for PM in real-world clinical settings in this study was comparable to or greater than previous reports in terms of PFS and OS, and the safety profile was tolerable. Additionally, it became evident that even in late-line treatment, Nivolumab administration should be actively considered for patients with good PS.

Keywords: PM, Nivolumab, TRAE

P4.14C MESOTHELIOMA, THYMOMA, AND OTHER THORACIC TUMORS - MESOTHELIOMA
MONDAY, SEPTEMBER 9, 2024 - 18:30 - 20:00

P4.14C.03 Real-World Prognostic & Predictive Implications of EORTC & MRS Scores for Immunotherapy and Chemotherapy in Pleural Mesothelioma (PM)

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Introduction: The EORTC prognostic score (EORTC-PS) was derived to classify patients with PM undergoing single-agent chemotherapy into good- versus poor-risk groups based on mainly clinicopathological characteristics. The Mesothelioma Risk Score (MRS) classified PM patients undergoing second-line single-agent anti-PD-1 immunotherapy or chemotherapy after prior platinum-doublet chemotherapy into favorable-, intermediate-, and poor-risk categories based on baseline laboratory values. This study explores the value of the EORTC-PS and MRS in the real-world setting in the modern era of first-line dual anti-CTLA-4 + anti-PD-1 immunotherapy.

Methods: A retrospective analysis was conducted using a cohort of 247 patients who were diagnosed with PM between 2010 to 2022 and received systemic therapy in British Columbia, Canada. Pre-treatment laboratory values (CBC+differential); and clinicopathological characteristics (pre-treatment performance status, sex, histological subtype, definitiveness of diagnosis) were used to calculate EORTC-PS and MRS. Overall survival (OS) from the date of diagnosis was analysed by the Kaplan-Meier method.

Results: Baseline characteristics: male 84%; median age at diagnosis 72 years (IQR 66 to 77); sarcomatoid (12%), epithelioid (66%), biphasic (11%), not otherwise specified (11%); ECOG performance status 0 (10%) and ≥1 (90%). The MRS and EORTC-PS scores were effective differentiators of favorable/good versus poor risk for patients receiving immunotherapy (Table 1). For patients receiving predominantly platinum-doublet chemotherapy, the EORTC-PS did not differentiate OS benefit and the MRS intermediate-risk group had better OS compared to the MRS favorable-risk group (Table 1). Patients in the EORTC-PS good-risk and MRS favorable-risk groups had a greater OS advantage from immunotherapy over chemotherapy compared to their poor-risk counterparts (Table 2), which is suggestive of predictive value.

Conclusions: The MRS showed greater prognostic value than the EORTC-PS in a real-world setting, especially for those receiving immunotherapy. Further evaluation is needed to confirm the utility of EORTC-PS and MRS in predicting immunotherapy advantage over chemotherapy.

Keywords: pleural mesothelioma, prognostic, predictive

Table 1. Prognostic value of EORTC-PS and MRS scores by treatment with hazard ratios for death (95%

	Immunotherapy in any line, n=60 (37 anti-CTLA4+anti-PD1; 23 anti-PD1)	Chemotherapy only, n=187 (178 platinum-doublet; 9 single-agent)
EORTC		
Good	1.00	1.00
Poor	1.90 (1.03 to 3.50), P = 0.04	1.15 (0.85 to 1.54), P = 0.37
MRS		
Favorable	1.00	1.00
Intermediate	1.31 (0.56 to 3.03), P = 0.53	0.59 (0.35 to 0.98), P = 0.04
Poor	4.33 (1.94 to 9.62), P = 0.0003	0.92 (0.59 to 1.43), P = 0.71

Table 2. Predictive value of EORTC-PS and MRS by treatment with hazard ratios for death (95% CI)

	EORTC-Good (n=109)	EORTC-Poor (n=138)	
Chemotherapy only	1.00	1.00	
Immunotherapy in any line	0.51 (0.33 to 0.78)	0.71 (0.48 to 1.05)	
	P = 0.002	P = 0.09	
	MRS-Favorable (n=48)	MRS-Intermediate (n=82)	MRS-Poor (n=117)
Chemotherapy only	1.00	1.00	1.00
Immunotherapy in any line	0.24 (0.13 to 0.48)	0.59 (0.35 to 1.03)	0.87 (0.54 to 1.40)
	P < 0.0001	P = 0.06	P = 0.56

P4.14C MESOTHELIOMA, THYMOMA, AND OTHER THORACIC TUMORS - MESOTHELIOMA
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P4.14C.04 Exhaled Breath Analysis for the Early Diagnosis of Malignant Pleural Mesothelioma and the Surveillance of Asbestos-Exposed At-Risk Subjects

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Introduction: Malignant Pleural Mesothelioma (MPM) is a rare neoplasm with still a poor prognosis and mainly caused by previous asbestos exposure (both occupational and environmental). The management of MPM is challenging due to the long latency period between the exposure and the diagnosis and due to symptoms appearing only at an advanced stage. Thus, there is an ever-increasing need to equip National Health Systems with a reliable diagnostic tool to integrate into large-scale screening programs. Quite recently, the chemical characterization of Volatile Organic Compounds (VOCs) in human breath and the identification of disease-related metabolites pattern has been recognized as non-invasive and promising approach for the early detection of various neoplastic diseases. In the present study, we report the main outcomes of a cross-sectional study aimed at identifying MPM-related VOCs pattern in human breath. Furthermore, breath analysis potentialities in detection of metabolic alterations in participants with previous asbestos exposure were explored.

Methods: A total of 58 subjects were recruited: 24 patients affected by MPM, 24 healthy controls (HC) and 10 former asbestos-exposed individuals (EXP). The enrollment of volunteers in the clinical trial fulfilled specific criteria, after approval by the Institutional Ethic Committee. The methodological approach was based on the sampling of end-tidal breath directly onto two-beds adsorbent cartridges (Biomonitoring steel tubes, Markes International) by means of the automated sampler Mistral (Predict srl). Ambient air samples (AA) were simultaneously collected at each sampling session. Breath samples (n. 116) were thermally desorbed (Unity Ultra-xr Markes) and analyzed by Gas Chromatography/Mass Spectrometry (GC Agilent 7890/MS Agilent 5975). Experimental data were statistically processed by non-parametric Wilcoxon signed rank test in order to identify the most weighting variables in the discrimination between MPM and HC breath samples. Based on the outcomes of the preliminary statistical treatment, Principal Components Analysis (PCA) and Linear Discriminant Analysis (LDA) were applied to the dataset to validate breath analysis-based methodology in the discrimination among MPM, HC and EXP subjects.

Results: PCA statistical treatment of experimental data, e.g., VOCs abundances in MPM and HC samples, resulted in the identification of two principal components (PC1, PC2) explaining 82% of the total variance and characterized by higher loadings of selected aldehydes, whose increased abundance in MPM breath samples is indicative of promoted lipid peroxidation due to cellular oxidative stress. Leave-one-out cross-validation method was applied to calculate the prediction accuracy obtaining sensitivity equal to 92% and diagnostic accuracy equal to 90% (ROC AUC: 0.905). Finally, LDA output allowed to discriminate among MPM, HC and EXP subjects through clustering of population groups.

Conclusions: The methodological approach applied in this study, e.g., VOCs collection directly onto sorbent tubes by an automated device, represents an advancement in human breath sampling procedure with respect to previous studies carried out by the same authors and in line with research in breath analysis worldwide. Despite the promising results, the size and the homogeneity of the sample population deserves further investigation to validate breath analysis as a helpful tool in the screening and clinical management of MPM.

Keywords: Volatile organic compounds, Breath analysis, Malignant Pleural mesothelioma

P4.14C MESOTHELIOMA, THYMOMA, AND OTHER THORACIC TUMORS - MESOTHELIOMA
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P4.14C.05 Incidence of Pseudoprogression and Hyperprogression in Patients with Pleural Mesothelioma Treated with Ipilimumab and Nivolumab

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Introduction: The immune checkpoint inhibitors (ICI) ipilimumab and nivolumab are now standard of care treatment for patients with pleural mesothelioma (PM). In other malignancies, ICI treatment can lead to an initial increase in tumor burden followed by tumor shrinkage (pseudoprogression), or an accelerated increase in tumor burden (hyperprogression). These phenomena have not been previously quantified in PM. We therefore investigated the clinical characteristics and incidence of pseudoprogression and hyperprogression in PM patients who received this regimen.

Methods: Patients presenting to a high-volume Mesothelioma Clinic were enrolled in an IRB-approved biorepository protocol. Clinical characteristics were abstracted from the medical record. Genomic DNA was assayed on a research-based germline panel. PD-L1 expression was quantified using Tumor Proportion Score (TPS). CT scans were obtained at baseline and approximately 6 and 12 weeks after starting immunotherapy, then every 3 months until treatment discontinuation. CT scans were interpreted and measured using mRECIST 1.1 by a single reference radiologist blinded to the clinical results. Pseudoprogression was defined as an interval increase in tumor burden at the first post-treatment scan that regressed at the next scan. Patients evaluable for hyperprogression had measurable disease per mRECIST 1.1 at baseline; hyperprogression was defined as either >50% growth in target lesions or marked new lesion growth within the first 12 weeks of treatment. Fishers exact and Wilcoxon ranked sum tests were used to determine statistical significance.

Results: Of 682 mesothelioma patients enrolled in the biorepository, 63 patients with pleural mesothelioma who received ipilimumab/nivolumab between January 2017 and February 2024 were included in this analysis. Patient characteristics: male 59%; median age: 70 years (range 23-86); performance status 0 33%, 1 54%, ≥2 13%; histology: epithelioid 62%, biphasic 32%, sarcomatoid 6%; PD-L1 TPS >1% (n=55) 64%; germline mutations (n=55) 14%; probable/definite asbestos exposure 70%; first-line treatment 59%. Of the 15 patients (24%) who had worsening disease at first reassessment, 10 had tumor regression at the subsequent scan, for an overall incidence of pseudoprogression of 16%. Pseudoprogression was more common in women (p=0.012). There was a trend towards higher PD-L1 expression in those with pseudoprogression that did not reach statistical significance (p=0.078). Of 44 patients evaluable for assessment of hyperprogression, 6 (14%) developed hyperprogression. No statistically significant differences in age, performance status, histology, PD-L1 expression, treatment line, asbestos exposure, or somatic or germline mutations were observed between patients with and without either pseudoprogression or hyperprogression.

Conclusions: In PM patients treated with ipilimumab/nivolumab, 67% of patients with worsening disease at first reassessment had subsequent tumor regression, for an overall rate of pseudoprogression of 16%. Women were more likely to experience pseudoprogression. The relatively high incidence of pseudoprogression we observed suggests that in the absence of significant clinical deterioration, PM patients on immunotherapy with suspected disease progression at the initial scan should consider continuing treatment until subsequent imaging is performed. Ongoing analyses evaluate the impact of hyperprogression on overall survival; correlate the incidence of pseudoprogression with objective response rate, response duration, and overall survival; and employ radiomics to discriminate between pseudoprogression and true progression.

Keywords: Pleural Mesothelioma, Hyperprogression, Pseudoprogression

P4.14C MESOTHELIOMA, THYMOMA, AND OTHER THORACIC TUMORS - MESOTHELIOMA
MONDAY, SEPTEMBER 9, 2024 - 18:30 - 20:00

P4.14C.06 Effect of Cytotoxic Chemotherapy Following Ipilimumab Puls Nivolumab Combination Therapy for Malignant Pleural Mesothelioma

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Introduction: Based on the outcomes of the Checkmate743 trial, ipilimumab and nivolumab combination treatment has been as a first-line regimen for malignant pleural mesothelioma (MPM) in Japan from June 2021. In non-small cell lung cancer (NSCLC), Immune checkpoint inhibitors (ICIs) have been reported to enhance antitumor effects of successive cytotoxic chemotherapy in some studies, which remains unclear in MPM.

Methods: This study aimed to retrospectively assess the effectiveness and safety of second-line cytotoxic chemotherapy in patients with MPM who received ipilimumab plus nivolumab combination treatment as first-line at Hyogo Medical University Hospital starting from June 2021 to January 2024.

Results: A total of 22 patients were analyzed. Patient characteristics were as follows. The median age: 71 (range 42-84), male/female:15/7, stage I/II/III/IV/relapse: 11/0/4/2/5, epithelioid/biphasic/sarcoma: 18/0/4, and CDDP+PEM/CBDCA+PEM: 13/9. Response rate was 9.1% and disease control rate were 50.0%, the median progression-free survival (mPFS) was 4.7 months and 1-year survival rate was 78.8%, respectively. The epithelioid type showed better PFS compared to the non-epithelial type (mPFS: 6.2 months vs. 2.4 months, p=0.035. HR=0.13) but no difference was observed in overall survival (OS) (1yr-OS rate: 79.6% vs. 75.0%, p=0.88. HR=1.18). As for safety, serious adverse events were observed in 3 patients, one anaphylactic shock and two grade 3 or higher renal dysfunction, which compelled treatment discontinuation.

Conclusions: Our findings suggest that the effectiveness of platinum plus pemetrexed successive to ipilimumab plus nivolumab was comparable to the data of first-line cisplatin plus pemetrexed reported in EMPHACIS study in which the mPFS was 5.7 months.

Keywords: Mesothelioma, Ipilimumab, Chemotherapy

P4.14C MESOTHELIOMA, THYMOMA, AND OTHER THORACIC TUMORS - MESOTHELIOMA
MONDAY, SEPTEMBER 9, 2024 - 18:30 - 20:00

P4.14C.07 A Combination of Routine and Novel Immunohistochemical Markers to Improve the Histological Diagnosis of Mesothelioma in Challenging Biopsies

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Introduction: Early diagnosis of malignant mesothelioma (MM) is essential to increase the chance of curative treatment. Unilateral accumulation of haemorrhagic effusion and pleural thickening/nodularity are the earliest clinical manifestations of MM. Despite the fact that effusion is easily accessible, compared to a thoracic surgical biopsy, cytomorphological criteria to diagnose MM are not clear-cut as previously investigated by the authors. Confident histological diagnosis requires a decent amount of material (presence of adipose tissue) which is not always achievable generating diagnostic challenges and requests for more tissue. This work will look into a combination of Immunohistochemical (IHC) markers to look for a diagnostic algorithm to confidently diagnose MM in limited samples.

Methods: We retrieved 37 pleural biopsies with a confirmed clinical and histological diagnosis of MM and 22 cases of benign mesothelial proliferation/reactive pleuritic between January 2016 and December 2021. An IHC panel including BAP1, MTAP, p16, p53 and Merlin was performed on all 59 pleural biopsies to look for a diagnostic algorithm. This algorithm will be prospectively applied to an additional set of 20 consecutive pleural biopsies morphologically suspicious for MM to assess its validity.BAP1 was considered as retained (positive nuclear staining) or lost (negative nuclear staining with a positive internal control). MTAP was considered as retained (positive cytoplasmic staining of same intensity as positive internal control) or lost (negative cytoplasmic staining with a positive internal control). P16 was considered positive when >10% of cells showed block staining (any weak staining will be interpreted as negative). P53 was considered positive when >10% of cells showed strong nuclear staining at 10x (any weak staining will be interpreted as negative). Merlin was considered as retained (crispy membranous staining at 10x objective with same intensity as positive internal control) or lost (nuclear and/or cytoplasmic staining). Statistical analysis were conducted using IBM SPSS Statistics (Pearson Chi-square Tests and Fisher exact bilateral tests).

Results: 64.9% biopsies with a diagnosis of MM showed loss of BAP1, 59.5% showed loss of MTAP and 32.4% showed loss of Merlin. BAP1, MTAP and Merlin were retained in 100% of biopsies negative for malignancy. P53 and p16 were negative in the majority of biopsies regardless the diagnosis (61% and 84.7% respectively) with this scoring system. Statistical analysis showed significant correlation between the type of diagnosis, BAP1 ($p<.001$), MTAP ($p<.001$) and Merlin expression ($p<.002$).

Conclusions: Early detection of MM has a major impact on patient survival however, histological diagnosis can be challenging on limited samples. A combination of well-established and novel IHC markers selected from the literature have been investigated in this work to support a histological criteria. Our preliminary results showed a high level of retention in benign mesothelial proliferation of all three markers BAP-1/MTAP/Merlin. This novel IHC panel, if confirmed by a larger series, could help in diagnostically challenging cases.

Keywords: Malignant Mesothelioma, Immunohistochemistry, Diagnostic accuracy

P4.14C MESOTHELIOMA, THYMOMA, AND OTHER THORACIC TUMORS - MESOTHELIOMA
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P4.14C.08 HIT-MESO: Hemithoracic Irradiation with Proton Therapy in Malignant Pleural Mesothelioma. UK National Proton Radiotherapy Study

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Introduction: Only 15% of patients with Mesothelioma in the UK receive any radiotherapy and this is predominantly given as a palliative treatment for symptomatic benefit to a limited area of pleural disease. However radical hemi-thoracic radiotherapy with conventional radiotherapy has demonstrated an overall survival benefit but with high rates of toxicity. Several planning studies have shown the potential benefit of proton beam therapy (PBT) in MPM for treatment of the hemi-thorax due to a reduction in the doses to normal tissues, however clinical data is limited to single centre retrospective studies.

Methods: HIT-Meso is a phase III, multicentre, randomised (1:1) controlled trial comparing radical hemi-thoracic PBT to standard of care, in 148 patients with histologically confirmed MPM confined to one hemi-thorax. HIT-Meso aims to explore a PBT as an option to delay the need for systemic anti-cancer therapy in MPM patients suitable for surveillance by evaluating the efficacy and safety of PBT.Trial endpoints: co-primary PFS (i) and OS (ii); safety and toxicity, QoL, health and social care resource use, and incremental cost-effectiveness (secondary); translational research (exploratory). A qualitative sub-study explore participant experience is included.

A sample size of N=148 (i.e. 74 patients per arm) is required to detect an OS hazard ratio of 0.58, equivalent to an improvement in 2-year OS from 30% to 50%, with 85% power and 5% two-sided alpha. Recruitment to complete in 3 years across 20 UK centres with 2 years of additional follow-up and up to 5% dropout. Using a fixed-sequence approach, a difference for OS will only be tested if the co-primary endpoint of PFS is statistically significant ($p<0.05$).The study has been funded by Asthma + Lung UK and Mesothelioma UK, and opened to recruitment in April 2024

Results: NA

Conclusions: NA

Keywords: Trial in Progress, Mesothelioma, Proton radiotherapy

P4.15A MULTIDISCIPLINARY CARE: NURSING, ALLIED HEALTH AND PALLIATIVE CARE - CLINICAL TRIALS IN PROGRESS
MONDAY, SEPTEMBER 9, 2024 - 18:30 - 20:00

P4.15A.01 Efficacy of Digital Therapeutics for the Perioperative Management in Patients with Lung Cancer: A Randomized Controlled Trial

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Introduction: To evaluate the efficacy of digital therapeutics (DTx) assisted management vs multidisciplinary management (MM) in the perioperative management of patients with lung cancer, an open-label, single-center, non-inferiority, randomized controlled trial conducted in China.

Methods: From July 2022 to June 2023, a total of 186 patients underwent minimally invasive lung surgery were randomized and 147 completed the study. Participants were randomly assigned 1:1 to receive DTx-assisted management (n=72) or traditional MM (n=75). The primary endpoint is the pulmonary function recovery rate measured by forced expiratory volume in the first second (FEV1) three weeks after surgery. Secondary endpoints include hospital stay duration, 90-day unplanned readmission rate, symptom scores, management efficacy and patient satisfaction rate. Exploratory endpoints include factors influencing postoperative lung function recovery.

Results: The lung function FEV1 recovery rate of DTx group was not inferior to that of the MM group (87.18±11.01% vs 84.21±11.75%). There were no significant differences between the two groups in terms of postoperative hospitalization duration and 90-day unplanned readmission rates. The average time required for each patient management in DTx group was significant shorter than that of MM group (P<0.001). Patient symptom scores showed a decreasing trend over time after discharge, the 5 target symptoms included pain, coughing, shortness of breath, disturbed sleep and fatigue. On the 7th day after discharge, the DTx group had a lower occurrence rate of the 5 target symptoms triggering alert threshold (P=0.002). Patients with higher education level achieved better FEV1% recovery rate by DTx-assisted management (P=0.021).

Conclusions: Compared to the MM group, the DTx group achieved non inferior results, therefore providing an alternative digitalized management mode for patients with lung cancer surgery.$$graphic_{0F56E6B4-F259-4DF9-B288-7BE0B90D8315}$$

Keywords: Lung cancer surgery, Digital Therapeutics, Perioperative Management

P4.15B MULTIDISCIPLINARY CARE: NURSING, ALLIED HEALTH AND PALLIATIVE CARE - EXERCISE
MONDAY, SEPTEMBER 9, 2024 - 18:30 - 20:00

P4.15B.01 Remote Exercise Program for Patients with Lung Cancer on Immune Checkpoint Inhibitors

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Introduction: Despite advancements in the treatment of lung cancer (LC) with the introduction of immune checkpoint inhibitors (ICI), patients with advanced LC often experience significant physical and psychological challenges that can impact their quality of life, ability to receive therapy and LC outcomes. Physical activity is a promising adjunctive therapy, offering potential benefits in symptom burden, and overall well-being. This prospective study aimed to investigate the efficacy of a remote physical activity program tailored for patients with advanced LC receiving ICI

Methods: This longitudinal study recruited patients diagnosed with LC and receiving ICI within a cancer network in Brazil. Eligible participants were invited to enroll, and those interested underwent screening for symptom burden (Edmonton Symptom Assessment System, ESAS) and quality of life (Functional Assessment of Cancer Therapy-General, FACT-G). Following assessment, a certified fitness trainer prescribed personalized physical activity regimens for home-based implementation. Over a 12-week period, patients engaged in weekly virtual appointments with their assigned personal trainer. During these sessions, the trainer assessed patients' physical capacity and adjusted the intensity of the exercise regimen to the patient's needs. The protocol included resistance exercises, aerobic activities, and mobility exercises, specifically tailored for home-based execution. At the conclusion of the 12-week intervention, patients underwent reassessment for symptom burden and quality of life. Statistical analyses were performed using linear mixed models to evaluate the effectiveness of the remote physical activity program.

Results: A total of 14 patients were recruited for the study, with a mean (M) age of 70 years (SD=6.2). Most participants were male (57%), married (57%), and had at least a college degree (64%). Seventy-one percent of the patients were diagnosed with metastatic disease. At baseline, patients reported experiencing higher levels of fatigue (M=4.2) and anxiety (M=3.7). Following participation in the remote physical activity program, there was a significant decrease in both fatigue (M=1.0) and anxiety (M=1.0 and M=1.5, respectively; P=0.001). Over the course of the intervention, there was a notable improvement in overall quality of life, with scores increasing by almost 10 points from baseline (MT1=84.7 to MT2=91.6, p=0.005). Additionally, there was a substantial reduction in symptom burden, with scores decreasing by almost 10 points over time (MT1=21.6 to MT2=10.7, p=0.01).

Conclusions: Our study highlights the critical role of physical activity interventions in addressing the multifaceted needs of patients with LC, often overlooked in trials due to associated symptoms. Patients with LC frequently present insufficient physical activity, contributing to quality of life impairment, functional decline, and symptoms like fatigue. Our remote program demonstrated significant improvements in symptom burden and overall quality of life, while the remote aspect of the proposed method also substantially increased patient adherence. These findings emphasize integrating tailored exercise programs for patients with advanced LC, warranting further research for validation and comprehensive support.

Keywords: Physical Activity, Quality of Life, immune checkpoint inhibitors

P4.15B MULTIDISCIPLINARY CARE: NURSING, ALLIED HEALTH AND PALLIATIVE CARE - EXERCISE
MONDAY, SEPTEMBER 9, 2024 - 18:30 - 20:00

P4.15B.02 Cardiopulmonary Rehabilitation Exercises Effectively Improve the Radiation-Induced Cardiopulmonary and Patients' Life Quality

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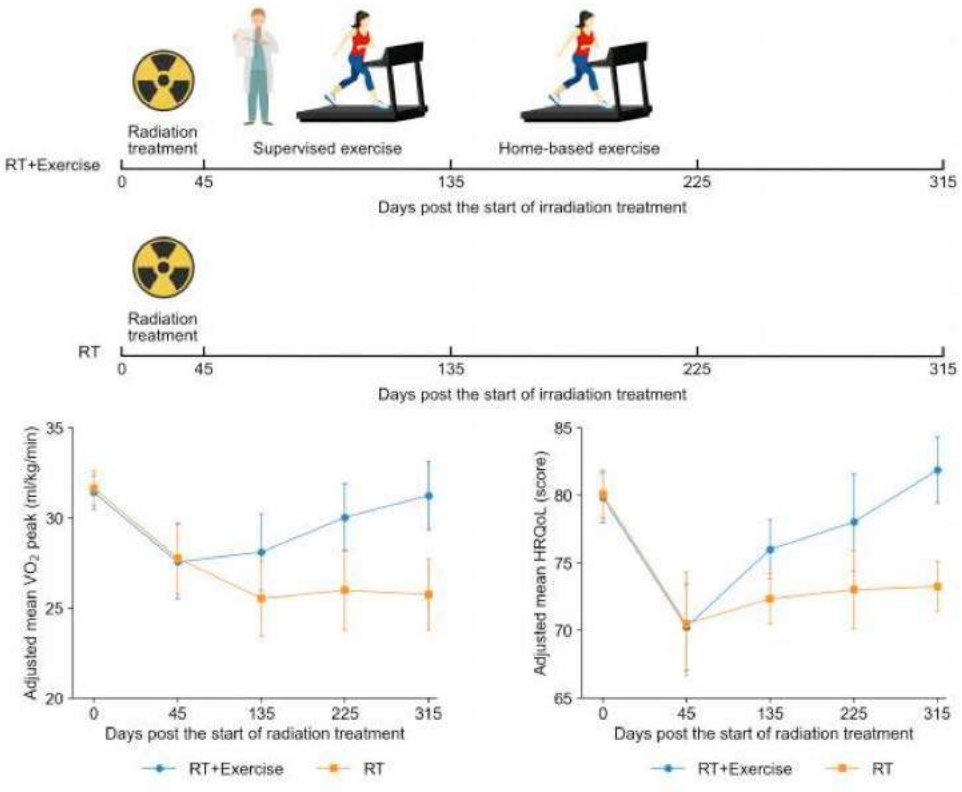
Introduction: In the process of radiotherapy for patients with non-small cell lung cancer,normal heart and lung tissues are inevitably exposed to different degrees of radiation,which may cause damage to the cadiopulmonary function.However,current studies about the rehabilitation of cardiopulmonary injury often focused on the heart and lung separately, which cannot simultaneously reflect the characteristics of the cardiopulmonary function in real life of patients.And there is no particularly effective way to prevent and improve the radiation-induced cardiopulmonary injury. In this study,cardiopulmonary rehabilitation exercise methods of common cardiovascular diseases were applied to the study of radiation-induced cardiopulmonary injury, and integrated exercise prescription intervention was used to improve the radiation-induced cardiopulmonary injury and improve the quality of life of patients.

Methods: The study lasted from September 2020 to December 2023. 82 patients with stage I-III non-small cell lung cancer receiving radiotherapy were randomly divided into trial group and control group. These patients received cardiopulmonary exercise test (CPET) and health-related quality of life (HRQoL) score before initial radiotherapy. CPET can reflect the real cardiopulmonary combined function in patients' lives. At the beginning of radiotherapy, the experimental group was given an integrated exercise prescription. The prescription includes aerobic exercise such as walking and traditional Chinese medicine-Baduanjin. It also includes resistance exercises for muscle strength training. The control group was given a fixed routine exercise prescription, and the two groups were followed up daily. The total dose of radiotherapy was 60-66Gy. The CPET and HRQoL score was performed after 45/135/225/315 days,and the results of the these tests were compared to evaluate the intervention effect of cardiopulmonary rehabilitation on radiation-induced cardiopulmonary injury.

Results: The maximum oxygen uptake (VO2max) reflected the maximum aerobic metabolism and cardiopulmonary reserve capacity of human body. After radiotherapy, many indexes of experimental group and control group were significantly decreased compared with those before radiotherapy ($P < 0.05$). However, the experimental group with integrated exercise prescription intervention did not decrease the VO2max and HRQoL score, while the control group significantly decreased the VO2max and HRQoL score($P < 0.05$). This indicates that cardiopulmonary rehabilitation exercise can improve radiation-induced cardiopulmonary injury.

Conclusions: Cardiopulmonary function rehabilitation can improve radiation-induced cardiopulmonary injury and the quality of life of patients by exercise prescription.It is an effective treatment method.

Keywords: Cardiopulmonary Rehabilitation Exercises, Cardiopulmonary exercise test, Radiation-induced Cardiopulmonary Injury



P4.15B MULTIDISCIPLINARY CARE: NURSING, ALLIED HEALTH AND PALLIATIVE CARE - EXERCISE
MONDAY, SEPTEMBER 9, 2024 - 18:30 - 20:00

P4.15B.03 Effects of Tai Chi and Qigong Interventions in Lung Cancer Patients: A Systematic Review

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Introduction: Exercise plays a crucial role in the journey of patients with lung cancer.

Tai Chi and Qigong have shown promise in improving the quality of life, alleviating symptoms, reducing stress, and enhancing physical functioning in cancer patients, including those with lung cancer.

Methods: Following PRISMA guidelines, electronic databases (MEDLINE, Web of Science, and Scopus) were searched from January 2014 to February 2024 using the MeSH terms, text word synonyms and key words for the topics addressed by the systematic review. Titles and abstracts were reviewed by 2 independent reviewers; disagreements were resolved by a third. All identified full papers were assessed independently by three researchers. Included studies were required to be RCT, and evaluate tai chi or qigong interventions in lung cancer patients.

Results: We found 107 studies through the database; after duplicate removal and eligibility evaluation, we identify 6 studies meeting the selection criteria to analyze in qualitative synthesis (Table 1). These studies included a total of 823 lung cancer patients mainly in advanced setting. The main relevant aspect emerging from the analysis is the interesting multifaced role of tai chi and qigong in alleviating symptoms, promoting an holistic approach.

Conclusions: For patients with lung cancer Tai Chi and Qigong may offer several benefits in palliative care settings including symptom management, improved quality of life and sleep quality, and stress reduction. Multidisciplinary support is crucial to implement lung cancer exercise programs and define interventions tailored to the specific needs of lung cancer patients.

Keywords: advanced lung cancer, tai chi, qigong

Table 1: Analysis of randomized controlled trials on the effects of tai chi or qigong interventions in lung cancer.

AUTHORS	SAMPLE	DESIGN	EXERCISE INTERVENTION	RESULTS
ZHANG LL et al, J Pain Symptom Manage 2016	96 advanced lung cancer patients undergoing chemotherapy	Prospective, randomized, controlled intervention trial	Tai Chi exercise group or low-impact exercise control group	Tai chi was an effective intervention for managing CRF
CHEUNG DST et al, Integr Cancer Ther 2021	30 advanced lung cancer patients	Assessor-blinded, exploratory randomized controlled trial	A tai chi group (both attending 12-week, twice-weekly supervised sessions), or a self-management control group	Tai chi group attained higher adherence than the exercise group
TAKEMURA N et al, Palliat Support Care 2023	99 advanced lung cancer patients	Randomized controlled clinical trial	Aerobic exercise versus Tai Chi intervention	Low fatigue levels contributed to higher attendance in Tai Chi and improves long-term effectiveness of sleep
TAKEMURA N et al, JAMA Oncol 2024	226 advanced lung cancer patients	Assessor-blinded, randomized clinical trial	Aerobic exercise versus Tai Chi intervention	TC demonstrating greater benefits on sleep and survival
MOLASSIOTIS A et al, Integr Cancer Ther 2021	156 lung cancer patients	Randomized controlled clinical trial	Qigong group (6 weeks of intervention) or a waitlist control group receiving usual care	Qigong did not alleviate the symptom cluster experience, but it was effective in managing respiratory symptoms
XU J et al, Support Care Cancer 2023	216 NSCLC postoperative participants	Randomized controlled clinical trial	Routine lung rehabilitation training versus Baduanjin qigong	Baduanjin qigong may have certain advantages in relieving cancer-related fatigue and FEV1%

P4.15C MULTIDISCIPLINARY CARE: NURSING, ALLIED HEALTH AND PALLIATIVE CARE - MULTIDISCIPLINARY CARE DELIVERY
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P4.15C.01 Improving Care Coordination to Address Healthcare Inequities in Lung Cancer

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Introduction: The Association of Cancer Care Centers (ACCC) developed the Improving Care Coordination (ICC) Model between 2016 and 2020, expanding on the Multidisciplinary Care (MDC) Assessment Tool from the National Cancer Institute's Community Cancer Centers Program (NCCCP). These models aimed to enhance multidisciplinary care quality for Medicaid-covered patients, ultimately improving their quality of life and treatment outcomes. The ICC Model consists of 12 assessment areas with 5 levels each, ranging from basic care provision (level 1) to optimal best practices for coordination (level 5). Designed for multidisciplinary teams including oncologists, advanced practice providers, navigators, social workers, and administrators, the Model is a tool for cancer programs to objectively assess how lung cancer care is provided at their institution and as scaffolding for building quality improvement initiatives to improve care coordination for patients with a lung cancer diagnosis. Cancer programs can employ the Model to measure strengths and improvement opportunities while conducting continuous assessment of care coordination in pursuit of optimal patient outcomes.

Methods: In late 2023, ACCC updated the Model with new quality metrics. To refine the Model, a working group was assembled featuring key stakeholders and cancer care professionals, including an oncology pharmacist, two medical oncologists with expertise in thoracic oncology and palliative medicine, and patient advocacy partners. The working group distributed the 12 assessment areas among its members based on expertise and interest, with each member reviewing and updating three sections. ACCC reviewed, consolidated, and collated all quality updates and conducted individual review sessions with each working group member. The final version of the Model was reviewed by the Working Group, editorial teams, and key advocacy partners before publication.

Results: Table 1 (Assessment Areas - Summary of Updates) summarizes the updates made to the Model across assessment areas. Although the Model was originally developed for the lung cancer population, many components may now be used across the cancer care delivery system independent of cancer type.

Conclusions: Continuous quality improvement in healthcare is crucial for enhancing patient care and provider satisfaction. The ICC Model serves as a tool to evaluate strengths and areas for improvement, aiming to achieve optimal patient care. With each assessment area offering five levels of care provision, the ICC Model supports cancer programs and practices in progressing towards their desired target level. Originally tailored for lung cancer, its adaptable components can benefit the broader cancer care delivery system.

Keywords: Care Coordination, Quality Improvement, Assessment Tool

Assessment Area	2023 Updates
Patient Entry into Lung Cancer Program	Added offering of navigation services & second opinion telehealth as high-level metrics.
Multidisciplinary Treatment Planning	Removed strict metrics regarding multi-visits—allowed the use of agreed upon treatment pathways if applicable to the disease state and program type.
Clinical Trials & Biomarker Testing	Moved metrics regarding coordinated portfolio of trials up from Level 3 to Level 4. Reduced percentages of patients screened for clinical trials (very hard to reach and measure, even for NCI cancer centers). Added metrics for biomarker testing, aligned with best practices
Supportive Care	Added prescription of prophylactic antiemetic therapy prior to first cycle chemotherapy as Level 2 metric. Advanced care planning should be in place for patients 65+
Survivorship Care	Added metrics for annual education of staff on providing supportive care services. Added that patients should be referred to resources when available. Added that a survivorship program with coordinator oversight is available for Level 5
Financial, Transportation, and Housing	Recommended visually separating metrics for the 3 areas (such as color-coding). Removed specifics (such as "discussion of bills received") as patients may ask to speak with financial counselors for other reasons.
Tobacco Education	Recommend listing the "assessment" (screening) step as the first bullet for Levels 1, 2 and 3 as assessing tobacco use is the first step prior to advising and assisting the patient and household member to quit (3 As: ask, advise, assist). Added details for clarity (example: changing "formal counseling" to "formal tobacco cessation counseling")
Navigation	Added medical interpreter services & structured education to navigation services. Added responsiveness to telephone inquiries re: medical care within 24 business hours
Treatment Team Integration	No updates needed.
Physician Engagement	Added metrics of physicians' completion of training in inclusivity, social determinants of heath, and barriers to care, either through credentialling program or outside organization.
Electronic Health Records (EHR) and Patient Access to Information	Added metrics for: (1) Increased patient access to EHR, (2) review of Problem & Medication list at every visit, (3) medication documentation via barcode, (4) telemedicine integration with EHR. Recommended use of clinical data sharing repositories or exchanges if possible
Quality Measurement and Improvement	Removing distinction of QOPI/RQRS data when describing Level 3 QI initiatives (to increase flexibility for average programs).

P4.15C MULTIDISCIPLINARY CARE: NURSING, ALLIED HEALTH AND PALLIATIVE CARE - MULTIDISCIPLINARY CARE DELIVERY
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P4.15C.02 Palliative Care Impact on Time Toxicity Among Patients with Advanced Lung Cancer at the End of Life

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Introduction: Time toxicity, reflecting the burdensome time commitments required from patients undergoing cancer treatment, is a significant concern in advanced lung cancer care. Patients with advanced lung cancer have frequent and intensive interactions with the healthcare system, primarily driven by the demanding nature of cancer treatments and significant disease burden. Studies have emphasized that early integration of palliative care improves patients' quality of life and leads to a decrease in unnecessary medical interventions, hospitalizations, and emergency department (ED) visits. This study examines the impact of palliative care on time toxicity by analyzing healthcare contact days in patients with advanced lung cancer within the last year of life.

Methods: A retrospective cohort analysis was conducted including patients with advanced (stage 4) lung cancer who died within one year of diagnosis at Kaiser Permanente Northern California between January 1, 2018, and December 31, 2021. The outcome was quantified as the number of days patients had physical contact with the healthcare system, including outpatient visits (lab work, imaging, treatment, provider appointments), ED visits, acute inpatient hospitalizations, and non-acute institutional stays from diagnosis to death (healthcare contact days), presented as both an absolute number and as a proportion of the total survival period (contact %). Our exposure was whether patients had received palliative care, characterized as being seen by outpatient or inpatient palliative care at least once between diagnosis and death. Multivariable negative binomial regression was utilized to model contact days with adjustment for demographic, treatment, and clinical variables.

Results: There was a total of 944 patients with advanced lung cancer (49.5% female, 73.3% White, median Elixhauser score of 4), 486 (51.5%) of which were seen by palliative care. Compared to those who did not receive palliative care, patients who received palliative care were younger (73 years vs 75 years), more likely to have received chemotherapy (46.3% vs 28.2%), radiation (38.7% vs 26.9%), and enrolled in hospice (45.3% vs 31.2%) (all $p<0.01$). Overall, patients receiving palliative care lived longer than those who never received palliative care (median survival, 140.5 days vs 81 days, $p<0.001$). The median percentage of contact % were similar between two groups (29.1% vs 33.2%, $p=0.05$). However, after adjustment and stratifying by types of contact, the palliative care group demonstrated significantly fewer ED or acute inpatient contact days (adjusted rate ratio [aRR] = 0.67, $p<0.001$) with an increased outpatient contact days (aRR = 1.15, $p<0.001$). Additionally, hospice enrollment was associated with significantly less contact days (aRR = 0.68, $p<0.001$).

Conclusions: The integration of palliative care significantly reduces time toxicity for advanced lung cancer patients by decreasing reliance on acute inpatient and ED services and promoting more manageable outpatient and in-home care options, including virtual care. These findings advocate for the broader implementation of palliative care in advanced lung cancer treatment protocols, highlighting its role in improving patient outcomes and quality of life.

Keywords: Palliative care, Time toxicity, Contact days

P4.15C MULTIDISCIPLINARY CARE: NURSING, ALLIED HEALTH AND PALLIATIVE CARE - MULTIDISCIPLINARY CARE DELIVERY
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P4.15C.03 Successful Implementation of a Lung Cancer Navigator Workshop: A Cancer Site-Specific Training Program by GO2 For Lung Cancer

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Introduction: Lung cancer is the leading cause of cancer-related deaths worldwide. This highly stigmatized disease is preventable and curable when people receive timely, evidence-based, efficient, and high-quality care. A growing body of evidence demonstrates the value of integrating patient navigation across the care continuum for improved outcomes and a well-accepted practice in lung cancer. Due to the paucity of comprehensive and site-specific training for lung cancer navigators, GO2 for Lung Cancer has initiated the Lung Cancer Navigator Workshop to elevate the standard of care and equitable health outcomes through effective care navigation for people at risk and living with lung cancer.

Methods: The curriculum for this didactic workshop was informed by a navigator advisory board (NAB) comprised of clinical and administrative experts representing the lung cancer continuum. The NAB provided diverse perspectives and insights on content areas that must be included in navigator training. Ten topics were prioritized for the day-long Lung Cancer Navigator Workshop held on October 12, 2023, in Washington, DC.

Results: This inaugural workshop was attended by 85 participants (nurses, pharmacists, social workers, scientists, and administrators) across oncology; A 70% higher attendance than the goal of 50 was appreciated. A post-test and survey were completed by 47% (40/85) of participants, with 100% (40/40) demonstrating competency and earning continuing education credit. Feedback on the workshop's effectiveness revealed high satisfaction levels and perceived competency in the course content, with 100% (40/40) of participants reporting the course was worth their time and would recommend it to others, and 97.5% (39/40) found the faculty effective in delivering the material. The professional value of the workshop content in improving their practice or job function was rated "highly valuable" (82.5%) and "valuable" (17.5%), and 92.5% (37/40) reported that the education and resources provided would be useful in their practice. Finally, upon completing the Workshop, participants rated their knowledge confidence highly in seven key content areas.

Conclusions: This comprehensive site-specific Lung Cancer Navigator Workshop, provided by GO2 for Lung Cancer, is the first of its kind. Providing didactic content orienting cancer navigators to current evidence, practice guidelines, and best practice standards for lung cancer care leverages the opportunity to prepare navigators to address the unique needs of people at risk and living with lung cancer. This ongoing Workshop enhances the provision of quality patient and family-centered lung cancer care, close care gaps, and improve equitable health outcomes critical to the lung cancer community.

Keywords: Navigator, Lung Cancer, Training

	VERY CONFIDENT	CONFIDENT	LESS CONFIDENT	NOT CONFIDENT	TOTAL
Identify preventable risks for the development of lung cancer.	82.50% 33	17.50% 7	0.00% 0	0.00% 0	40
List the most common types of lung cancer.	82.50% 33	17.50% 7	0.00% 0	0.00% 0	40
Discuss the eligibility criteria and government mandates for lung cancer screening.	87.50% 35	12.50% 5	0.00% 0	0.00% 0	40
Summarize the value of biomarker testing as a means for personalized cancer care.	60.00% 24	37.50% 15	2.50% 1	0.00% 0	40
Describe how smoking cessation services are most effectively integrated into the lung cancer care continuum.	80.00% 32	20.00% 8	0.00% 0	0.00% 0	40
Identify critical administrative and leadership responsibilities in establishing, growing, and maintaining clinical programs.	75.00% 30	20.00% 8	5.00% 2	0.00% 0	40
Identify different types of lung nodules on radiologic films.	45.00% 18	42.50% 17	10.00% 4	2.50% 1	40

P4.15D MULTIDISCIPLINARY CARE: NURSING, ALLIED HEALTH AND PALLIATIVE CARE - SURVIVORSHIP
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P4.15D.01 Beyond Survival: A Pilot Study Analyzing Physician and Patient Perspectives on Lung Cancer Survivorship Care at Weill Cornell Medicine

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Introduction: Lung cancer survivors constitute a significant and continually growing segment of the healthcare landscape. This increase can be attributed to the remarkable advancements in treatment modalities, including surgery, targeted therapy, and immunotherapy. These have enabled the 5-year lung cancer survival rate to rise from a meager 13% in the early 1990s to a promising 22% in the 2010s. 1 However, surviving cancer brings its own set of complex needs related to the long-term physical and psychological effects of cancer and its treatment. 2 With the rising number of lung cancer survivors and their unique, multifaceted needs, the demand for structured lung cancer survivorship programs has never been more pronounced.

Methods: Our study aimed to conceptualize and create a lung cancer survivorship program, beginning with a comprehensive understanding of our current approach to survivorship care. To accomplish this, we employed the Plan-Do-Study-Act (PDSA) cycles 1 and 2. In cycle 1, we developed and adapted a survey tool from the validated Concerns Checklist3, specifically tailored to understand the existing approach to the care of lung cancer survivors. This survey was distributed to physicians who treat lung cancer patients, who were then provided with a list of survivorship concerns. In cycle 2, we developed a patient-centric survey tool, which was given to all patients diagnosed with early-stage lung cancer who were eligible for survivorship care. This patient survey evaluates multiple domains of survivorship including symptoms, pain, sexual dysfunction, practical concerns, psychosocial needs, spirituality, nutrition concerns, and use of complementary therapies.

Results: Physician surveys were completed by 12 respondents from various specialties. The most addressed concerns were breathing difficulties, cough, pain, smoking cessation, and fatigue. However, concerns like sexual functioning, fertility, and complementary therapies were areas where most respondents felt uncomfortable addressing. Faith or spirituality, sexual functioning, fertility, and practical concerns like shopping and housework were aspects that most respondents did not routinely address. Thus far, 34 patient surveys have been completed, providing baseline understanding of our current approach and gaps in services for survivorship care in lung cancer.

Conclusions: The results of these surveys will lay the groundwork for a new Thoracic Oncology Survivorship Program designed to best serve the needs of our lung cancer survivors, and our focused training needs for providers. By identifying and addressing the areas of concern, we aim to enhance the quality of life for lung cancer survivors, catering to their unique needs and challenges. In doing so, we hope to transform the landscape of survivorship care, providing a model for comprehensive, patient-centered care for lung cancer survivors.

Keywords: survivorship, lung cancer, early stage

P4.15D MULTIDISCIPLINARY CARE: NURSING, ALLIED HEALTH AND PALLIATIVE CARE - SURVIVORSHIP
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P4.15D.02 Risk of Osteoporosis and Bone Fracture by Systemic Therapy in Lung Cancer Survivors

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Introduction: Increased risk of bone fracture (fx) is reported in survivors of multiple myeloma, lymphoma, and breast cancer. Malnutrition, muscle atrophy, and chemotherapy (chemo) may contribute to increased fx risk in these populations. Limited studies on fx risk in lung cancer survivors (LCS) have mixed findings, with smoking postulated as a risk factor. No studies have reported the impact of type of systemic therapy on osteoporosis and fracture in LCS.

Methods: Data from TriNetX, a de-identified network of over 110 million patients from 78 US health care organizations, was used. All adult patients (pts) diagnosed with primary lung cancer were stratified based on the presence of metastases at diagnosis. Pts with rheumatoid arthritis, pathologic fxs, or secondary malignancies were excluded. We investigated the outcomes of any bone fx and osteoporosis/bone density disorder (O/BDD). 1:1 greedy nearest-neighbor propensity score matching (PSM) based on demographics, smoking, and systemic therapy (chemo, immunotherapy (IO), or targeted therapy (TT)) was used. Independent t-tests were performed for continuous data; chi-square analysis for categorical data. We assessed outcomes using logistic regression with covariates age, sex, race, smoking history (hx), and systemic therapy use, both before and after PSM (doubly robust approach). All tests were two-tailed with alpha 0.05.

Results: Of 474,352 LCS, 43,454 had metastases at diagnosis (LCS-M), and 430,898 did not (LCS-NM). All results reported are after PSM. LCS-M were more likely to have O/BDD (OR 1.14, 95% CI 1.07-1.21, p<.001) and any fx (OR 1.54, 95% CI 1.49-1.59, p<.001) than LCS-NM. Male LCS were less likely to have O/BDD (OR 0.39, 95% CI .36-.41, p<0.001) or fx (OR 0.70, 95% CI 0.67-0.73, p<0.001). LCS with hx of smoking, received chemo, or TT were more likely to have O/BDD (Table). Odds of fx were only elevated in LCS who had smoked, although trended towards significance in those having received TT. Among LCS-M, receiving chemo (OR 1.32, 95% CI 1.14-1.52, p<0.001)) or TT (OR 1.55, 95% CI 1.23-1.93, p<0.001) increased odds of having osteoporosis/BDD; receiving TT increased odds of fx (OR 1.31, 95% CI 1.09-1.55, p=0.003).

Conclusions: LCS-M have increased risk of O/BDD and non-pathologic fracture than LCS-NM. Type of systemic therapy may contribute to these increased risks, with increased risk of O/BDD in LCS treated with chemo, and increased risk of fx and O/BDD in LCS treated with TT. Prospective studies are needed to validate these findings and identify interventions to evaluate and allay these risks.

Keywords: Lung cancer survivors, Bone fractures, Chemotherapy

Odds Ratios of Osteoporosis and Bone fracture in Lung cancer Survivors

	OR	95% CI	p-value
Osteoporosis/BDD			
Smoke hx	1.26	1.18-1.34	<0.001
Chemo	1.30	1.16-1.45	<0.001
IO	0.98	0.82-1.16	0.8
TT	1.43	1.19-1.70	<0.001
Fracture			
Smoke hx	1.39	1.33-1.46	<0.001
Chemo	1.06	0.97-1.15	0.2
IO	0.94	0.83-1.07	0.4
TT	1.14	0.99-1.31	0.056

P4.15D MULTIDISCIPLINARY CARE: NURSING, ALLIED HEALTH AND PALLIATIVE CARE - SURVIVORS
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P4.15D.03 The Lung Cancer Stigma Communications Assessment Tool: Supporting Engagement with the Lung Cancer Community

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Introduction: Lung cancer stigma poses a critical barrier to improving lung cancer outcomes, limiting optimal delivery of innovative and effective lung cancer risk reduction, early detection, treatment, and survivorship interventions. Stigma in the context of lung cancer can lead to feelings of shame and blame and prevent individuals from accessing care that can dramatically improve reduce mortality. In developing and disseminating patient- and public-facing educational materials and interventions, it is essential to be aware of how words, imagery, and context have the potential for creating or contributing to stigma in the lung cancer community. The Lung Cancer Stigma Communications Assessment Tool (LCS-CAT) was created to help content developers who are creating or modifying public facing materials to identify, remove, and replace potentially stigmatizing language, imagery, and context that could contribute to societal and individual stigma.

Methods: With support from the American Cancer Society National Lung Cancer Roundtable, a multifaceted tool was developed to assist lung cancer content developers in creating more effective engagement tools by removing and avoiding stigmatizing language and imagery. Additionally, the tool was intended to guide consideration of the context in which lung cancer content and engagement materials are to be used and to provide alternative approaches to replace language and imagery and alter contexts to maximize engagement with the lung cancer community. Leveraging extensive expertise from lung cancer professionals and integrating insights garnered from other health stigmas (e.g., HIV/AIDS, mental health, obesity, etc.), the development team prepared and revised the LCS-CAT.

Results: The development team identified a structure including three essential considerations: language, imagery, and contexts that must be considered when developing and disseminating lung cancer content and engagement materials. Similarly, the development team developed a process for identifying, removing, and replacing potentially stigmatizing language, imagery, and contexts. Following several iterations of feedback and pilot testing, the LCS-CAT Version 1.0 consists of six components and an implementation manual. The six components include: (1) a Language Audit Tool, (2) a Language Alternatives Guide, (3) an Imagery Audit Tool, (4) an Imagery Alternatives Guide, (5) a Context Audit Guide, and (6) a Context Alternatives Guide.

Conclusions: Although innovative and effective lung cancer risk reduction, screening, treatment, and survivorship interventions have the potential to rapidly improve lung cancer outcomes, societal constraints, including lung cancer stigma, can pose barriers to implementation. Building on the influential and impactful work of the IASLC Language Guide Version 1, the LCS-CAT expands consideration of stigma-inducing content to include imagery and contexts and provides alternatives for content developers to consider when developing any effort to engage or educate the community regarding lung cancer. To support the destigmatization of lung cancer, it is critical for communication creators to consider a “stigma biopsy” on all patient- and public-facing lung cancer campaigns to help identify, eliminate, and replace messages that could compromise engagement with the lung cancer community. The LCS-SAT is designed to facilitate these efforts. Ongoing research continues to evaluate the tool, build a web-based dissemination platform, and transcreate the LCS-CAT for other languages and cultures.

Keywords: Lung Cancer Stigma, Health Communications, Community Engagement

P4.15D MULTIDISCIPLINARY CARE: NURSING, ALLIED HEALTH AND PALLIATIVE CARE - SURVIVORSHIP
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P4.15D.04 Association Between Emotional Distress and Immunotherapy Response in Advanced NSCLC (STRESS-LUNG-1): Biomarkers Exploratory Analyses

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Introduction: Emotional distress, with hallmarked symptoms of depression and anxiety, is prevalent among patients with cancer. The field of "Psycho-oncology" is gaining increasing attention in cancer management. STRESS-LUNG-1 study is a prospective observational cohort study to investigate the association between emotional distress and efficacy of first-line treatment of immune checkpoint inhibitors (ICIs) in advanced non-small-cell lung cancer (NSCLC). We have previously reported the independent relationship between distress and lower objective response rate and shorter progression-free survival. We here updated the overall survival (OS) and explore the biomarkers including blood distress hormones, tumor microenvironment (TME), and gut microbiota.

Methods: STRESS-LUNG-1 study is a prospective, observational cohort study with the predetermined primary endpoint to explore the association between emotional distress and the efficacy of first-line treatment of ICIs in cancer (NCT05477979). Stage IIIB-IV NSCLC treated with first-line therapy of ICIs were enrolled. Emotional distress was assessed using PHQ-9 and GAD-7 scales. The data was as of November 30, 2023. Tumor microenvironment was detected by multiplex immunofluorescence, and gut microbiota by 16S rDNA sequencing.

Results: A total of 227 NSCLC patients were enrolled with 111 patients (48.9%) presence of distress. The baseline characteristics between distressed and no-distressed groups were well-balanced. With the median follow-up of 16.0 months, and the OS maturity of 30.4%, the distress group had a lower 1-year (70.4% vs. 80.8%) and 2-year survival rate (46.5% vs. 64.9%) with higher risk of OS events of death (HR=1.82, 95% CI 1.12 to 2.97; p=0.016). For biomarkers exploratory analyses, the distressed group had higher serum cortisol levels (443.4 vs 386.0 nmol/L, p=0.019), which is also associated with poor PFS and OS. The TME in the distress group exhibited lower infiltration of M1 macrophages (564 vs 1558 cells/mm2, p=0.035). Notably, patients with distress had the reduced abundance of Genus Bacteroides, especially in species of Bacteroides stercoris (0.7% vs 0.1%, p=0.011). The reduction of Bacteroides stercoris was associated with worse survival outcomes.

Conclusions: The study underscored the association between emotional distress and the worse efficacy of ICIs. Blood cortisol, gut Bacteroides stercoris and TME macrophages may play pivotal roles in the correlation of emotional distress and efficacy of ICIs.

Keywords: Lung cancer, Immunotherapy, Emotional distress

P4.15E MULTIDISCIPLINARY CARE: NURSING, ALLIED HEALTH AND PALLIATIVE CARE - SYMPTOM MONITORING AND MANAGEMENT
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P4.15E.01 Association Between Dynamic Patient-Reported Outcome-Based Symptom Exacerbation and Postoperative Complication in Lung Cancer

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Introduction: Recent studies highlight the association of dynamic changes in patient-reported symptoms such as cough and pain in the immediate postoperative period, with recovery outcomes. However, the temporal association between patient-reported outcome-based symptom exacerbation following lung surgery and postoperative (post-op) complications has not been effectively investigated. This study aims to investigate whether there is a transient increase in risk of postoperative complications after symptom exacerbation at post-op Day 2 (POD2) in patients with lung cancer. By focusing on quantifiable, threshold-based symptom management, this study seeks to provide insights into effective strategies for minimizing postoperative complications and enhancing patient recovery.

Methods: A prospective observational study was conducted using electronic health records from the Department of Thoracic Surgery, Guangdong Provincial People's Hospital in China between Jan 06, 2022 and Feb 18, 2023. A multivariable nested case-control study was performed among 405 patients with lung cancer receiving surgery. Postoperative symptom exacerbations are recorded via an electronic Patient-reported Outcome (ePRO) platform. Cases were identified with postoperative complications occurrence defined by Clavien-Dindo classification (Grade≥2). Controls were matched to cases (4:1). Multivariate Cox regression models estimated postoperative complications risk for patient-reported symptom exacerbation at POD 2 with hazard ratio (HR), adjusted for 3.231(95% CI 1.673,6.241). Cox regression analysis was adopted in subgroup analysis to determine the most susceptible cohorts.

Results: The total sample of 405 individuals (median age [IQR], 56 (47 - 64) years) included 81 cases and 324 matched controls. The alterations observed in patient-reported sleep disturbance from postoperative day one (POD1) to postoperative day two (POD2) exhibited a statistically significant difference when comparing the case group to the control group. Amongst the 81 individuals who encountered postoperative adversities, 47 (58.0%) had inpatient complications while 37 (45.7%) experienced outpatient complications. Multivariate Cox regression analysis showed that the combined sleep disturbance and shortness-of-breath is a significantly independent risk factor (HR: 3.231, 95% CI [1.673-6.241], P = 0.0005) for postoperative complications.

Conclusions: In this nested case-control study, combined sleep disturbance and shortness of breath exacerbation at POD2 was associated with higher risk of postoperative complications. These findings suggested that combined symptom exacerbation pattern may serve as an early indicator for postoperative complications and that early interventions to manage sleep disturbances and respiratory symptoms could be implemented to mitigate the risk of complications. Enhanced follow-up procedures might be warranted for patients who exhibit these risk factors, especially after hospital discharge to address outpatient complications.

Keywords: Patient-reported outcomes, Postoperative complications, Lung cancer

P4.15E MULTIDISCIPLINARY CARE: NURSING, ALLIED HEALTH AND PALLIATIVE CARE - SYMPTOM MONITORING AND MANAGEMENT
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P4.15E.02 Acceptability and Feasibility of Integrating A Chatbot into Routine Lung Cancer Care: Patient and Clinician Perspectives

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Introduction: Across the digital health landscape, technologies that draw upon augmented or artificial intelligence to mimic human conversation (i.e., chatbots) have rapidly increased. Yet, little is known regarding how best to integrate these technologies into clinical practice. This mixed-methods study shares patient and clinician perspectives on the use of a chatbot ("Penny") to support symptom management and oral anticancer agent adherence in lung cancer care and examines factors that shape the acceptability and feasibility of implementing Penny into routine care.

Methods: Penny engages with patients via text messaging and provides reminders and motivational cues to promote medication adherence. Penny also assists with management of disease symptoms and treatment side effects. Following a randomized controlled trial assessing the effects of Penny on medication adherence and symptom management in patients with advanced non-small cell lung cancer who were taking oral targeted therapies, we conducted a mixed-methods study among 18 enrolled patients and 12 clinicians who care for this population. Using the Information-Motivation-Behavioral Skills model and the Consolidated Framework for Implementation Research, we designed interview guides to systematically assess factors shaping the acceptability, effectiveness, and feasibility of future implementation of Penny into routine cancer care. Qualitative data were analyzed using the constant comparative method. Close-ended responses were analyzed using descriptive statistics and triangulated with qualitative findings.

Results: Participants were interviewed between December 2022-February 2023. During the trial, among all patients who were randomized to use Penny and completed the final survey (n=36), the net promoter score (NPS) [From 0 (Not at all likely) to 10 (Extremely likely), how likely is it that you would recommend Penny to a friend or colleague with lung cancer?)] was 6.9. The patient interview sample was stratified to include patients who ranked Penny with low, middle, and high NPS; yet, during the interviews, 17 out of 18 patients said that they would recommend Penny to a friend taking oral cancer medication, and 1 patient said that it would depend on the individual's personal health situation. When asked if they would continue using Penny as part of their personal cancer care, responses were mixed, with some patients stating that Penny wasn't necessary for them. Few patients used Penny to manage symptoms, but they appreciated having another line of communication about their care if needed. Patients also appreciated the emotional support and reminders provided by Penny. Among clinicians (n=12), when asked if they would recommend Penny to their patients, 6 agreed, 5 strongly agreed, and 1 remained uncertain. When asked if Penny would be useful in managing patient care, 7 agreed, 4 strongly agreed, and 1 remained uncertain. Clinicians commented that technological limitations (e.g., not having mobile phones or knowing how to text) would be a key barrier to implementing Penny into routine care among some patient groups.

Conclusions: Our findings show that integrating a chatbot into cancer care is largely acceptable and feasible, can provide needed reminders and emotional support to patients, and can potentially alleviate clinician burden. Further study of chatbots in this context is warranted.

Keywords: Mixed-Methods, Symptom Management, Chatbots

P4.15E MULTIDISCIPLINARY CARE: NURSING, ALLIED HEALTH AND PALLIATIVE CARE - SYMPTOM MONITORING AND MANAGEMENT
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P4.15E.03 Assessing the Utilization of Palliative Care in Advanced NSCLC Patients with Brain Metastases

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Introduction: Non-small cell lung cancer (NSCLC) represents a significant global health burden, with stage IV disease presenting particularly challenging clinical scenarios, often accompanied by brain metastases (BMETS). Palliative care (PC) plays a pivotal role in addressing the needs of patients with advanced NSCLC, focusing on improving symptom control, overall quality of life, and survival. This retrospective cohort study aimed to elucidate the influence of PC involvement on outcomes, including survival, advance directives, hospice, and ER visits among patients with NSCLC and BMETS.

Methods: In this retrospective cohort study, data were extracted from electronic medical records of patients with advanced NSCLC who had brain metastases at the University of Vermont Medical Center (UVMMC) between 1/1/2017 and 12/31/2019. Patients with at least six months of follow-up or until death were included, with exclusion criteria comprising patients with leptomeningeal or dural/calvarial metastases. We utilized the Recursive Partitioning Analysis (RPA) prognostic tool to categorize patients into two RPA classifications: class II and class III. RPA is based on age, KPS, and disease status at BMETS diagnosis. Overall survival was calculated from the diagnosis of NSCLC with brain metastasis to death or the last follow-up.

Results: The study comprised 92 NSCLC patients with brain metastasis, including 48 RPA class II and 44 RPA class III. The median age was 67 years with 68% male representation. Palliative care was not received by 38 (41.3%) patients. Analysis revealed that 16/44 (36.3%) RPA class III patients and 22/48 (45.8%) RPA class II patients did not receive palliative care consultation. The median overall survival (OS) for patients without palliative care was 236 days (7.8 months) compared to 224 days (7.4 months) for those receiving palliative care, with no statistically significant difference (p = 0.52). Patients receiving palliative care exhibited higher rates of hospice utilization (78% vs. 47%, p = 0.002) and advanced directive completion (82% vs. 43%, p = 0.003). Although patients receiving palliative care had a seemingly higher number of emergency room (ER) visits, the difference was not statistically significant (p = 0.45).

Conclusions: Our study highlights no survival difference in patients who receive PC care; however, the palliative consult group utilized hospice and advanced directives more. PC involvement can assist patients and clinicians in making better-informed decisions based on the patient's values and realistic outcomes using brain-directed treatment options.

Keywords: Non-small cell lung cancer (NSCLC), Palliative care (PC), Brain metastases (BMETS)

Table 1: Comparing the Effectiveness of the Palliative Care Consultation Group versus the Standard Care Group

OUTCOME	PALLIATIVE CARE (n-54)	NO PALLIATIVE CARE (n-38)	P-VALUE
Median Survival	7.4 months	7.8 months	0.52
Hospice Utilization	75%	47%	0.002
Advance Directives Completed	82%	43%	0.003

P4.17C GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS - DISPARITIES
MONDAY, SEPTEMBER 9, 2024 - 18:30 - 20:00

P4.17C.01 Clinical Trial Enrollment at a Thoracic Oncology Program at a Single-Academic Institution Serving Primarily Underrepresented Patients

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Introduction: Participation in oncology-directed clinical trials ranges between 2-8% worldwide. A meta-analysis found that barriers contributing to low participation rates included lack of an available clinical trial (56%), ineligibility based on clinical trial criteria (22%) and non-enrollment despite being eligible for study (15%). Additionally, recent studies demonstrated that underrepresented (Black, Hispanic) patients have lower enrollment rates (4% and 6%, respectively) compared to their White counterparts (8%). The Thoracic Oncology Program at UI Health, a tertiary academic center, serves primarily underrepresented individuals from the South and West sides of Chicago. Therefore, we sought to characterize and analyze clinical trial enrollment rates and patterns in our program.

Methods: We retrospectively collected and analyzed data from 249 patients with lung cancer from 2021-2023. Enrollment in clinical trials was defined as: patients who were either successfully enrolled or initially enrolled but subsequently found not to meet eligibility criteria. The demographic and clinical characteristics of enrollees and non-enrollees were compared using two-sample t-tests, chi-square tests, or Fisher's exact tests, as appropriate. Multivariate logistic regression was employed to identify the factors that significantly associated with clinical trials enrollment.

Results: Cohort race demographics: 65% Black, 10% Asian, 16% White, 9% Hispanic. 35% enrolled into clinical trials. When excluding patients for whom no trial was available, 72% of patients enrolled into clinical studies. Additionally, we found that 52% of patients did not have a clinical trial available while 5% enrolled but were later deemed ineligible and 14% of patients declined to participate. A significant association was found between race/ethnicity and enrollment. Of those who enrolled onto a clinical trial, 24% were White, 64% were Black and 12% were individuals of other races/ethnicities. Of those that declined to enroll, 3% were White, 76% Black and 21% other races/ethnicities. After conducting multivariate logistic regression, both race/ethnicity and insurance type were found to be significantly associated with enrollment among all predictors. White patients were significantly more likely to enroll into a clinical study than Black patients (OR, 10.85; 95%CI,1.36-86.47; p=0.0244). Additionally, patients with Medicaid insurance were more likely to enroll onto a clinical study than patients with Medicare insurance coverage (OR, 3.33; 95% CI, 1.19-9.29; p=0.0218).

Conclusions: In the present analysis of clinical trial enrollment at a single-academic institution serving primarily undeserved, underrepresented patients, our enrollment rate far exceeded the national average at 35%. Additionally, we were successful in enrolling underrepresented patients at a far higher rate than what has been reported nationally. Our ineligibility rate is far below what has previously been reported. However, we found that White patients were over 10 times more likely to enroll onto a clinical study compared to Black patients. Therefore, a significant racial disparity exists between those enrolling and declining clinical trials. Future work will focus on evaluating the underlying reasons behind a patient's choice to enroll or decline a clinical study. We hope to utilize this data to develop educational materials for physicians and patients to improve not only our own clinical trial enrollments at UI Health but across the US and world.

Keywords: Clinical Trial Enrollment, Lung Cancer, Health Disparity

P4.17D GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS - EPIDEMIOLOGY
MONDAY, SEPTEMBER 9, 2024 - 18:30 - 20:00

P4.17D.01 Incidence Correlation Between Different Diseases and Lung Cancer: A Global Cross-Sectional and Time-series Study

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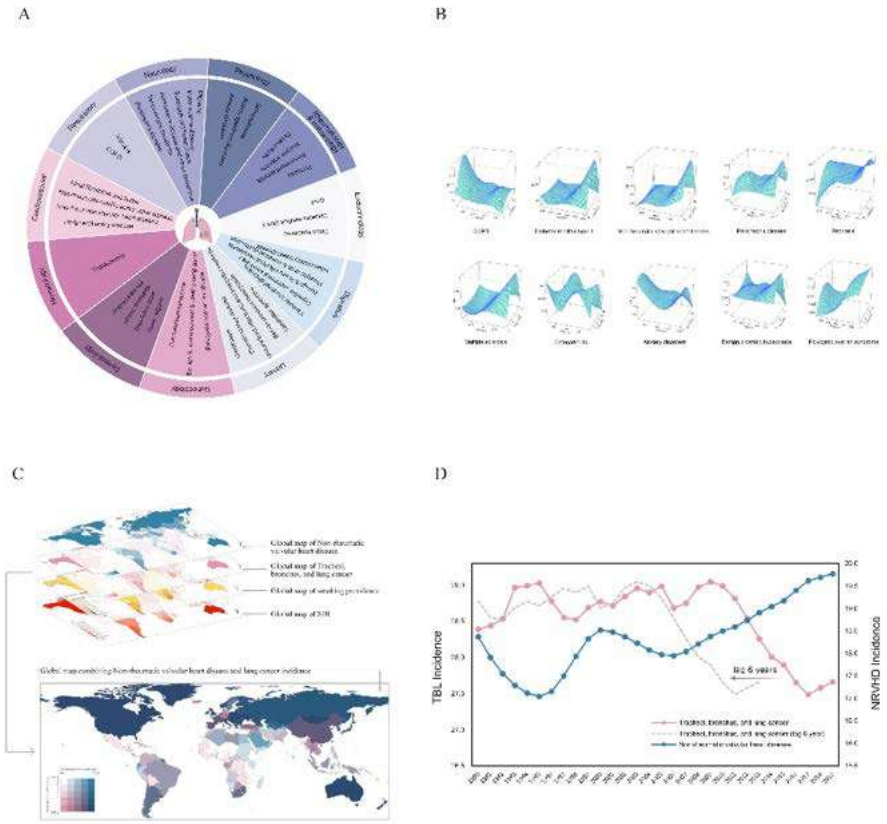
Introduction: Patients with lung cancer often have diverse comorbidities. However, a comprehensive and systematic review exploring the association between different diseases and lung cancer is currently lacking. This study aims to explore the correlation between various diseases and lung cancer, generating a comprehensive correlation map.

Methods: This study collected the incidence of 102 diseases across 204 countries from the Global Burden of Disease (GBD) database (1990-2019). In the cross-sectional analysis conducted each year, adjusted for smoking and SDI, explored the relationship between diseases and lung cancer using Spearman correlation. To mitigate the bias of low diagnostic rates and premature mortality, the study just focused on diseases positively correlated with lung cancer. Additionally, a 30-year time-series analysis employed a distributed lag non-linear model (DLNM) to investigate the lag effects of chronic diseases on lung cancer incidence.

Results: The analysis revealed potential positive correlations between lung cancer and 40 diseases. For instance, non-rheumatic valvular heart disease (correlation coefficient (CC): 0.736-0.789, p<0.001), peripheral artery disease (CC: 0.738-0.766, p<0.001), alopecia areata (CC:0.609-0.631, p<0.001), schizophrenia (CC: 0.561-0.612, p<0.001) and vascular intestinal disorders (CC: 0.548-0.590, p<0.001) demonstrated significant positive associations with lung cancer. Additionally, several chronic diseases such as chronic obstructive pulmonary disease (COPD, CC: 0.531-0.564, p<0.001), diabetes type 1 (CC: 0.343-0.405, p<0.001), Parkinson's disease (CC: 0.490-0.565, p<0.001) and psoriasis (CC: 0.489-0.577, p<0.001) exhibited positive correlations with lung cancer. Specifically, gout (CC: 0.156-0.190, p<0.05) showed a positive correlation in males, while paralytic ileus and intestinal obstruction (CC: 0.253-0.383, p<0.001), hernia (CC: 0.404-0.447, p<0.001) and rheumatoid arthritis (CC: 0.310-0.340, p<0.001) showed a positive correlation in females. Finally, the lag effects of 10 common chronic diseases were evaluated using the distributed lag non-linear model (DLNM). For instance, when the incidence rate of COPD was 207.8 (per 100,000), it exerted the greatest promoting effect on lung cancer risk with a lag of 6 years. Conversely, when the incidence rate of COPD was 213.4 (per 100,000), the impact on lung cancer was minimal, with a lag of 13 years.

Conclusions: By conducting population-level correlation mapping of disease incidences, this study unveiled potential associations between lung cancer and 40 diseases documented in the GBD database. This research could provide hints for studying the mechanism between lung cancer and certain associated diseases, and also established a paradigm for screening risk factors from the populational perspective.

Keywords: Lung neoplasms, disease, correlation



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P4.17D.02 Global Trends in Lung Cancer Survival by Morphology: Analysis from 61 Countries During 2000-2014 (CONCORD-3)

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Introduction: In 2015, the CONCORD programme established global surveillance of trends in population-based cancer survival as a metric of the effectiveness of health systems, and to inform global policy on cancer control. In 2018, CONCORD-3 updated the worldwide surveillance of cancer survival trends to 2014. The third cycle of the CONCORD programme (CONCORD-3) included data on over 37 million adults (15-99 years) diagnosed with one of 18 common cancers or groups of cancers during 2000-2014, including 6.1 million adults with lung cancer. Anonymised individual records were provided by 290 population-based cancer registries in 61 countries.

Methods: Tumours were categorised in three main groups by ICD-O-3 morphology codes: small-cell lung cancer (SCLC), non-small cell lung cancer (NSCLC) (adenocarcinoma, large cell carcinoma and squamous cell carcinoma) and lung cancer, not otherwise specified (NOS). We estimated trends in 5-year net survival by morphology for patients diagnosed during 2000-2004, 2005-2009 and 2010-2014, using the non-parametric Pohar Perme estimator. To control for background mortality, we used life tables of background mortality rates by single year of age, sex, calendar year and (where possible) race/ethnicity in each country. All-ages survival estimates were standardised with the International Cancer Survival Standard weights.

Results: Overall, 19% of tumours were categorised as lung cancer, NOS, ranging from 8% in Belgium to over 50% in China, India and Thailand. The proportion of NSCLC ranged from 36% in China to over 80% in Guadeloupe, Martinique and Taiwan. Overall, 13% of patients were diagnosed with SCLC (range 3-17%). In 2010-2014, age-standardised 5-year net survival for lung cancer, NOS ranged from less than 1% in Chile to 27% in Belgium. Five-year net survival for NSCLC was lower than 10% in Bulgaria, Chile and Guadeloupe, but reached 39% in Japan. Age-standardised 5-year net survival for SCLC was less than 15% in all countries. Five-year survival trends between 2000-2004 and 2010-2014 were generally flat for each morphology group and in most countries. For NSCLC, 5-year survival increased by 10% or more in Korea (from 16% in 2000-2004 to 29% in 2010-2014) and Taiwan (from 13% to 23%).

Conclusions: The current results represent worldwide survival trends in lung cancer survival by morphology based on data from population-based registries. Together with incidence and mortality, this contributes to a comprehensive picture of the global lung cancer burden, and can support public health strategy to reduce disparities in outcome. Accurate morphology data are crucial to understanding worldwide inequalities in survival from lung cancer. Population-based registries with high-quality data are essential for this purpose.

Keywords: lung cancer survival, morphology, global oncology

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P4.17D.03 Analysis of Lung Cancer Mortality Trends and Factors Impacting Years of Life Lost: A 20-Year Hospital-Based Cohort Study in São Paulo, Brazil.

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Introduction: Lung cancer stands as the second leading cause of years of life lost (YLL) among the 30 major diseases, surpassing all other cancer types. Its severity is evidenced by the high mortality rate, making it the primary cause of cancer-related death globally. This study aims to analyze the main factors influencing YLL and mortality trends in lung cancer over a 20-year period in São Paulo, Brazil.

Methods: This descriptive hospital-based cohort study utilized data from the Sao Paulo's State Hospital Cancer Registry (SPHCR), managed by the Sao Paulo's Oncocentro Foundation Information and Epidemiology Directorate (FOSP), encompassing 72 institutions. Analyzed variables included both genders, clinical stage, histological type, complexity level in centres in oncology hospitals (CLCOH), disease recurrence, 5-year YLL period and Annual Percent Change (APC - measure of annual variation in YLL based on the first and last year of a given period). YLL correspond to the difference among the estimated years of life expectancy (LE) for the respective year of death and the age of death for the individual. The YLL were described as the mean and median for each variable.Statistical analysis for the mean and median of YLL involved the Wilcoxon Mann Whitney method for two-categorical variables and Kruskal Wallis for three or more categorical variables. The difference between the groups were considered statistically, if p-value < 0.05

Results: The study included 5.419 patients from 2000 to 2019, aged 18 years or older, who died before reaching the mean LE. Analysis revealed that stage IV patients experienced approximately double the YLL compared to stage I (median=15.1 versus 8.6, respectively; p<0.0001). Patients who died in the periods of 2005-2009, 2010-2014, and 2015-2019 exhibited similar YLL rates confirmed with APC (-0.89% versus 0.05% versus -0.01% respectively). In addition, was observed that female had higher YLL than male (median=18.6 versus 11.6, respectively; p<0.0001), and patients without disease recurrence had lower YLL compared to those with disease recurrence (median=14.2 versus 14.9, respectively; p=0.0346). (Table 1). Being diagnosed with large cell lung carcinoma (LCLC) impacted on two and a half more YLL than squamous cell carcinoma (SCC) (median= 14.8 versus 12.3 respectively; p<0.0001).

Conclusions: Our results reveal the APC remained small over 15 years, indicating stable YLL. Significant YLL disparity among lung cancer stages underscores the need for early detection and tailored interventions. Gender differences and disease recurrence highlight the importance of personalized care and active surveillance in improving patient outcomes.

Keywords: Lung Neoplasms, Life Expectancy, Trends

Table 1– Analysis of the mean and median in years according to each variable and Annual Percent Change (%).

Variable	Category	Mean	Median	*p-value*
Gender*	Male	12.5	11.6	*p<0.0001*
	Female	18.9	18.6	
Clinical Stage**	I	10.7	8.6	*p<0.0001*
	II	12.0	9.9	
	III	14.1	13.2	
	IV	16.1	15.1	
Histological Type**	Squamous cell carcinoma (SCC)	13.2	12.3	*p<0.0001*
	Adenocarcinoma (ADN)	16.2	15.2	
	Small cell lung cancer (SCLC)	16.3	15.6	
	Large cell lung carcinoma (LCLC)	15.7	14.8	
Complexity Level in Centres in Oncology Hospitals (CLCOH)*	High complexity assistance units (HCAU)	15.4	14.6	*p=0.7682*
	High complexity oncology care centers (HCOCC)	15.4	14.3	
Disease Recurrence*	No	15.2	14.2	*p=0.0346*
	Yes	15.9	14.9	
Stage I Recurrence*	No	10.7	8.6	*p=0.9293*
	Yes	10.8	7.7	
Stage II Recurrence*	No	11.5	9.9	*p=0.4781*
	Yes	13.4	9.8	
5-Year YLL Period**	2000-2004	13.4	10.5	*p=0.0204*
	2005-2009	15.5	14.4	
	2010-2014	15.7	14.6	
	2015-2019	15.3	14.3	
			(%)	
APC	2000-2004		4.62	
	2005-2009		-0.89	
	2010-2014		0.05	
	2015-2019		-0.01	

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P4.17D.04 Insights into Lung Cancer During Pregnancy: Analysis of the National Inpatient Database (NIS)

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Introduction: Lung cancer (LC) remains the second most diagnosed cancer in both genders and the leading cause of cancer-related deaths in the USA, making up 21% of fatalities. The American Cancer Society estimates 118,270 new cases in women in 2024. While cancer rates are decreasing overall, the decline is more significant in men (2.5%) compared to women (1%). The higher incidence in women, often diagnosed later due to pregnancy-related factors like delayed imaging due to radiation concerns, warrants attention. Notably, lung cancer rates among young women, particularly white non-Hispanic and Hispanic women, surpass those of young men, highlighting an unexplained disparity. Given the knowledge gap, we analyzed NIS data to characterize reproductive-age women, both pregnant and non-pregnant.

Methods: This retrospective cohort analysis focused on women aged 15-49 admitted to USA hospitals from 2016 to 2020 with primary LC diagnosis during pregnancy. Data for this study was obtained from the NIS Database, excluding long-term acute care hospitals and rehabilitation centers. Primary goal: describe LC trends and compare incidence across socio-demographic groups. Secondary goal: assess care settings' impact (teaching vs. nonteaching hospitals) on outcomes and analyze hospital stay length (LoS). We used the Chi-Square-test for categorical variables and the Student's-t-test for continuous variables, with significance defined as $P < 0.05$.

Results: Among 32,405 reproductive-age women meeting the criteria, 80 were pregnant (PP) patients, and 32,325 were non-pregnant (NPP). Lung cancer incidence in reproductive-age-women was approximately 16.38 cases per 1000, and during pregnancy was 0.04 per 1000. PP's average age was 33, significantly younger than NPP's 43.9 ($p<0.001$). The average LoS was 7.5 days for PP and six days for NPP ($p=0.4$). Hospitalization costs were higher for PP: $100,241 vs. $73,119 for NPP ($p=0.4$). PP mortality was 12.5%, higher than NPP's 7.55% ($p = 0.4$). Most patients were white (62.5% PP vs. 64.8% NPP), followed by Black (19% PP vs. 15% NPP), Hispanic (12.5% PP vs. 9.6% NPP), Asian (0 PP vs. 6% NPP), and Native American (0 PP vs. 4% NPP). However, mortality didn't significantly differ by race (p:0.87). The primary hospital location was south (Delaware-Maryland-District of Columbia-Virginia-West Virginia-North Carolina-South Carolina-Georgia-Florida-Kentucky-Tennesse-Mississippi-Alabama-Oklahoma-Texas-Arkansas-Louisiana) (44% PP, 42% NPP). Most hospitals were large (69% PP vs. 60% NPP), followed by medium (25% PP vs. 25% NPP) and small hospitals (6% PP vs. 15% NPP) ($p=0.59$). PP documented complications: acute MI (6%, $p = 0.38$) and mechanical ventilation (44%). NPP complications: COPD (5%, $p = 0.35$), stroke (4%, $p=0.4$), sepsis (3%, $p=0.4$), and acute MI (3%, $p=0.38$). Thrombosis was more significant in PP than NPP (p:0.002). Income had no impact (p:0.75).

Conclusions: Our analysis of NIS highlights the incredible challenges and outcomes entwined with LC during pregnancy. Pregnant patients endure elevated mortality rates and heightened hospitalization costs compared to their nonpregnant counterparts, possibly attributable to the comprehensive care required for both mother and fetus. The study highlights the necessity for tailored management strategies and heightened vigilance in caring for pregnant patients with LC. Furthermore, further research is essential to optimize care and outcomes for this vulnerable population.

Keywords: Lung Cancer, Pregnancy, Disparities

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P4.17D.05 Squamous Cell Lung Cancer Still Remains the Most Common Histological Subtype of Lung Cancer in Rural India

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Introduction: As per the UN population data India is the most populous country in the world. Majority of epidemiological data about lung cancer from India, comes from National Cancer Registry Program (NCRP) steered by Indian council of Medical Research which has 272 sites under its umbrella. However, most of these sites are in metro cities catering predominantly to urban population. Despite the 65% contribution of rural population towards total population, lung cancer data from rural population remains underrepresented in the epidemiological reports. In the current report we have analyzed and reported the demographic and clinical data of the patients treated at a university-teaching hospital from northern India which caters predominantly to rural population.

Methods: Data of all patients managed at thoracic oncology clinic from September 2022 to March 2023 was retrieved and analyzed. Apart from demographic data, smoking profile and clinical information was also collected. Data of patients residing in urban areas was excluded from analysis. We further compared this data with the NCRP report published in 2022 (doi:https://doi.org/10.4103%2Fijmr.ijmr_1364_21).

Results: Over the above-mentioned period 540 subjects of lung cancer were treated at the clinic. Data of 36 subjects with urban residence was excluded. The mean age of the patient population was 59.8±10 years. 82.9% were males and 95.2% were smokers. Among the smoker's group 81.7% were current smokers and the remaining were former smokers. Out of the current smokers, 44.9% were still smoking at the time when they were being evaluated for the diagnosis of lung cancer. Among the smokers, 96.7% were bidi smokers. Bidis are hand rolled, small indigenous cigarettes with tobacco rolled into tendu leaves. They have significantly higher tobacco and tar component as compared to commercial cigarettes. Also, they lack filter. Mean BMI at the time of treatment initiation was 18.4±3 Kg/m2. Majority patients presented with ECOG PS (eastern cooperative oncology group performance status) 1 (41.9%) followed by ECOG PS 2 (32.9%). In 56.2% cases primary lesion was central (defined as location in the medial one third of the axial section, around the trachea and main bronchi). Endobronchial biopsy was used for obtaining tissue in 49.8% whereas Endobronchial ultrasound guided TBNA was employed in 21%. 71.4% of cases were also found to have emphysema on CT thorax. 46.4% were diagnosed with Squamous cell subtype (all p40 or p63 positive on immunohistochemistry- IHC). 28.8% were adenocarcinoma, 11.3% were small cell and the remaining were either NSCLC NOS (not otherwise specific), Large cell, undifferentiated or lacked sufficient tissue for IHC markers. Stage IIIB and IVA were the most common stages of presentation- 39.7% and 33.9%, respectively. As compared to the NCRP data- mean age was similar (61 compared to 59.8 years), male proportion was higher in rural data (76.7% versus 82.9%,) and Squamous cell subtype was distinctly higher in the rural data (23.4% versus 46.4%).

Conclusions: Majority of lung tumors in patients from rural India are central and of squamous histological subtype. Smoking habits of the rural population are also different from what is reported from urban areas.

Keywords: Squamous Cell Lung Cancer, Epidemiological Data, Tobacco Smoking

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P4.17D.06 Pan-Canadian Lung Cancer Observational Study (PALEOS): A Multicentre Ambispective Real-World Database Study in a Publicly Funded Health System

S. Kuruvilla[1,2], P. Wheatley-Price[3,4], F. Gwadry Sridhar[5], P. Joubert[6,7], O.I. Aseyev[8,9], L. Young[5], R. Sachdeva[1], B. Sheffield[10], M. Richardson[3], J. Bafaro[6], R. Seeger[3], A. Wojtyk[3], K. Bisson[10], A. Foo[10], G. Liu[11,12], P.K. Cheema[10,12], [1]London Health Sciences Centre, London/ON/CA, [2]Western University, London/ON/CA, [3]The Ottawa Hospital Cancer Centre, Ottawa/ON/CA, [4]University of Ottawa, Ottawa/ON/CA, [5]Pulse Infoframe Inc., London/ON/CA, [6]Institut de Cardiologie et de Pneumologie de Québec-Laval Universit, Quebec City/QC/CA, [7]Universite Laval, Quebec City/QC/CA, [8]Thunder Bay Regional Health Sciences Centre, Thunder Bay/ON/CA, [9]Northern Ontario School of Medicine, Thunder Bay/ON/CA, [10]William Osler Health System, Brampton/ON/CA, [11]Princess Margaret Cancer Centre, Toronto/ON/CA, [12]University of Toronto, Toronto/ON/CA

Introduction: In the dynamic landscape of healthcare decision-making, stakeholders are increasingly relying on real-world evidence (RWE) alongside evidence from randomized controlled trials. Regulatory bodies such as the US Food and Drug Administration, Health Canada and the European Medicines Agency are advocating for increased utilization of RWE to support new indications, signaling a paradigm shift in evidence-based medicine practices. Lung cancer is a heterogeneous disease with diverse subgroups defined by various factors including sociodemographic, molecular, and treatment characteristics. PALEOS aims to address key questions regarding the epidemiology and natural history, treatment patterns and effectiveness, safety, patient reported outcomes and health economic impact in Canadian lung cancer patients.

Methods: PALEOS (NCT04706754) is a multicentre, ambispective observational study conducted across multiple sites in Canada in adult patients with a confirmed non-small cell lung cancer. Patient clinico-demographic information, medical history, diagnostic, pathological and molecular data, treatment details, resource utilization and patient-reported outcomes, are collected retrospectively and prospectively. The study will recruit 25,000 patients over 20 years, with 6 initial sites that comprise a catchment area of approximately 30% of the Canadian population (mix of urban and rural populations), with plans to expand. Descriptive statistics are generated and survival analysis conducted based on primary and secondary objectives.

Results: Since first site initiated in 2019, 1,273 non-small cell lung cancer patients have been enrolled. Median age is 69 years (range 22-97; n-949) at diagnosis, 46% were females, and 19%, 9%, 19%, 53% were stages I, II, III, and IV, respectively (n=706). 48% had first-line metastatic treatment initially involving immunotherapy (24% monotherapy; 24% combination chemoimmunotherapy; n=544). Among all patients tested, 15% had EGFR-mutated (number tested =639) and 5% were ALK-rearranged (n=621) tumours. Median follow-up in Stage I-III patients was 20 months; in Stage IV patients, 9 months. Median OS survival for Stages I, II, III, IV were 35, 20, 12, and 10months, respectively. Annual recruitment rates are growing exponentially, from 69 new cases in 2020 to 835 new cases in 2023.

Conclusions: PALEOS provides a comprehensive framework for evaluating the natural history, treatment patterns, and outcomes of lung cancer patients across Canada. The study aims to enhance understanding of the impact of new diagnostic and treatment modalities in clinical practice and identify gaps in efficiencies within our publicly funded health care system. This initiative will facilitate knowledge translation and inform evidence-based decision-making in the management of lung cancer across disciplines. It is anticipated to support health technology assessments for new therapeutics and have meaningful impact on patient advocacy.

Keywords: Real World Data, Lung Cancer, Registry

P4.17D GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS - EPIDEMIOLOGY
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P4.17D.07 Temporal Improvements in Overall Survival in Metastatic Non-Small Cell Lung Cancer in the United States Since 2004

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Introduction: In metastatic non-small cell lung cancer (mNSCLC) targeted therapy was first approved in 2003, and immunotherapy was first approved in 2015. To characterize the population-level survival benefit of improved systemic therapy, we estimated the effect of diagnosis year on overall survival. These estimates can also be instrumental to external validation of long-term economic models of new therapies.

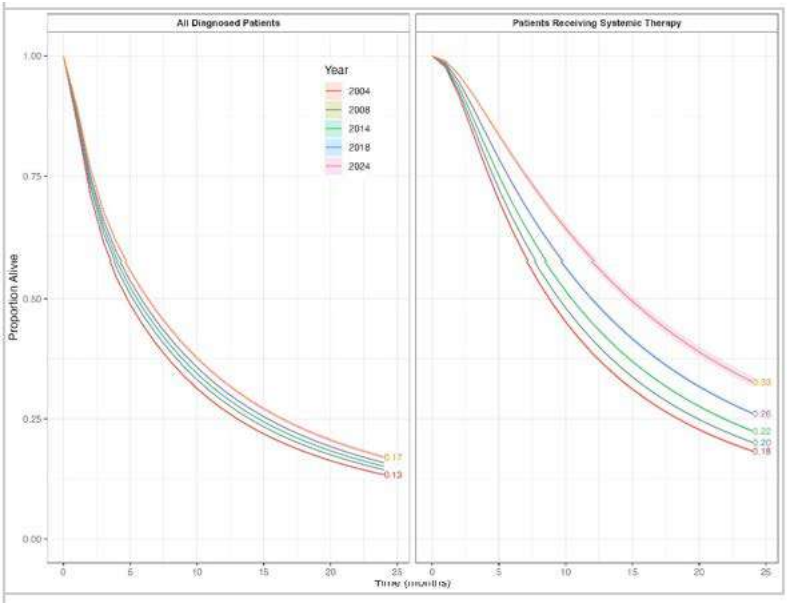
Methods: Surveillance, Epidemiology, and End Results data were used to identify adult patients with histologically-confirmed mNSCLC diagnosed from 2004 through 2018 and followed through 2019. Analyses of 2-year overall survival were conducted using flexible parametric survival models. We used g-computation to estimate the effect of diagnosis year on survival accounting for differences in age, sex, race, pleural effusion, marital status, large metropolitan area status, registry, histology, census-tract income. Sensitivity analyses were conducted using the subset of patients known to be treated with systemic therapy, and by projecting expected overall survival in 2024. All analyses were conducted using R.

Results: Among 238,680 patients with mNSCLC diagnosed from 2004-2018, mean age was 68 years and 55% were male. Using an adjusted model of survival for all diagnosed patients based on categorical diagnosis year, the hazard ratios for each diagnosis year (compared to 2004) declined over time and were 0.95 (95% CI 0.91-0.99) in 2010, 0.87 (95% CI 0.83-0.90) in 2014, and 0.76 (95% CI 0.73-0.79) in 2018. In the subset of 118,829 patients receiving systemic therapy, the hazard ratios were 0.91 (95% CI 0.86-0.97) in 2010, 0.77 (95% CI 0.73-0.82) in 2014, and 0.57 (95% CI 0.54-0.61) in 2018.

Overall survival improved over calendar time for all diagnosed patients and for the subset known to receive systemic therapy based on models using continuous diagnosis year (Figure). From 2004 to 2018, 24-month overall survival improved from 13% to 16% in all diagnosed patients, and from 18% to 26% in the systemic therapy subset. Extrapolating to 2024 showed that 24-month overall survival would be 17% for all diagnosed patients and 33% for patients who received systemic therapy.

Conclusions: Overall survival in mNSCLC has improved since 2004, particularly among patients who received systemic therapy who showed a 43% mortality risk reduction in 2018 compared to 2004. However, assuming a continued reduction in mortality risk through 2024, 24-month overall survival in patients receiving systemic therapy was estimated to be only 33%. While these trends highlight the results of meaningful treatment advances, further improvements are still needed.

Keywords: survival, non-small cell lung cancer



P4.17E GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS - HEALTH ECONOMICS
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P4.17E.01 Navigating from Target to Treatment: Early Impact of the Lung Precision Oncology Navigation Program (LPOP)

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Introduction: Molecular testing is essential for treatment decisions in non-small cell lung cancer (NSCLC). However, many patients have either missing or delayed results, leading to delays in treatment initiation or lost opportunities to access targeted therapy. The Lung Precision Oncology Navigator Program (LPOP) was developed to ensure and accelerate complete genotyping for patients and enhance access to precision medicine.

Methods: The Princess Margaret Cancer Centre (Toronto, Canada) LPOP entails detailed review of molecular testing results and communication with appropriate pathology, molecular, and treatment teams to facilitate complete molecular testing including through liquid biopsy prior to initial oncology consultation. The Navigator suggests potential targeted therapy trials and special access programs as appropriate based on biomarker results. We compared outcomes pre- and post-LPOP implementation including the: 1. proportion of patients with complete genotyping (non-squamous NSCLC); 2. proportion with results by initial oncology consultation; 3. turnaround time (TAT) for complete molecular results from biopsy; 4. time to treatment (TTT) from initial oncology consultation. Health care providers (HCPs) were surveyed at baseline and at six months to assess program impact and perceived gaps in care.

Results: Between 9/1/2023-11/30/2023, 75 patients were identified prior to LPOP implementation. Another 101 patients were identified post-LPOP implementation (12/1/2023-3/1/2024). Post-implementation of LPOP, we observed a numerical decrease in TAT for complete molecular results from biopsy (post 14.3 days vs. pre 15.9 days, $p = 0.09$) and a trend to reduced time from initial consultation to treatment start (12.6 days vs. 16.9 days, $p = 0.09$). There was a significant increase in the proportion of patients who had complete genotyping by their first consultation (81.2% vs. 44.1%, $p < 0.0001$) after LPOP implementation. When complete results were available for the initial consultation, there was no significant difference in the time to treatment initiation between the two periods (post-LPOP 12.9 days vs. pre-LPOP 15.7 days, $p = 0.60$). Patients without results available at the time of initial consultation had a longer time to treatment initiation in both time periods (17.1 days post, 18.2 days pre). Ten of 24 HCPs surveyed responded, reporting moderate familiarity with the LPOP Navigator's role. Challenges highlighted by respondents include incomplete genotyping and delays in obtaining results. HCPs recommended ongoing proactive review of molecular results, expediting testing and results, and facilitating clinical trial access. Respondents reiterated the importance of ensuring complete genotyping results at the initial oncology consult.

Conclusions: Our results showed an increase in the proportion of patients with complete genotyping by initial consult, indicating improved efficiency with LPOP. Survey feedback emphasized the need for ongoing navigator role refinement. We await results from the planned survey six months post-LPOP for insights into program efficacy and improvement areas.

Keywords: non-small cell lung cancer, precision medicine, navigator

P4.17F GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS - HEALTH SYSTEM
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P4.17F.01 Effective EGFR Testing Rates in Advanced Stage NSCLC Patients Treated in Community Oncology Practices: Impact of a Decision Support Program

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Introduction: The current standard of care in advanced-stage NSCLC patients who harbor EGFR mutations such as exon 19 deletions is small molecule targeted therapies. However, not all newly diagnosed patients receive biomarker testing before initiating first-line anticancer therapy (i.e. effective testing). Indeed, a proportion of these patients are offered a checkpoint inhibitor, even though such agents are of limited clinical benefit. We hypothesize that an early engagement program to inform oncologists on the importance of biomarker testing on all newly diagnosed patients will improve effective EGFR testing rates. The main objective of the current study was to measure the impact of a decision support program (DSP) on EGFR testing rates in advanced-stage NSCLC patients treated in community oncology practices across the United States (US).

Methods: The DSP consisted of multiple components such as early patient identification prior to their clinic appointment, their candidacy for benefiting from biomarker testing before initiating first-line therapy, and links to NCCN guidelines for treating actionable mutations in advanced NSCLC. Prior to the implementation of the program, a multistage random sampling technique was used to identify 201 control patients who were managed at the Quality Cancer Care Alliance or the National Cancer Care Alliance, for a combined 23 community oncology clinics across the US. The intervention group consisted of a random sample of 174 patients who were diagnosed in the 12 months following the launch of the DSP in participating clinics. The primary endpoint was the effective testing rate, defined as the EGFR test being ordered and the results received by the oncologist before initiating therapy. Secondary endpoints consisted of overall testing rates and test outcomes. Group comparisons were presented as proportions with 95%CI and odds ratios (OR).

Results: Median patient age in the intervention and control group was 72 vs. 68 years, 53.4% vs. 48.4% were female, and 78.2% vs. 92.4% had stage IV disease. EGFR testing rates are presented in the table below. Overall testing rates were comparable between groups (OR = 1.33, p = 0.35). However, effective EGFR testing rates significantly increased over the 12-month intervention period relative to the control period (OR = 1.74, p = 0.014).

Conclusions: The implementation of a DSP significantly improved effective EGFR testing rates across participating community oncology practice sites in the US.

Keywords: Non Small Cell Lung Cancer, EGFR, Biomarker testing

Outcome (95%CI)	Control Group (n=201)	Intervention Group (n=174)
Overall testing rate	84.6% (95%CI: 78.8 to 89.3%)	87.9% (95%CI: 82.1 to 92.4%)
Effective testing rate	62.2% (95%CI: 55.0 to 68.9%)	74.1% (95%CI: 67.0 to 80.5%)

P4.17F GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS - HEALTH SYSTEM
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P4.17F.02 Sociodemographic and Clinical Predictors of Diagnosis of Lung Cancer in the Emergency Department in a Large, Integrated Health System

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Introduction: Between 20-30% of patients with lung cancer (LC) are diagnosed in the emergency department (ED). While ED presentations of LC are sometimes necessary to address life-threatening symptoms or facilitate rapid diagnostic workup, they are time and resource-intensive and often reflect missed opportunities for earlier diagnosis. Patients diagnosed with LC in the ED have been shown to have adverse clinical outcomes, including higher mortality rates. Prior studies have demonstrated that patients of lower socioeconomic status and who belong to racial/ethnic minoritized groups, as well as patients with a higher number of comorbidities, are more likely to be diagnosed with LC in the ED. However, such studies are largely single center and conducted outside of the United States. In this study, we sought to identify sociodemographic and clinical predictors of an ED diagnosis of LC in a large, sociodemographically diverse integrated health system.

Methods: This retrospective cohort study included all adults diagnosed with any stage or histology of primary LC between 1/1/2018-12/31/2021 within Kaiser Permanente Northern California (KPNC), encompassing twenty-one medical centers. Analyses were restricted to patients who had continuous health plan enrollment with KPNC for one year both before and after diagnosis. Sociodemographic and clinical variables were abstracted from institutional databases. An ED diagnosis of LC was defined as an ED visit within 30 days before LC diagnosis. A Quasi-Poisson regression model was developed to identify predictors of an ED diagnosis of LC.

Results: Of the 5443 patients with LC, 2007 (37%) were diagnosed in the ED (Table 1). In the Quasi-Poisson regression model, Black patients were more likely to be diagnosed in the ED compared with Non-Hispanic white patients (RR 1.22, 95% CI:1.07-1.38). In addition, patients with a higher comorbidity burden (RR 1.22, 95% CI: 1.07-1.38), prior or current smoking status (RR 1.11, 95% CI: 1.01-1.22), and Stage IV disease (RR 2.68, 95% CI: 2.4-3.0) were more likely to be diagnosed in the ED. There were no differences in likelihood of ED diagnosis by age, gender, or neighborhood deprivation index.

Conclusions: Even in an integrated health system with universal access to primary care, there remain disparities in rates of diagnosis of LC in the ED. Patients diagnosed with LC in the ED also have a higher rate of medical comorbidities and present with higher stage disease. Future studies should characterize potential diagnostic delays in this patient population to identify opportunities for earlier diagnosis and intervention in the outpatient setting.

Table 1: Demographic and clinical predictors of an ED diagnosis for patients with LC

	Diagnosed in ED (n=2007, 36.9%)	Not diagnosed in ED (n=3436, 63.1%)	Adjusted Relative Risk[2] (95% CI)
Age at diagnosis Mean (SD)	72.5 (11.2)	71.4 (10.2)	1.00 (1.00-1.01)
Sex N (%)			
Male	929 (46)	1486 (43)	Ref
Female	1077 (54)	1949 (57)	1.02 (0.95-1.10)
Other	1 (<0.1)	1 (<0.1)	NR
Race/ethnicity N (%)			
Non-Hispanic White	1276 (64)	2216 (64)	Ref
Black or African American	193 (9.6)	238 (6.9)	1.22 (1.07-1.38)
Asian	295 (15)	651 (19)	0.88 (0.78-0.98)
Hispanic or Latino	216 (11)	305 (8.9)	1.08 (0.95-1.21)
Other[1]	27 (1.3)	26 (0.8)	1.33 (0.95-1.80)
Neighborhood Deprivation Index N (%)			
1st Quartile (Least Deprived)	384 (19)	763 (22)	Ref
2nd Quartile	587 (29)	1093 (32)	1.01 (0.91-1.12)
3rd Quartile	550 (27)	936 (27)	1.03 (0.93-1.15)
4th Quartile (Most Deprived)	485 (24)	644 (19)	1.12 (1.00-1.26)
Insurance type N (%)			
Commercial	453 (23)	825 (24)	Ref
Medicare	1375 (69)	2470 (72)	0.94 (0.84-1.05)
Medicaid	33 (1.6)	48 (1.4)	1.18 (0.87-1.56)
Dual-eligible	38 (1.9)	67 (1.9)	1.01 (0.76-1.33)
Other	108 (5.4)	26 (0.8)	1.50 (1.23-1.81)
Charlson Comorbidity Index N (%)			
0 (None)	435 (22)	856 (25)	Ref
1-2 (Mild)	571 (28)	1382 (40)	0.93 (0.84-1.04)
3-4 (Moderate)	390 (19)	688 (20)	1.16 (1.02-1.31)
5+ (Severe)	611 (30)	510 (15)	1.59 (1.42-1.78)
Stage N (%)			
I	234 (12)	1073 (32)	Ref
II	94 (5.0)	296 (8.9)	1.35 (1.12-1.63)
III	254 (13)	630 (19)	1.56 (1.35-1.80)
IV	1311 (69)	1329 (40)	2.68 (2.40-3.00)
Smoking Status N (%)			
Never	423 (21)	950 (28)	Ref
Current/Former	1582 (79)	2481 (72)	1.11 (1.01-1.22)

1 Includes American Indian/Alaskan Native (n=19), Native Hawaiian/Other Pacific Islander (n=32), and Decline to State (N=2)
2 Adjusted relative risk and associated confidence intervals from the quasi-poisson regression output

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P4.17F.03 Utilizing AI for Automated Data Entry and Analysis to Pre-Screen Lung Cancer Clinical Trial Candidates

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Introduction: In cancer research, patient selection for clinical trials mainly depends on physicians identifying eligible participants, a process prone to oversight. Automated, innovative approaches to expand patient screening at an institutional level could enhance trial accrual and shorten inclusion times. Here, we propose an artificial intelligence (AI) tool capable of assessing essential inclusion and exclusion criteria to identify trial candidates.

Methods: This retrospective study involved patients with thoracic cancer seen at Gustave Roussy between February 2021 and June 2023. Utilizing unstructured patient notes, we automated the entry and structuring of 83 variables covering demographic details, disease features (e.g., histology, PD-L1 expression, molecular and metastatic status, central nervous system metastases), comorbidities, systemic treatment history, and life status. Automated data entry (ADE) was performed by large language model actions with prompt engineering and tailored few-shot examples. A cohort of patients with manual data entry (MDE) was used for comparison with ADE. ADE's correctness was measured by data concordance with MDE, including mismatches where ADE was accurate, and considering missing data. ADE's completeness was gauged by the data filled post missing value abstraction. Primary objectives were assessing ADE's correctness and completeness. Secondary objectives included evaluating the correctness of simultaneously entered multiple variables, verified by randomly selecting 20 sets of 3 and 5 variables, respectively, always including life status.

Results: Data from 1,057 patients were processed through ADE, with a subset of 137 patients also undergoing MDE. Within this dual-entry cohort (N=137), ADE achieved an overall correctness of 96% [range: 71.9-100% per variable]. ADE performed best (95-100% correctness) in identifying demographic information, life status, histology, number of prior lines, and classes and types of systemic treatments received. Variable-specific details are presented in the Table. For the entire group of 1,057 patients, ADE automatically filled 144,499 data points, with a median completeness of 96.7% per patient [range: 59.6%-100%] and 3 minutes per patient. Correctness of ADE for randomly selected combinations of 3 and 5 variables was 81.9% [IQR: 77.7-85.4] and 81.3% [IQR: 75-85.7], respectively, leading to an overall combined correctness of 81.6%.

Conclusions: This study highlights the effectiveness of ADE in identifying selected eligibility and non-eligibility criteria for lung cancer clinical trials with over 90% accuracy. It estimates an 80% probability of simultaneously correctly structuring multiple criteria for a patient. ADE may offer scalable solutions for patient matching to trials, a task unfeasible for manual search in the absence of structured data.

Keywords: artificial intelligence, large language model, automated data entry

Correctness range (%)	Variables
95-100%	sex, birthdate, life status, history of cardiac disease, autoimmune disease, HIV, hepatitis B and C, histology, treatment class (immunotherapy, targeted therapy, antiangiogenic, antibody-drug conjugates), number of lines, drugs received
90-95%	Metastatic from diagnosis, metastatic anytime, alterations in *EGFR, BRAF, ROS1, RET, MET, HER2, PIK3CA, SMARCA4, KEAP1, NRG1, NTRK*, treatment class -chemotherapy
85-90%	Thromboembolic events, *TP53* mutations, PD-L1 expression, leptomeningeal metastases
80-85%	Subtype of *KRAS* mutations
70-80%	Subtype of *EGFR* mutations, brain metastases

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P4.17F.04 Feasibility of Comprehensive Genomic Profiling for Advanced NSCLC in Public Healthcare System - The Hong Kong Experience

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Introduction: Lung cancer is the most common cancer worldwide. In recent 10 years, there were more than 35 additions to FDA-approved targeted therapies, targeting over 10 oncogenic drivers. Co-mutations predicting response towards targeted therapies and immune-checkpoint inhibitors are also increasingly recognized. In Hong Kong where universal healthcare is provided to citizens, over 90% of lung cancer patients receive testing and treatment in public healthcare. The current lung cancer testing algorithm in Hong Kong public healthcare included sequencing of individual or a small panel of actionable target genes. Upfront comprehensive cancer genomic profiling (CGP) will enable complete understanding of currently actionable and emerging biomarkers in a single testing, but the real-world diagnostic yield, logistics feasibility and clinician acceptance in integrating CGP in routine testing pathway in a public healthcare setting is not well reported.

Methods: The University of Hong Kong-Hospital Authority (HKU-HA) lung cancer CGP project is a territory-wide project which aims to provides CGP testing to all advanced NSCLC cancer patients in Hong Kong since 2021. All 6 public cancer centers in Hong Kong participated. FoundationOne CDx and Liquid CDx were used as the CGP platform. Survey was conducted among thoracic oncologists in all participating cancer centers. The feasibility of routine CGP in advanced lung cancer is assessed and reported in terms of diagnostic yield (success rate and identification rate of druggable mutation), logistic feasibility (report turnaround time and estimates on time spent on explanation) and clinician acceptance.

Results: As of January 2024, 874 patients have been enrolled to the territory-wide CGP project. For diagnostic yield, the success rate for tissue CGP is 63.9%, and 91.2% for liquid CGP. The identification rate of druggable mutation has doubled with the use of CGP in our cohort, amounting to 32.6% in standard assay and 65.3% in CGP. In addition, 72.5% of patients were noted to have other important cancer-associated mutations which could be of predictive and prognostic value. For logistical practicalities, the turnaround time for CGP is 2-3 weeks, which is comparable to current in-house gene-based and small panel testing. The median estimated time taken for informed consent is 5 minutes (IQR 5-10), and the median for the estimated additional time taken to explain the details of CGP to patients was 5 minutes (IQR 5-10). For clinician acceptance, all 22 participating thoracic oncologists are willing to adapt the new CGP approach. 85.7% of clinicians opined that the additional information could improve identification of therapy compared to standard assay, 95.2% expressed CGP could help in prediction of treatment effect and 81% think that CGP helps with prognostication.

Conclusions: The introduction of routine CGP testing in workflow of management of advanced NSCLC into public healthcare setting yields improvement in detection rate of actionable mutations at comparable turnaround time and a high success rate. While a median of additional 10 minutes is required for the additional explanation, thoracic oncologists are willing to adapt routine CGP in management of advanced NSCLC and most find the additional information provided helpful to patient management.

Keywords: Comprehensive Genomic Profiling (CGP), University of Hong Kong-Hospital Authority(HKU-HA), Advanced lung cancer patients

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P4.17F.05 Adherence to Clinical Practice Guideline - Analysis of 89 Multidisciplinary Team Discussed Patients with Stage III Lung Cancer

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Introduction: The management of stage III lung cancer patients is complex, involving careful consideration of tumor severity, patient health status, and treatment feasibility. Multidisciplinary teams (MDTs) are pivotal in ensuring tailored treatment decisions that optimize patient survival and quality of life while avoiding over or undertreatment. Guidelines from organizations like ASCO, NCCN, ESMO, and CSCO provide evidence-based recommendations, yet research on patient guideline adherence post-MDT is limited. This study aims to assess stage III lung cancer patient adherence to CSCO guidelines post-MDT and its impact on treatment outcomes, quality of life, and satisfaction.

Methods: We organized over 20 cross-institutional MDT meetings nationwide for lung cancer, involving 89 stage III patients. Data collected included patient medical histories, pre-MDT diagnostic and treatment decisions, MDT recommendations and treatment outcomes. Statistical analysis compared changes in patient plans before and after MDT discussions and assessed MDT's impact on guideline adherence for stage III lung cancer patients.

Results: In terms of staging, approximately half of the cases (49.4%) underwent staging adjustments post-MDT discussions, indicating a prevalent issue of incomplete testing before MDT. Moreover, a considerable proportion (30.3%) of initially deemed unresectable cases were reevaluated as potentially resectable after MDT deliberations. In terms of treatment recommendations, three main categories of alterations were observed post-MDT discussions: 1) shifts in the overall treatment trajectory from Plan A to Plan B, 2) supplementation of treatment strategies from Plan A to Plan A+B, and 3) elimination of redundant interventions from Plan A+B to Plan A. Importantly, patients demonstrated a high satisfaction 98% (87/89) with treatment plans endorsed during MDT discussions, 79.8% (71/89) experienced the improvement of quality of life, and 80.9% (82/89) followed up with tumor examinations, including 64.6% (53/82) using RECIST 1.1 and the remaining 35.4% (29/82) using the physician-reported response method. The majority of MDT discussed cases (n=80, 89.9%) are adherent to 2023 CSCO guideline, with a median follow-up of 8.4 months, during which 66 individuals remained progression-free.

Conclusions: This study underscores the significant impact of MDT discussions on stage III lung cancer. Integrating MDT meetings is crucial for standardizing and customizing the management of stage III lung cancer, leading to advancements in patient prognosis and quality of life. Future research will concentrate on evaluating long-term outcomes, such as five-year survival rates and long-term progression-free survival.

Keywords: Stage III Lung Cancer, Guideline adherence, Multidisciplinary Team

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P4.17F.06 Review of State Legislation Mandating Biomarker Coverage in Cancer Care

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Introduction: Biomarkers, measurable biological molecules serving as indicators of various processes, conditions, or diseases, including cancer, have revolutionized precision therapy. Particularly in non-small cell lung cancer (NSCLC), precision therapy guided by biomarker testing has demonstrated significant improvements in overall survival compared to conventional treatments. The FDA approval of targeted therapies against biomarkers such as EGFR, ROS1, BRAF, ALK, RET, and PD-L1 has reshaped the landscape of NSCLC treatment. However, despite these advancements, disparities in access to biomarker testing persist, impacting patient outcomes. Our study aims to assess disparities in biomarker testing coverage for NSCLC and explore mechanisms to overcome these disparities.

Methods: We conducted a comprehensive analysis of existing legislation by locating and downloading official legislative documents from respective state government websites. These documents included bills, statutes, regulations, and other policy documents relevant to biomarker testing coverage for NSCLC. We systematically reviewed each document to extract pertinent information into a table regarding biomarker testing legislation, coverage requirements, populations covered, prior authorization, costs, and any other relevant details. This method ensured the inclusion of official and up-to-date legislative information in our analysis.

Results: Our analysis revealed significant disparities in biomarker testing coverage across states (Table 1). As of March 2024, only 13 states - Arkansas (AR), Arizona (AZ), California (CA), Georgia (GA), Illinois (IL), Kentucky (KY), Louisiana (LA), Maryland (MD), Minnesota (MN), New Mexico (NM), New York (NY), Oklahoma (OK), Rhode Island (RI), and Texas (TX) - have enacted legislation mandating coverage. However, many states still lack comprehensive measures, leaving gaps in accessibility. It's worth noting that assessing coverage solely based on legislation may not accurately reflect disparities, as affordability remains a critical issue. Without mandating affordable co-pays, insurance companies retain discretion over cost-sharing, potentially exacerbating disparities. Fifteen additional states, including Colorado (CO), Connecticut (CT), Hawaii (HI), Iowa (IA), Indiana (IN), Florida (FL), Massachusetts (MA), Maine (ME), New Jersey (NJ), Nevada (NV), Ohio (OH), Pennsylvania (PA), Washington (WA), West Virginia (WV), and Vermont (VT), are expected to introduce legislation regarding biomarker testing in 2024.

Conclusions: Our findings underscore the urgent need to address disparities in biomarker testing coverage for NSCLC. While legislative efforts are crucial, ensuring affordability is paramount in reducing disparities. Mandating affordable co-pays alongside coverage requirements may help mitigate disparities and improve access to biomarker testing, ultimately enhancing outcomes for NSCLC patients. These conclusions are supported by data highlighting disparities in coverage and the potential impact of affordability measures.

Keywords: Biomarker, Legislation, NSCLC

State	Bill(s)	Enactment Date	Coverage Requirement	Populations Covered	Prior Authorization	Costs Provisions
AR	HB 1121	Apr 4, 2023	Cancer biomarker testing	Cancer patients	Timely determinations required	Standard deductibles, copays
AZ	HB 2144	Jan 1, 2023	Biomarker testing with clinical utility	Individuals under health plans	Timely response for authorizations	Plan-consistent deductibles, copays
CA	SB 496	Apr 25, 2023	Medically necessary testing	Broad coverage for medically necessary testing	Streamlined access	N/A
GA	HB 85	Jul 1, 2023	Biomarker testing supported by evidence	Enrollees needing testing	Fixed response times for authorization	Minimize care disruptions
IL	HB 1779	Jan 1, 2024	Necessary biomarker testing	Patients needing testing	Prior authorization with efficient conduct	Minimize patient care disruptions
KY	HB 180	Jan 1, 2024	Prescribed biomarker testing	Insured individuals	Streamlined access	Standard plan terms
LA	SB 104	Aug 1, 2023	Testing for personalized care	Individuals needing care	Care disruption minimization	Standard plan terms
MD	SB 805	Jan 1, 2024	Testing supported by evidence	Broad coverage for testing for medical conditions	Allows prior authorization	Not exceeding similar coverages
MN	HF1978	Jan 1, 2025	Testing providing clinical utility	Broad coverage for testing as a part of medical care	Utilization controls allowed	Usual deductibles, coinsurance


EPOSTERS

EP.01A RISK FACTORS, RISK REDUCTION & TOBACCO CONTROL - DISEASE PROFI
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EP.01A.01 Role of Diet and Exercise in Young Lung Cancer Patients with Driver Mutations (NCT04640259)

A. Wu[1], M. Bittoni[2], A.M. Harper[3], N. Florez[4], C.A. Granville[5], R. Erwin[3], B.J. Addario[6], D.P. Carbone[7], B.J. Gitlitz[8], J. Nieva[1], [1]University of Southern California, Los Angeles/CA/USA ,[2]Ohio State University James Cancer Center, Columbus/OH/USA ,[3]Addario Lung Cancer Medical Institute (ALCMI), San Carlos/CA/USA ,[4]Dana-Farber Cancer Institute – Harvard Medical School, Boston/MA/USA ,[5]GO[2] for Lung Cancer, Washington/DC/USA ,[6]GO[2] for Lung Cancer, San Carlos/CA/USA ,[7]Ohio State University, Columbus/OH/USA ,[8]Roche/Genentech, San Francisco/CA/USA

Introduction: The Epidemiology of Young Lung Cancer Study (EoYLC) is an innovative, virtual case-case study that explores environmental, lifestyle and genetic factors in young persons with lung cancer (LC), and the largest epidemiology study in young lung cancer (YLC) patients to date. Previous EoYLC results showed that relative to ALK rearranged LC, EGFR patients were more likely to be female and older, had increased smoking exposure, lower body mass index (BMI), increased oral contraceptive and antihistamine use, and fewer allergies during adolescence. However, information on dietary and exercise patterns in YLC patients by driver mutations has been largely lacking, and is the focus of this report.

Methods: We are actively recruiting individuals with YLC (<age 50) from our established LC registry and social LC networks using a virtual study strategy. Eligibility criteria include age > 18, primary non-small cell LC (any stage), documented testing of target mutations, plasma collection, and willing to complete a comprehensive 10-module risk factor survey. We analyzed the EGFR and ALK groups regarding usual pre-diagnostic diet and exercise using validated instruments, including the International Physical Activity Questionnaire (IPAQ), which measured frequency, intensity, and amount of activity per week, as well as a Food Frequency Questionnaire (FFQ- nutritionquest.com), from which the Healthy Eating Index (HEI-2015- a validated measure of diet quality) was calculated. Descriptive statistics were calculated and associations between lifestyle factors and driver mutations were assessed using t-tests and chi-squares.

Results: Preliminary results from the first 141 individuals who completed risk factor surveys and donated blood specimens showed that 85% were females, with a mean age of 38, and had adenocarcinoma (95%), Stage 4 (80%), and mostly ALK (42%) or EGFR driver mutations (38%). The IPAQ results classified 69% of participants as engaging in high intensity, 19% in moderate intensity and 12% in low intensity activity. Those with EGFR mutations had significantly higher combined high/moderate activity compared to ALK (p=0.031). EGFR patients also had higher vigorous MET min/week and total MET min/week compared to ALK patients (p=0.007 and p=0.036, respectively). A significantly lower mean BMI was observed for EGFR vs ALK patients (23.9, and 27.3, respectively, p=0.07). The mean HEI-2015 score was 66.7 (range 43.6-91.0) compared to the US average of 58; 4% of participants were in the “good” category (score >80), 69% in the “needs improvement” category (score 51-80), and 26% in the “inadequate” category (score <51). No statistically significant associations were found between genetic mutations and HEI-2015 score.

Conclusions: Younger ALK and EGFR patients (<age 50) had similar HEI-2015 diet quality scores which were better than the US average. However, BMI and physical activity levels appeared to differ significantly between EGFR vs ALK driven lung cancers, with higher physical activity and lower BMI among those with EGFR mutations. Further research on these factors among younger lung cancer populations is ongoing and updated analyses will be presented upon completion of enrollment.

Keywords: Epidemiology, Biomarker, Risk Factors

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EP.01A.02 Risk Factors and Nomogram Construction of Early Death in Patients with Stage IV Lung Squamous Cell Carcinoma: A SEER-Based Study

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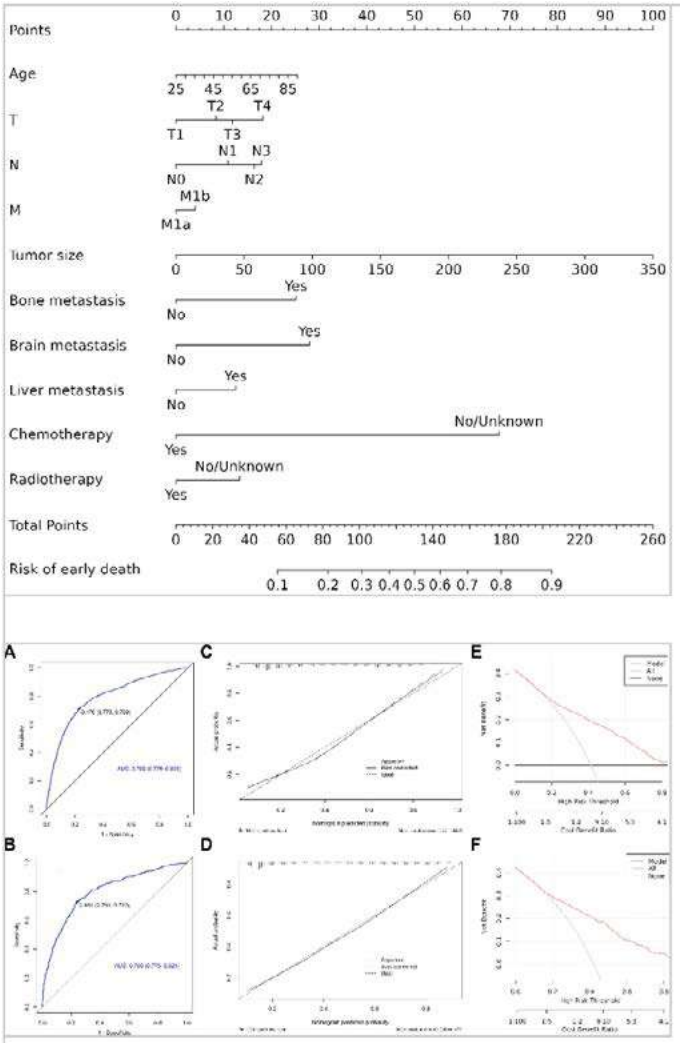
Introduction: Stage IV lung squamous cell carcinoma (LUSC) has a poor prognosis and takes the risk of early death. However, risk factors of early death remain to be explored for optimizing decision-making.

Methods: Data on stage IV LUSC patients diagnosed between 2010 and 2015 was extracted from the Surveillance, Epidemiology, and End Result (SEER) database. The least absolute shrinkage and selection operator (LASSO) logistic regression and multivariate analysis were used to select the independent risk factors and build a predictive nomogram. The receiver operating characteristic (ROC) curve, calibration curve, and decision curve analysis (DCA) were performed to assess the performance of the nomogram.

Results: 4,908 stage IV LUSC patients were enrolled and divided into the training (3,436) and validation cohort (1,472). 41.6% had early death and were predominantly attributed to cancer-specific-early death (92.7%). The early death rate exhibited a substantial increase in correlation with advancing age. Independent risk factors for constructing a nomogram included age, T stage, N stage, M stage, tumor size, bone metastasis, brain metastasis, liver metastasis, chemotherapy, and radiotherapy. The AUC was 0.793 (95%CI: 0.778-0.809) and 0.798 (95%CI: 0.775-0.821) in the training and validation cohorts respectively. Calibration and DCA curves both demonstrate the reliability of this model.

Conclusions: We identified the incidence, causes, and risk factors of early death. A comprehensive nomogram was established to predict early death in stage IV LUSC patients. The nomogram revealed excellent discrimination and clinical usability to predict the probability of early death accurately

Keywords: Lung squamous cell carcinoma (LUSC), Stage IV, Early death



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EP.01A.03 Disparities Inepidemiological Characteristics, Clinical Profiles,and Survival Forever-Smokers and Never-Smokers with Lung Cancer in China

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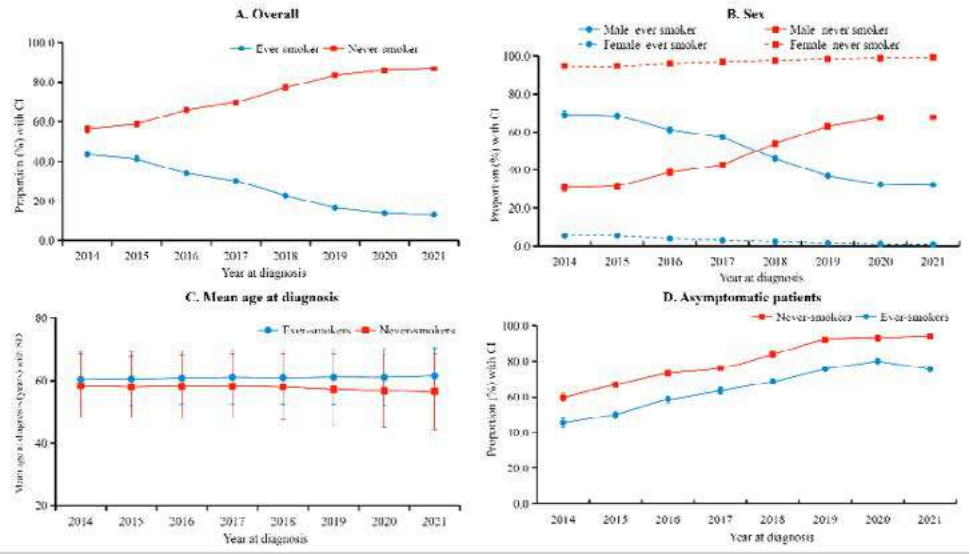
Introduction: Lung cancer in never-smokers poses a health burden worldwide, particularly in East Asian countries like China. It is crucial to identify epidemiological and clinical characteristics of lung cancer patients between ever-smokers and never-smokers. However, there have been limited related data to date in China.

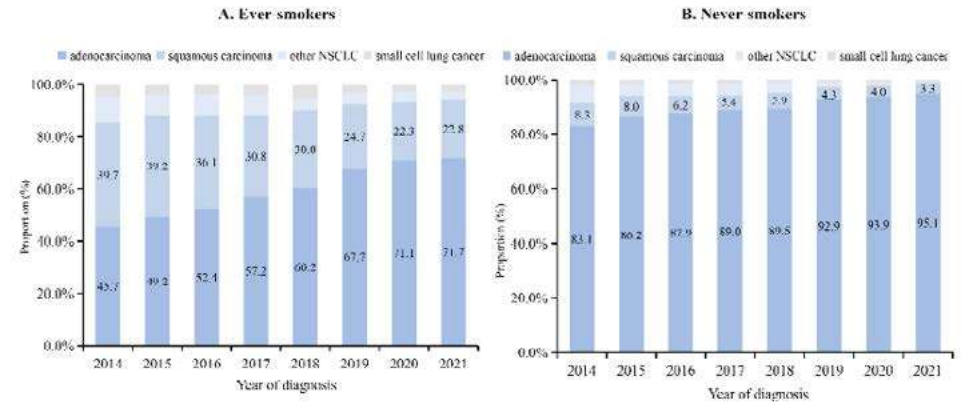
Methods: This study included lung cancer patients who underwent surgical procedures from January 2014 to December 2021 at 26 hospitals in China. The hazard ratio (HR) with 95% confidence interval (CI) for survival was estimated using the Kaplan-Meier method and multivariable Cox proportional hazard model. This is a part of the nationwide real-world study (NCT06255197).

Results: A total of 24,164 ever-smoking and 100,815 never-smoking lung cancer patients undergoing surgery were included in this study. From 2014 to 2021, the proportion of non-smoking patients increased from 56.5% to 86.8%; a consistent upward trend was observed in the proportion of never-smokers among male patients, from 30.8% in 2014 to 67.8% in 2021. Adenocarcinoma remained the most common histologic subtype, with its proportion increasing from 45.7% to 71.7% for ever-smokers and 83.1% to 95.1% for never-smokers, respectively. Patients who had ever smoked had a significantly higher risk of mortality compared to those who had never smoked (adjusted HR: 1.24 [95% CI: 1.15, 1.34]). Further subset analyses revealed that the increased risk of mortality was observed among ever-smokers patients with adenocarcinoma (adjusted HR: 1.37 [1.24, 1.52]), at stages I (adjusted HR: 1.45 [1.29, 1.64]) and III (adjusted HR: 1.26 [1.11, 1.42]). Female gender was found to be a significant prognostic factor only for non-smoking patients, with an adjusted HR of 0.66 (0.60, 0.72).

Conclusions: The disparities in lung cancer between ever-smokers and never-smokers in China provide further evidence that these two groups are distinct entities. It is crucial to conduct future research focusing on biological explanations and population-based studies.

Keywords: Never-smokers, Clinical epidemiology, Trend analysis





EP.01A RISK FACTORS, RISK REDUCTION & TOBACCO CONTROL - DISEASE PROFILE
SATURDAY, SEPTEMBER 7, 2024 - 11:58 - 11:59

EP.01A.04 Predictive Value of a Prognostic Model Based on Clinicopathologic Features in Lung Adenocarcinoma

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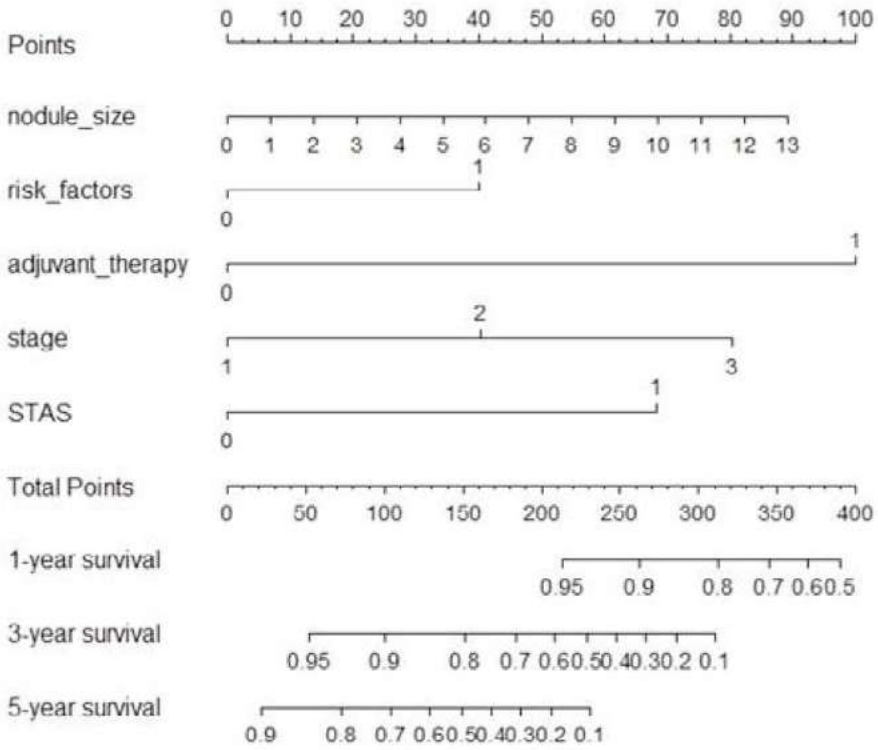
Introduction: The presence of tumor spread through air spaces (STAS) was reported to be associated with worse prognosis in early-stage lung adenocarcinoma. However, STAS was also associated with other clinicopathologic features affecting prognosis. This study aims to explore the independent prognostic value of STAS and develop a prognostic model for survival prediction in lung invasive adenocarcinoma.

Methods: The medical records of 2144 stage I to IIIA patients with resectable lung adenocarcinoma who received surgical treatment at our institution from 2015 to 2019 were retrospectively reviewed. Clinicopathological variables that were statistically significant in multivariate Cox regression were included in the nomogram to create a recurrence predictive model.

Results: STAS was observed in 931 patients (43.4%). Univariate and multivariate Cox regression analyses revealed that STAS, adjuvant therapy, stage and risk factors including poorly differentiated tumors, lymphovascular invasion and visceral pleural invasion were independent risk factors for lung invasive adenocarcinoma. A prognostic model based on above features was developed to predict the 1-year, 3-year and 5-year recurrence-free survival. The concordance index (C-index) of the prognostic model was 0.858 in the internal validation cohort.

Conclusions: The presence of STAS, adjuvant therapy, stage and risk factors including poorly differentiated tumors, lymphovascular invasion and visceral pleural invasion were significant prognostic factors for poorer RFS. The prognostic model we developed could effectively predict the recurrence-free survival.

Keywords: Tumor spread through air spaces, Prognostic model, Lung adenocarcinoma



Univariate and multivariate analyses of prognostic factors of recurrence-free survival.

Variable	Univariate analyses		Multivariate analyses	
	HR (95% CI)	P	HR (95% CI)	P
Age	1.005(0.990-1.020)	0.552		
Sex (male vs. female)	1.741(1.309-2.316)	<0.001	1.112(0.829-1.493)	0.477
STAS (presence vs. absence)	13.658(9.274-20.113)	<0.001	2.095(1.097-4.002)	0.025
Tumor size	1.499(1.423-1.580)	<0.001	1.077(0.998-1.162)	0.056
Histopathological type				
Lepidic	Reference	<0.001	Reference	0.197
Acinar	3.607(1.566-8.306)	0.003	1.400(0.576-3.403)	0.458
Papillary	3.445(1.459-8.131)	0.005	1.123(0.451-2.800)	0.803
Micropapillary	11.349(4.590-28.060)	<0.001	1.190(0.444-3.188)	0.729
Solid	15.102(6.373-35.792)	<0.001	1.857(0.722-4.777)	0.199
Risk factors (high risk vs. low risk)	12.625(8.927-17.854)	<0.001	2.471(1.473-4.146)	0.001
Surgery (lobectomy vs. sublobar resection)	3.071(1.839-5.127)	<0.001	1.519(0.888-2.596)	0.127
Adjuvant therapy (with vs. without)	18.641(13.025-26.677)	<0.001	3.659(2.110-6.346)	<0.001
Pathologic stage				
I	Reference	<0.001	Reference	0.001
II	12.360(7.993-19.111)	<0.001	1.662(0.995-2.775)	0.052
IIIA	22.338(15.719-31.745)	<0.001	2.428(1.541-3.825)	<0.001

EP.01A RISK FACTORS, RISK REDUCTION & TOBACCO CONTROL - DISEASE PROFILE
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EP.01A.05 Analysis of Diagnostic Delay and Its Impact on Survival in Lung Cancer Cases. Results from the Spanish Thoracic Tumor Registry

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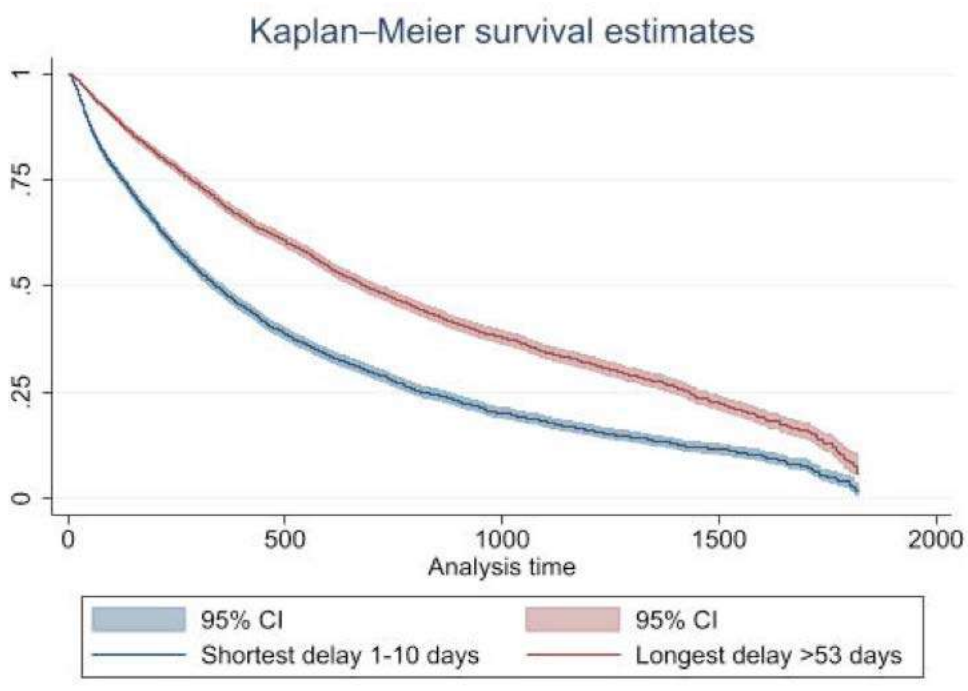
Introduction: Lung cancer is the leading cause of cancer mortality worldwide, and early detection is crucial to improve survival rates. Delays in diagnosis can occur due to various factors and these delays might negatively impact the prognosis of the disease. This study aims to analyze the diagnostic delay in lung cancer patients, examine the characteristics of cases associated with long delay and describe potential associations between delay and survival.

Methods: The data source used was the Thoracic Tumour Registry of the Spanish Lung Cancer Group, a monographic lung cancer registry representative of cancers diagnosed in Spain by age and sex. This analysis was restricted to lung cancer cases with information on the first date of consultation by symptoms or when the patient attended the emergency room as a consequence of an undiagnosed lung cancer and date of diagnosis. The delay was calculated as the number of days between the two dates and categorized as follows: the shortest delay 1-10 days, short delay 11-23 days, long delay 24-53 days and the longest delay >53 days. A descriptive analysis was performed, and ordinal logistic regressions were fitted with the dependent variable being delay. Kaplan-Meier survival analysis and Cox regression were performed.

Results: 22,755 cases were included. Most were men (73.68%), the median age at diagnosis was 66 years (interquartile range 59-73), and most were smokers (44.66%) and ex-smokers (44.70%). Multivariate analysis showed that never smokers were 1.14 (95%CI 1.04-1.25) times more likely to register longer delay than smokers. Stage 0-I-II cases had a 3.09 (95%CI 2.88-3.32) times higher risk of longer delay compared to III-IV stages. Overall, the 5-year survival rate after diagnosis was 23.64% (95%CI 22.88-24.41). In those categorized as having the shortest delay it was 17.67% (CI95% 16.31-19.07) and in the longest delay was 32.96% (CI95% 31.26-34.67) ($p<0.005$). The Cox regression showed a mortality risk higher in men (adjusted Hazard Ratio (HR) 1.20; 95%CI 1.14-1.25), in stage III and IV (HR 3.37; CI95% 3.17-3.59) and in ever-smokers (exsmokers HR 1.25, CI95% 1.16-1.34; smokers HR 1.51, CI95% 1.41-1.63). The mortality risk was higher in those with the shortest delay (HR 1.37, CI95% 1.30-1.45) in comparison with the longest delay.

Conclusions: Diagnostic delays are generally short among Spanish lung cancer patients, indicating a relatively quick diagnostic process. The longest delays appear to be associated with higher survival rates, possibly attributed to slow-growing tumors or early-stage at diagnosis.

Keywords: lung cancer, diagnostic delay, survival



EP.01A RISK FACTORS, RISK REDUCTION & TOBACCO CONTROL - DISEASE PROFILE
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EP.01A.06 Characteristics of Non-Small Cell Lung Cancer with High Serum CEA Levels

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Introduction: Serum carcinoembryonic antigen (CEA) level is a predictive factor for recurrence, and a high preoperative CEA level is a poor prognostic factor for non-small cell lung cancer (NSCLC). Because serum CEA can be easily examined using blood biochemistry, it is widely used in clinical practice for the preoperative and postoperative management of NSCLC in Japan. However, although serum CEA levels of smokers have been reported to be higher than those of nonsmokers, the characteristics of NSCLC with high serum CEA levels have not fully elucidated. Therefore, we aimed to evaluate the characteristics of patients with NSCLC and high serum CEA levels.

Methods: This retrospective study used a prospectively collected database from two institutions. We examined surgical cases of patients with NSCLC with high serum CEA levels. We determined the cutoff value as 10 ng/ml, which is twice the in-house CEA cutoff value. Between 2004 and 2023, 3482 patients underwent surgery for lung cancer. Among them, we evaluated the characteristics of 297 patients (8.5%) who underwent surgery for NSCLC and had a preoperative serum CEA level ≥10 ng/ml.

Results: The median age of the patients was 72 years (range:41-89), with 220 men (74.1%) and 77 women (25.9 %). The median serum CEA level was 18 ng/ml (range: 10.0-1584 ng/ml). The median smoking index was 780(0-2500), 236 were smokers (79.5%) and 61 (20.5%) were nonsmokers. Regarding history of other cancers, 68 patients (22.9 %) had a history of cancer of other organs, of which gastric cancer was the most common (19 cases), followed by colorectal cancer (15 cases), and prostate cancer (7 cases). Chronic obstructive pulmonary disease was the most common pulmonary comorbidity (109 patients, 36.7%), followed by interstitial lung disease (51 patients, 17.2%). Regarding clinical stage, 148(49.8%) had stage I, 55(18.5%) had stage II, and 149(31.7%) had stage III and IV. A total of 222 (74.7%) patients underwent lobectomy or pneumonectomy, 11(3.7%) underwent segmental resection, and 37 (12.4%) underwent partial resection. The pathological stage was stage I in 140 (47.1%) patients, stage II in 55(18.5%), and stage III and higher in 102 (34.3%) patients. Histologically, 201 cases (67.7%) were adenocarcinoma, 61 cases (20.5 %) were squamous cell carcinoma, and 7 cases (2.4 %) were adenosquamous carcinoma. During the postoperative follow-up, 109 patients (36.7 %) developed recurrence, 20 had locoregional lymph node recurrences, 20 had ipsilateral or contralateral lung recurrences, 19 had pleural dissemination, and 17 had brain metastasis. The overall 5-year survival rate after surgery was 25% in all patients.

Conclusions: Patients with NSCLC with a high serum CEA level tended to be advanced stage of NSCLC and proportion of COPD was approximately 40%. As the percentage of smokers was around 80%, smoking could affect the level of higher serum CEA.

Keywords: Non small cell lung carcinoma, carcinoembryonic antigen, smoking

EP.01B RISK FACTORS, RISK REDUCTION & TOBACCO CONTROL - DISPARITIES, INEQUITIES & GEOGRAPHIC DIFFERENCES
SATURDAY, SEPTEMBER 7, 2024 - 10:58 - 10:59

EP.01B.01 Geospatial Characterization of DNA Damage Repair (DDR) Mutations in Lung Cancer Patients in an Underserved Urban Population

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Introduction: DNA-damage repair (DDR) mutations in lung cancer have shown potential for use as therapeutic targets and predictive biomarkers. However, the relationship between DDR mutations and socioeconomic factors remains largely unknown. In this study, we characterize the geospatial distribution of DDR mutations in lung cancer patients at a single academic medical center serving a population of primarily underserved, underinsured patients.

Methods: All lung cancer patients seen at the University of Illinois Chicago (UIC) between 11/2/2015 and 9/11/2023 with TEMPUS genetic data available were included in the study (N = 235). DDR mutations of interest were ARID1A, ATM, ATR, ATRX, BAP1, BRCA1, BRCA2, BRIP1, CHEK2, ERCC3, FANCA, FANCC, MLH3, MRE11, MSH6, MUTYH, NBN, PALB2, and RAD50. The home addresses of each patient were geocoded and DDR mutational status was visualized by zip code across Chicago. DDR mutational status was then correlated with various population-level social determinants of health (SDOH) and cancer risk factors that were compiled by the University of Illinois Cancer Center Data Integration Shared Resource.

Results: The overall frequency of DDR mutations in the population was 28.5% (n = 67). The most common DDR mutations were ARID1A (20.7%), CHEK2 (12.8%), ATM (9.9%), BRCA2 (9.9%), ATRX (7.9%), and MUTYH (7.9%). There was a significant effect in tumor mutational burden (TMB), t(55) = 2.97, p = 0.004, with a higher mean TMB in the DDR positive group (M = 14.4, SD = 11.1) compared to the DDR negative group (M = 9.4, SD = 5.1). The most common zip codes in the DDR positive group were 60629 (9.0%), 60616 (9.0%), and 60608 (9.0%) compared to 60616 (8.4%), 60609 (5.4%), and 60644 (4.8%) in the DDR negative group; all zip codes were located in the West and South sides of the city. Table 1 summarizes the comparison of selected population-level SDOH and cancer risk factors between the two groups.

Table 1. Comparison of selected population-level SDOH based on DDR mutational positivity

	DDR positive (mean) (n = 67)	DDR negative (mean) (n = 168)	p value
Area deprivation index[1]	52.0	54.8	0.27
Median household income (annual)	$56,691	$53,044	0.21
Poverty rate	19.9%	21.5%	0.16
Violent crime (crimes per 100k residents/yr)	1308	1471	0.16
Severe housing cost burden	20.5%	22.0%	0.08
Life expectancy (years)	76.3	75.7	0.21
Obesity (BMI ≥30)	36.3%	37.2%	0.33
Cigarette smoking rate	17.0%	17.7%	0.24
Binge drinking	16.0%	15.3%	0.08
Visited doctor for routine checkup	76.3%	77.3%	0.08
Federally Qualified Health Centers (number)	5.96	4.81	0.05
Lung cancer diagnosis rate (per 100k residents/yr)	70.6	75.4	0.10
Proximity to superfund (toxic waste) sites[2]	0.0712	0.0865	0.17
Proximity to hazardous waste management sites[2]	8.75	8.16	0.47
Proximity to water polluting sites[2]	109	106	0.94
Particulate matter (PM2.5) concentration ($\mu g/m^3$)	10.09	10.07	0.44

[1]Higher values represent more disadvantage.
[2]Higher values indicate closer proximity.

Conclusions: The frequency and distribution of DDR mutations in lung cancer at UIC appears similar to what has been previously reported in the literature. There is a higher tumor mutational burden in lung cancers with DDR mutations, which may suggest greater susceptibility to immunotherapy. There may be associations between the presence of DDR mutations and certain SDOH and cancer risk factors. Future work will involve analysis of correlations between the presence of DDR mutations and individual risk factors, stage at diagnosis, and median survival, as well as a broader array of population-level measures.

Keywords: DDR mutations, lung cancer, socioeconomic factors

EP.01B RISK FACTORS, RISK REDUCTION & TOBACCO CONTROL - DISPARITIES, INEQUITIES & GEOGRAPHIC DIFFERENCES
SATURDAY, SEPTEMBER 7, 2024 - 10:58 - 10:59

EP.01B.02 Association Betweensocial Isolation and Loneliness, and the Risk of Lung Cancer: A Prospective Cohort Study

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Introduction: Globally, lung cancer is the leading cause of cancer-related mortality. Social isolation and loneliness are growing concerns in the development of lung cancer, while the relationship between social isolation and loneliness, and the risk of lung cancer remains inconclusive.

Methods: The prospective cohort was conducted based on the data from UK Biobank. Social isolation was evaluated based on the number of household members, frequency of social activities, contact with others. Meanwhile, loneliness was assessed by the subjective feeling of loneliness and the willingness to confide in others. The association between social isolation, loneliness and incident lung cancer was estimated by Cox regression models.

Results: A total of 3,692 lung cancer cases were documented among 415,366 participants during a mean follow-up of 13.8 years. Compared with participants with the least social isolation, approximately 10% [Hazard Ratio[HR] 1.10, 95% Confidence Interval[CI] 1.03-1.18] and 21% [HR 1.21, 95%CI 1.10-1.34] increase in risk of lung cancer were identified among individuals with moderate isolated and most isolated, respectively. Meanwhile, we also found that loneliness was associated with 11% increased risk of lung cancer [HR 1.11, 95% CI 1.04-1.18]. In addition, the stratified analysis showed the aforementioned relationship was substantially modified by age, gender, genetic risk, smoking, drinking, and diet behaviors.

Conclusions: Social isolation and loneliness were identified to be associated with significant increased risk of developing lung cancer. The evidence highlights the significance of managing social isolation and loneliness for lung cancer prevention.

The association of social isolation and loneliness with risk of lung cancer

Keywords: Social Isolation, Loneliness, Lung Cancer

The association of social isolation and loneliness with risk of lung cancer

Separate effects	Cases/N	Model 1	Model 2	Model 3
Social isolation				
Least isolated	1,572/219,762	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
Moderate isolated	1,557/158,108	1.40 (1.31, 1.51)	1.24 (1.15, 1.33)	1.10 (1.03, 1.18)
Most isolated	563/37,496	2.14 (1.94, 2.35)	1.60 (1.45, 1.77)	1.21 (1.10, 1.34)
P_{trend}		<0.001	<0.001	<0.001
Loneliness				
No loneliness	2,209/280,665	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
Loneliness	1,483/134,701	1.40 (1.31, 1.50)	1.22 (1.15, 1.31)	1.11 (1.04, 1.18)

EP.01C RISK FACTORS, RISK REDUCTION & TOBACCO CONTROL - EPIDEMIOLOGY
SATURDAY, SEPTEMBER 7, 2024 - 11:58 - 11:59

EP.01C.01 Evolution of Lung Cancer Mortality Rates in Brazil (1996-2022).

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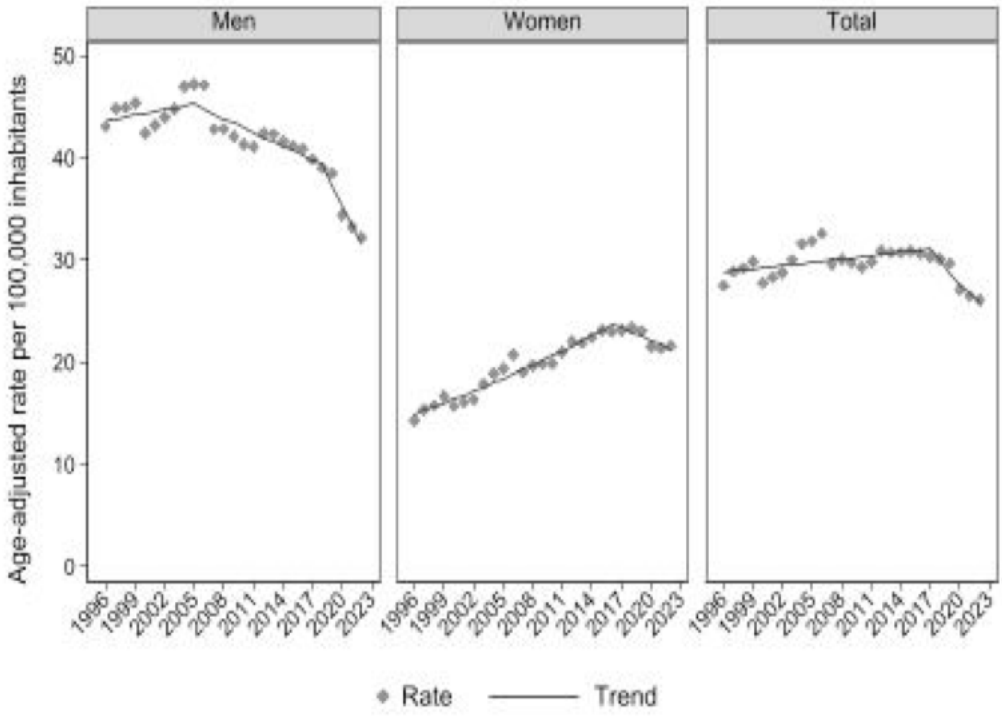
Introduction: Although Brazil is the leading country in South America in the implementation of tobacco control measures, lung cancer is the main cause of cancer-related deaths among men and the second cause among women in Brazil. The objective of this study was to analyze the evolution of lung cancer mortality rates in Brazil from 1996 to 2022.

Methods: Lung cancer mortality data for individuals aged ≥35 years were obtained from the Sistema de Información de Mortalidad del Sistema Único de Salud de Brasil (ICD-10 C33-C34). Crude and age-adjusted rates were calculated by applying the direct method. Trend analysis was conducted using joinpoint regression models. Annual percentage changes (APC) and 95% confidence intervals (95%CI) are presented.

Results: During the period 1996-2022, 570,594 persons aged ≥35 years died from lung cancer in Brazil. Of these deaths, 61.8% (352,577 deaths) occurred in men. The overall crude mortality rate increased by 15.1% during this period, from 24.4 deaths per 100,000 inhabitants in 1996 to 28.1 in 2022. The crude mortality rate for men decreased by 11.6% from 36.6 deaths (1996) to 32.3 (2022). For women the rate increased by 84.4%, from 13.2 (1996) to 24.3 deaths (2022). When analyzing the trend of the overall age-adjusted rates, two periods were identified. The first between 1996-2017 with an increasing trend (APC: 0.4 [95%CI 0.1 to 0.7]) and the second between 2017-2022 with a decreasing trend (APC: -3.7 [95%CI -7.6 to -1.9]). For men, the joinpoint identified three periods. The first period with a stable trend between 1996-2005 (APC: 0.4 [95% CI -0.3 to 3.8]) and the second and third periods with a decreasing trend (APC: 2005-2018 = -1.1 [95% CI -2.0 to -0.5]; APC: 2018-2022= -5.2 [95% CI -9.7 to -2.9]). For women, the analysis of age-adjusted rates showed an increasing trend between 1996 and 2016 (APC: 2.3 [95% CI 2.0 to 2.7]) followed by a decreasing trend between 2016 and 2022 with an APC: -1.7 [95% CI -5.0 to -0.03]) (Figure-1).

Conclusions: Crude lung cancer mortality rates have decreased in men since 2005, while in women they have remained stable since 2016. However, crude mortality rates in women have almost doubled since 1996. Analyzing the trend of age-adjusted rates in women has shown a decrease since 2016, which may explain that the stabilization observed with crude rates is due to the aging of the population. The evolution of lung cancer mortality in Brazil is favorable.

Keywords: mortality, lung cancer, Brazil



EP.01D RISK FACTORS, RISK REDUCTION & TOBACCO CONTROL - RISK FACTORS BEYOND SMOKING
SATURDAY, SEPTEMBER 7, 2024 - 11:58 - 11:59

EP.01D.01 Exploring the Association Between Connective Tissue Diseases and Lung Cancer: Analysis of the Mediating Role of Immune and Inflammatory Markers

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Introduction: Early researches indicate that patients with certain connective tissue diseases (CTDs) may have an increased risk of lung cancer, yet these studies often focus on specific diseases or populations, lacking a systematic analysis. This study examines the relationship between CTDs and lung cancer.

Methods: This study prospectively followed 457,959 participants from the United Kingdom Biobank cohort who were free of lung cancer at baseline. The risk of lung cancer in patients with CTDs was assessed using Cox proportional hazards models, adjusting for 14 covariates including age and gender. Mediation analysis was employed to investigate the connections between thirteen CTDs associated with lung cancer risk and ten key immune and inflammatory markers.

Results: The study included a total of 457,959 participants, with an average follow-up time of 9.21 (SD = 4.06) years. The median age was 57 years and 54.20% female. During the follow-up period, there were 157273 cases of CTDs and 4229 cases of lung cancer. Compared to individuals without CTDs, patients with CTDs had a lung cancer HR of 0.899 (0.842-0.959), p=0.001, which included thirteen CTDS related to lung cancer risk: seropositive rheumatoid arthritis[1.67(1-2.77),p=0.049], other rheumatoid arthritis[1.27 (1.02-1.57),p=0.033], gout[1.3(1-1.69),p=0.049], other acquired deformities of limbs[1.49(1.05-2.11),p=0.024], systemic sclerosis [3.41(1.62-7.16),p=0.001], scoliosis[1.53(1.02-2.31),p=0.041], spondylosis[1.19(1.01-1.41),p=0.038], other spondylopathies [1.26(1.01-1.57),p=0.037], other intervertebral disk disorders[1.37 (1.14-1.63),p=0.001], dorsalgia[1.2(1.05-1.37),p=0.007], fibroblastic disorders [1.37(1.09-1.72),p=0.007], other enthesopathies[1.3(1-1.69),p=0.049], other soft tissue disorders(not elsewhere classified)[1.47(1.29-1.68),p<0.001]. Mediation analysis revealed that among thirteen CTDs associated with lung cancer risk, the associations of specific diseases such as rheumatoid arthritis, gout, acquired deformities of fingers and toes, and systemic sclerosis with lung cancer were predominantly mediated through significant roles of lymphocyte count, monocyte count , neutrophil to lymphocyte ratio, and systemic immune inflammation index.

Conclusions: The findings of this study suggest that CTDs do not increase the risk of lung cancer. However, significant associations were observed between certain CTDs and an elevated risk of lung cancer, with some immune and inflammatory markers playing a key mediating role between CTDs and lung cancer risk. These findings offer new perspectives for the prevention and treatment strategies of both CTDs and lung cancer.

Keywords: Connective Tissue Diseases, lung cancer, Immune and Inflammatory Markers

EP.01D RISK FACTORS, RISK REDUCTION & TOBACCO CONTROL - RISK FACTORS BEYOND SMOKING
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EP.01D.02 Heterogeneous Germline Variants Detected in EGFR-Mutant Familial Lung Cancer Patients and Family Members

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Introduction: Management of familial lung cancer has gradually become a clinical unmet need in recent years. Lung cancer patients with family history have been reported to demonstrate clinical characteristics including a higher frequency of non-smoker, driver gene-positive. Some previous studies have investigated the prevalence and role of germline EGFR mutation in EGFR-mutant familial lung cancer patients. In addition to germline EGFR mutations, our study aims to comprehensively investigate the germline characteristics of EGFR-mutant familial lung cancer.

Methods: We first retrospectively enrolled EGFR-mutant lung cancer patients who had family history of cancer and underwent tissue next-generation sequencing (NGS) in Guangdong Provincial People's Hospital from November 2020 to 2023, to analyze the clinical characteristics of this subset of patients. Familial aggregated EGFR-mutant lung cancer families who provided consent for whole exome sequencing (WES) of peripheral blood for germline alteration analysis were prospectively enrolled to investigate the germline characteristics. Germline variants were further screened according to ACMG evidence level.

Results: In the retrospective cohort, a total of 110 EGFR-mutant lung cancer patients with family history of cancer were enrolled, with 70% female, median age of lung cancer diagnosis was 56 (25-84) and 84% were never-smoker, 65% presented with multiple lung nodules. For the type of cancer family history, top 4 included 62% of patients with a family history of lung cancer, 13% with liver cancer, 11% with colon cancer and 9% with breast cancer. Nine patients (8.2%) have a family history of ≥3 family members with cancer. Pathogenic(P) and Likely pathogenic (LP) germline variants mutations were detected in 5 patients (2 suspected LP due to no match peripheral blood test) by NGS, involving alterations in DNA repair genes FANCI,FANCA,PALB2 and RAD54L. In our prospective cohort, a total of 25 individuals (10 lung cancer, 1 liver cancer, 13 healthy individuals) from 4 familial aggregated EGFR-mutant lung cancer families underwent WES of peripheral blood nucleated cells. These families have 4 to 9 first-degree family members with cancer diagnosis. Likely pathogenic (LP) variants detected involving multiple DNA repair genes such as RECQL, ATR, and ZRANB1, metabolic pathway genes such as PMVK and CD36 were also identified. In addition, novel germline nonsynonymous mutation (ACMG: VUS) in EGFR exon14, EGFR exon 1 were also detected in two separate families respectively.

Conclusions: Heterogenous germline P/LP variants mostly involving DNA repair genes and metabolic pathway, as well as germline EGFR mutation of unknown significance were detected in familial aggregated EGFR-mutant lung cancer. Our finding indicates that the hereditary trace might differ between individuals in this rare population with high risk of lung cancer and a potential "multiple hit" genetic predisposition.

Keywords: Family history, EGFR-mutant lung cancer, germline characteristics

EP.01D RISK FACTORS, RISK REDUCTION & TOBACCO CONTROL - RISK FACTORS BEYOND SMOKING
SATURDAY, SEPTEMBER 7, 2024 - 11:58 - 11:59

EP.01D.03 Analysis of Lung Cancer Risk in Never Smokers with a Family History of Lung Cancer: A Cohort Study

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Introduction: In Eastern Asia, the incidence of lung cancer among never-smokers is increasing. Therefore, it is necessary to devise alternative screening strategies for individuals at high risk due to factors other than smoking. The aim of this research is to evaluate how familial lung cancer history influences lung cancer risk among individuals who have never smoked.

Methods: The Kangbuk Samsung Health Study is a longitudinal cohort study designed to investigate various factors influencing health and the development of chronic diseases among South Korean adults. This cohort draws its participants from individuals undergoing comprehensive health screenings at the Kangbuk Samsung Hospital Health Screening Centers from 2002 to December 31, 2022. After applying exclusion criteria, our analyses were performed with 216,618 Korean adults who were free of cancer history at baseline and followed up to 18 years. Non-smokers are defined as individuals who have never smoked in their lifetime or have smoked fewer than 100 cigarettes. Diagnosis of lung cancer were ascertained through linkage to Korea National Cancer Incidence Database. Utilizing Cox regression analysis, the study scrutinizes various factors such as sex, average body mass index (BMI) during survival time, average alcohol consumption (g/day), frequency of vigorous exercise per week, alongside family history of lung cancer.

Results: Over a follow-up period of 3,474,970,672 person-years, 31 incident lung cancer cases were identified in 14,156 individuals with a familial history of lung cancer, compared to 172 cases in 202,462 individuals without such a familial history. In univariate analysis, a history of familial lung cancer was significantly associated with elevated risks of lung cancer (HR 1.77, 95% CI 1.21-2.59, p=0.003). In multivariate analysis, a family history of lung cancer was associated with an increased risk of lung cancer (adjusted HR 1.85 95% CI 1.25-2.73, p=0.002) when accounting for other variables like sex, BMI, alcohol consumption, exercise frequency and past medical history. Nortably, lifestyle factors such as average BMI also displayed an association with lung cancer risk, underscoring the multifaceted nature of lung cancer etiology.

Conclusions: In individuals who do not smoke, a family history of lung cancer significantly associated with the increased risk of lung cancer. It highlights the significant role of genetic predisposition, especially in never smokers, and calls for a broader perspective on lung cancer prevention strategies. These findings could guide targeted screening and intervention strategies, potentially leading to early detection and better outcomes for high-risk populations. Further research could explore the mechanisms behind this familial risk.

Keywords: familial lung cancer, never smoker

EP.01D RISK FACTORS, RISK REDUCTION & TOBACCO CONTROL - RISK FACTORS BEYOND SMOKING
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EP.01D.04 Impacts of Household Tobacco Smoke on Life-Long Non-Smoking Adults: An Internet-Based Population Survey in India.

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Introduction: In India, tobacco use is highly prevalent. An estimated 28.6% of the population use some form of tobacco. India accounts for 12% of all tobacco users globally. Of the eight million deaths worldwide from tobacco use each year, approximately 16% are in people breathing second-hand tobacco smoke. In India, it is estimated that 39% of adults are exposed to second-hand tobacco smoke at home and 30% in the workplace. Despite the meticulous documentation of the burden of disease-based morbidity and mortality from second-hand tobacco smoke and its associations with cardiorespiratory and cardiothoracic diseases, little is known at a population level about the symptoms with which people live because of this exposure.

The aim of this population-based survey in India was to quantify the prevalence of long-term breathlessness limiting exertion in life-long non-smokers currently living with someone who smokes.

Methods: A national, English language internet survey in India, drawn from population panels. Recruitment was stratified by age, sex and rurality based on the 2011 Indian national census.

Breathlessness limiting exertion was defined as modified Medical Research Council breathlessness scale ≥1. Using the new International Classification of Disease code, long-term was defined as breathlessness for >8 weeks. Respondents were asked if anyone currently smoked in their household.

A multivariable binary logistic regression model explored any associations between long-term breathlessness and currently living in the same house as a smoker.

Results: The survey (February 2023) had 2,989 adult responses when weighted to the 2011 Indian census of whom 1,561 (52.2%) were life-long non-smokers.

One in three non-smokers reported long-term breathlessness with prevalence increasing from 38.5% (age ≤29) to 81.8% (age ≥40; p<0.001 for trend). Younger, urban women were more likely to report currently living with someone who smoked.

The regression showed that non-smokers living with someone who smoked increased the risk of long-term breathlessness compared to non-exposure (AOR=2.06, 95% CI 1.02, 4.16; p=0.04) as did age ≥40 (AOR 2.59 (95% CI 1.22, 5.52; p=0.01).

Conclusions: Living with someone who smokes significantly increases the risk of long-term breathlessness limiting exertion in non-smokers. This long-term symptom burden generated for non-smokers is further evidence of the impact of tobacco smoke on the health of the population. In the clinic setting, in people presenting with long-term breathlessness, it is important for clinicians to ask about exposure to other people's smoke at home or in the workplace. Equally importantly, people who smoke need to be educated on the impact that their tobacco smoke may have on the long-term well-being of people who live in the same household.

Given that the consequences of second-hand tobacco smoke include all the diseases associated with smoking tobacco and thus the risk of premature morbidity and mortality, at a population level, greater efforts need to be made to reduce the risk of exposure to other people's smoke at home, in the workplace, in cars, and places where people congregate such as dining areas, sporting events, transport queues.

Keywords: Tobacco smoke, Breathlessness, Population survey

EP.01D RISK FACTORS, RISK REDUCTION & TOBACCO CONTROL - RISK FACTORS BEYOND SMOKING
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EP.01D.05 Environmental Asbestos Exposure and Lung Cancer

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Introduction: Environmental asbestos exposures have been reported with increasing frequency. Apart from living near an asbestos industry site, mine or in an asbestos-contaminated house environmental asbestos exposure is observed in certain regions in the world. The people living in these areas will be exposed while working in the fields (agriculture) and/or when using contaminated soil for whitewhashing, plastering, insulating and waterproofing of their houses. The aim of the study was to determine the relationship between environmental asbestos exposure and lung cancer risk as well as the characteristics of lung cancer patients.

Methods: The study included 6,446 lung cancer patients diagnosed and followed up to death between 1990 and 2022 in rural areas where environmental asbestos exposure is common. The epidemiologic and clinical characteristics of the patients were recorded. The predictive variables among the findings were determined using logistic regression analysis. To calculate the relative risk of lung cancer associated with asbestos exposure, we designated the four districts with asbestos in the soil samples as asbestos-exposed zones, and two other districts without asbestos in the soil samples as control zones.

Results: The mean age of the patients was 62.82±9.48 (21-92) years, and 89.6% were male. Overall, 51.0% of patients had a history of environmental asbestos exposure, 57.7% were active smokers and 32.1% were former smokers, 16.2% had an occupational risk of lung cancer. Radiologic evidence of asbestos exposure was found in 445 (12.9%) of the patients with asbestos exposure. The most common histopathological subtypes were squamous cell carcinoma, adenocarcinoma and small cell carcinoma (37.2%, 28.7% and 18.6%, respectively). A total of 3,344 (51.9%) of the patients were in stage IV. The survival time of patients with asbestos exposure was longer than that of patients without asbestos exposure (9.00±0.21 and 8.00±0.21 months, respectively; p=0.017). The determining variables for lung cancer patients exposed to asbestos are advanced age (p<0.001), male gender (p<0.001), occupational risk (p<0.001), non-smoking (p<0.001) and early stage of disease (p=0.034). In the asbestos-exposed zones, 629 lung cancer cases (559 males and 70 females) were detected. There were 46 lung cancer cases (44 males and 2 females) in the control zones. Thus, the relative risk of lung cancer was 4.34 (95%CI: 3.71-5.08) times higher in the asbestos-exposed zones than in the control zones. No mesothelioma diagnoses were reported in the control zones but there were 235 mesothelioma diagnoses in the asbestos- contaminated zones. The risk of lung cancer versus mesothelioma was 2.68 (95% CI: 2.48-2.89) times higher in the asbestos-exposed zones.

Conclusions: Environmental asbestos exposure is able to increase the risk of lung cancer. The relative risk values are significant. Since rural residents with environmental asbestos exposure in Turkey are part of well-monitored cohorts, they represent a useful group for future studies. It is unlikely that we will be able to prevent environmental asbestos exposure completely, we must increase our efforts to stop smoking especially in asbestos-exposed groups and include people exposed to environmental asbestos in screening programs.

Keywords: Lung cancer, Asbestos, Epidemiology

EP.01D RISK FACTORS, RISK REDUCTION & TOBACCO CONTROL - RISK FACTORS BEYOND SMOKING
SATURDAY, SEPTEMBER 7, 2024 - 11:58 - 11:59

EP.01D.06 Radon Exposure in Colombian Never-Smoker Non-Small Cell Lung Cancer Patients. A Pilot Study

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Introduction: Lung cancer (LC) is the leading cause of cancer-related death globally, with 1.8 million deaths estimated in 2022. In Colombia, up to 74% of patients with LC are diagnosed with stage IV which negatively impacts survival, with 6,000 estimated deaths in 2022. The most critical strategy for reducing LC is the reduction of tobacco exposure; however, up to 38% of LC cases are not related to tobacco. Among other risk factors different from tobacco smoke; indoor radon, a radioactive gas found naturally in closed spaces, stands out and could be the most important one. In Latin America, information on the influence of radon on the incidence of LC is scarce. This study aims to establish the prevalence of Radon exposure in Colombian never-smoker LC patients

Methods: This is a Pilot study, Adult patients with de novo NSCLC diagnosis (<6 mo) were included. Past smokers (≥100 cigarettes in life or ≥1 cigarette daily for 6 mo) or patients with a change in place of living in the last 10 years were excluded. Sociodemographics, clinical, and molecular information were obtained and included in an eCRF using REDCap®, Radon measurement was done using a DTPA-type detector (Alfa-track). The detector was located in the patient's home, (60-140 cm from the floor at the point of least ventilation of the space to be measured), for 90 days, Subsequently an automated count quantification was carried out using the Radosys® system at a certified lab (Universidad Santiago de Compostella Radon Lab). The Radon levels were reported in Bq/m3, using the average value observed during the measurement period (The threshold was 20 Bq/m3)

Results: Between February 2022 to May 2023, 30 patients were included in the study, 86.7% were women, 73% had stage IV disease at inclusion, 53% had an identified driver mutation, with EGFR being the most frequent (62,5%) followed by ALK (31.3%). The mean Radon levels were 25.6 Bq/m3 (5 - 48). No patient had Radon levels ≥100 Bq/m3.

Conclusions: In this pilot study, we didn´t find high radon exposure among never-smoker NSCLC patients. Two other studies on indoor Radon concentrations have been done in Colombia, with only one demonstrating high radon levels (≥100 Bq/m3) in Bogotá. These differences could be explained by the type of house, rainfall adjustment, or underlying rock composition in our study. It´s important to increase the sample size for a definitive conclusion and to explore other risk factors in non-smoker patients as the quality of air or occupation, among others.

Keywords: Radon exposure, Never-somoker, Colombia

EP.01E RISK FACTORS, RISK REDUCTION & TOBACCO CONTROL - TOBACCO
SATURDAY, SEPTEMBER 7, 2024 - 11:58 - 11:59

EP.01E.01 Understanding the Choices of Those who Smoke Post-cancer Diagnosis

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Introduction: Continued smoking after a cancer diagnosis leads to worse morbidity and mortality. Unfortunately, smoking prevalence remains high amongst cancer patients and survivors. Interventions to improve cessation rates amongst cancer patients have been largely unsuccessful. A starting point to designing an optimal cessation program is to understand the demographics of and circumstances that these patients are exposed to. We developed a questionnaire intended to assess patients' demographics, tobacco smoking history, motivation to quit, and their social network dynamics.

Methods: We designed a three-page questionnaire to gain more information about a patient's past and current smoking history, level of nicotine dependence, assessment of their motivation to quit smoking, and their social network. Inclusion criteria included patients who have been diagnosed with lung or head and neck cancer and reported tobacco use at some point in their lifetime. For this abstract, patients who reported continued tobacco use after cancer diagnosis were included. Since these questionnaires were anonymous, Northwell IRB granted an exempt status. Questionnaires completed between June 2022 and December 2023 were included in the analysis. Descriptive statistics was used to analyze and report results.

Results: Of the 140 respondants, 72 patients reoported continued smoking after cancer diagnosis. The mean age of this cohort was 67 years (SD 11.02), and 42 (58.3%) were males. 52 (72%) patients had lung cancer and 20 (28%) head and neck cancer. The majority (47, 65.3%) were diagnosed within six months, with 15 (20.8%) having had the diagnosis more than a year prior. Family dynamics played a significant role, with 31 (43%) being married individuals and 49 (68%) reporting living with someone who smoked for a median of 27.5 years. Educational levels varied, but 61 patients (84.7%) had completed high school or above. The median age of starting smoking was 16 years. 17 (23.6%) patients had successfully quit for a period of time but relapsed. Only 38 (52.8%) patients reported increased motivation post-diagnosis, while others experienced decreased or no change and only 5 (6.9%) patients were enrolled in a tobacco cessation program at the time of survey. Barriers to quitting included stress, a desire to maintain control, and skepticism about the direct link between smoking and cancer.

Conclusions: We believe that this study provides valuable insights into the characteristics and motivations of individuals who continue smoking after a cancer diagnosis. The cohort's diversity in age, marital status, cancer type, and time since diagnosis underscores the need for personalized support strategies. Family and social network are huge influences that should be taken into account in designing cessation programs.

Keywords: tobacco smoking, cancer diagnosis, questionnaire

EP.02A TUMOR BIOLOGY - PRECLINICAL BIOLOGY - EARLY STAGE DISEASE/STEM CELLS
SATURDAY, SEPTEMBER 7, 2024 - 11:58 - 11:59

EP.02A.01 Gender-Specific Onset Age Distribution Among Different Driver Mutations in Lung Cancer

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Introduction: Different driver gene mutations play a crucial role in the pathogenesis of lung cancer, and their distribution across ages and genders may exhibit distinct characteristics, current study remains insufficient yet.

Methods: We employed next-generation sequencing to analyze genetic testing results on lung cancer patients from the First Affiliated Hospital of Guangzhou Medical University, including point mutations and gene fusions. Based on their genomic profiles, we categorized patients into 11 distinct gene subtypes, including EGFR, KRAS, ALk, Wild-type and so on. Furthermore, we investigated the distribution characteristics of different types of gene mutations across age and genders as well as age at disease onset.

Results: Cumulatively, 8705 patients were included in our study cohort. Across various age brackets, the distribution of EGFR mutations exhibited consistent rates among males (P=0.927). While in females, a higher enrichment of EGFR mutations was identified (P<0.01), particularly evident in L858R mutations showing significant age correlation(P<0.001). Conversely, 19del mutations in females exhibit a declining trend around the age of 65. The enrichment of Kras mutations in males increases with age(P<0.001), whereas the trend is less pronounced in females(P=0.07). Additionally, the frequency of male wild-type patients gradually increases with age(P<0.05), while in females, it decreases gradually (P<0.05).Regarding the age of onset, Alk (Mean age: 53.96, 95% CI: 52.88 to 55.04), Ros1 (Mean age: 57.47, 95% CI: 56.11 to 58.83), and ERBB2 (Mean age: 55.64, 95% CI: 54.31 to 56.98) were associated with earlier onset compared to the mean age (Mean age: 59.1, 95% CI: 58.86 to 59.34), all P<0.05. Conversely, mutations in RAS family genes (KRAS, NRAS, BRAF, MET) are associated with delayed onset (P<0.01). EGFR 19del mutation was associated with earlier onset in males (Mean age: 57.95 vs. 60.47, 95% CI: [57.18, 58.72] vs. [60.16, 60.78], P<0.01), while EGFR L858R mutations tended to occur later in females (Mean age: 60.66 vs. 57.35, 95% CI: [57.35, 60.09] vs. [56.98, 57.72], P<0.01). Braf mutations are associated with earlier onset in females and delayed onset in males(P<0.01). ERBB2 and ALK were associated with earlier onset in both males and females (P<0.05), while NRAS, KRAS, MET, and wild-type were associated with delayed onset in both genders (P<0.05). The co-mutation of TP53 had minimal impact on the age of onset (Mean age: 58.39 vs. 60.43, 95% CI: [58.09, 58.70] vs. [60.04, 60.81], P=0.25), but ERBB2 co-mutation with tp53 may delay the age of onset in both males and females, meanwhile TP53 co-mutation on the age of onset in ALK patients shows opposite effects between males and females. All in all, the impact of TP53 co-mutation exerting a protective effect in males, not in females.

Conclusions: Different gene subtypes exhibit distinct characteristics of onset age across different gender, Gender and age exert significant and varying influences on lung cancer patients with different gene types.

Keywords: NSCLC, onset age, genetic mutations

EP.02A TUMOR BIOLOGY - PRECLINICAL BIOLOGY - EARLY STAGE DISEASE/STEM CELLS, SATURDAY, SEPTEMBER 7, 2024 - 11:58 - 11:59

EP.02A.02 The Stroma Cell Function in the Border Region Between Lung Cancer and Normal Lung

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Introduction: Stromal cells in the intratumoral microenvironment of lung cancer are important for lung cancer progression. Stromal cells in the normal lungs are stimulated by lung cancer and undergo phenotypic changes. The biological characteristics of stoma cells in lung cancer and normal lung tissues have been previously reported. This time, we defined the margin between lung cancer tissue and normal lung tissue as the "border" and aimed to clarify the biological characteristics of the stromal cells in "border."

Methods: Tissues in lung cancer, normal lung, and border were collected from the excised lungs of three female non-smokers who underwent curative lobectomy for lung adenocarcinoma. By cutting the tissues into small pieces and culturing them in vitro, we observed differences in the morphology and gene expression of stromal cells extending from the tissue pieces. We also used a cytokine array to search for differences in cytokine expression in the second-passage culture supernatants of each stromal cell.

Results: In each cultured tissue sample, Vimenntin-positive and Cytokeratin-negative stromal cells spread and proliferated around the tissue. Morphologically, the stromal cells in the lung cancer region had a thick cytoplasm, while those in the normal lung region had a thin cytoplasm, and the stromal cells in the border region had an intermediate cytoplasm. Polymerase chain reaction showed that the expression of the COL11A1 gene in stromal cells in the lung cancer region was higher than that in the normal lung region, and the expression in the border region was similar to or slightly lower than that in the normal lung region. According to the cytokine array, there were differences in cytokine expression between the lung cancer, normal lung, and border regions. The expression of GM-CSF in the culture medium was highest in the border region, followed by the lung cancer region and then the normal lung region. In addition, the expression of uPA in the culture medium was more than three times higher in the border region and normal lung region than in the lung cancer region.

Conclusions: Stroma cells cultured individually from lung cancer, normal lung, and border regions showed differences in morphology and genes as well as in cytokine expression in the culture medium. It has become clear that there is a "border" between lung cancer and normal lung regions and that stromal cells in this area are involved in the progression and proliferation of lung cancer. Whether stromal cells in this border region contribute to the prevention or promotion of tumor progression depends on cancer histology.

Keywords: Stroma cell, Border region, Intratumoral microenvironment

EP.02B TUMOR BIOLOGY - PRECLINICAL BIOLOGY - GENOMICS
SATURDAY, SEPTEMBER 7, 2024 - 11:58 - 11:59

EP.02B.01 PIK3C2A Potentiates Angiogenesis of Non-Small Cell Lung Cancer by Regulating ADRB2/VEGFA Signaling Pathway

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Introduction: Non-small cell lung cancer (NSCLC) is a aggressive tumor with a unfavorable prognosis, and the potential mechanisms underlying tumor progression is not yet clearly. There is increasing evidence to support that β2AR is responsible for cancer growth, angiogenesis and metastasis in NSCLC. However, the molecular mechanism underlying the cancer angiogenesis of β2AR in NSCLC hasn't been fully clarified.

Methods: We screened proteins that interact with β2AR proteins and are significantly associated with NSCLC angiogenesis by using the TCGA database and STRING database. Through CO-IP and IF experiments, we further verified the proteins that interacted and co-located with β2AR in NSCLC. The interaction between PIK3C2A and β2AR and the effect on NSCLC angiogenesis were explored through WB, PCR, IF and angiogenesis experiments.

Results: We revealed a novel regulation mechanism by which ADRB2 and PIK3C2A cooperated to promote NSCLC angiogenesis. PIK3C2A interacts with β2AR, and its expression is positively correlated with ADRB2 expression in NSCLC. Knocking down the expression of PIK3C2A can also reduce the expression of vascular endothelial growth factor A (VEGFA). Loss-of-function experiments demonstrate that PIK3C2A potentiates HUVEC proliferation, migration and tube formation. Immunohistochemistry (IHC) analysis confirmed that PIK3C2A expression was positively correlated with microvessel density (MVD) expression in patient specimens.

Conclusions: This study not only sheds light on the emerging roles of PIK3C2A/β2AR interaction in the progression of NSCLC, but also offer a new strategy for the inhibition of angiogenesis in NSCLC.

Keywords: PIK3C2A, Tumor angiogenesis, β2AR

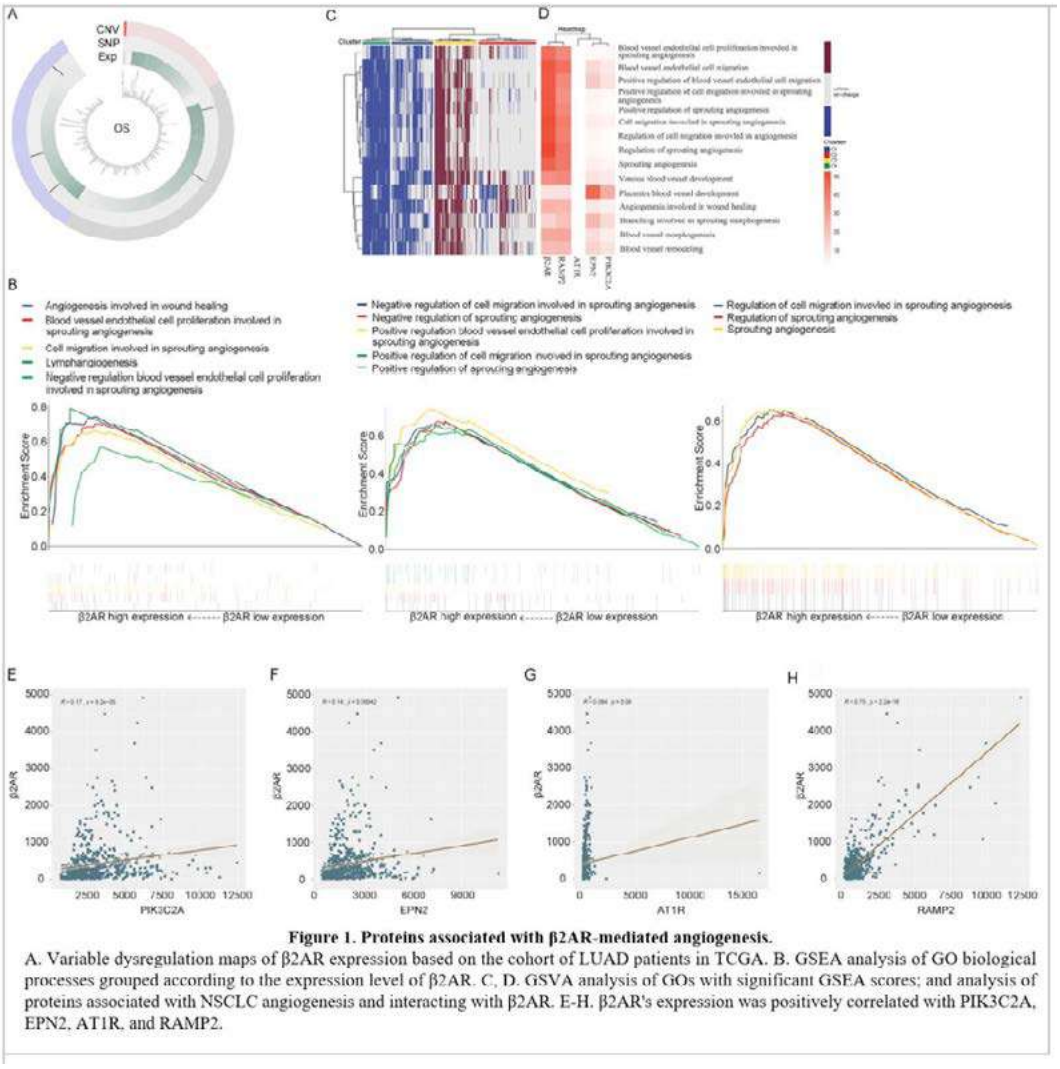

Figure 1. Proteins associated with β2AR-mediated angiogenesis.
A. Variable dysregulation maps of β2AR expression based on the cohort of LUAD patients in TCGA. B. GSEA analysis of GO biological processes grouped according to the expression level of β2AR. C, D. GSVA analysis of GOs with significant GSEA scores; and analysis of proteins associated with NSCLC angiogenesis and interacting with β2AR. E-H. β2AR's expression was positively correlated with PIK3C2A, EPN2, AT1R, and RAMP2.

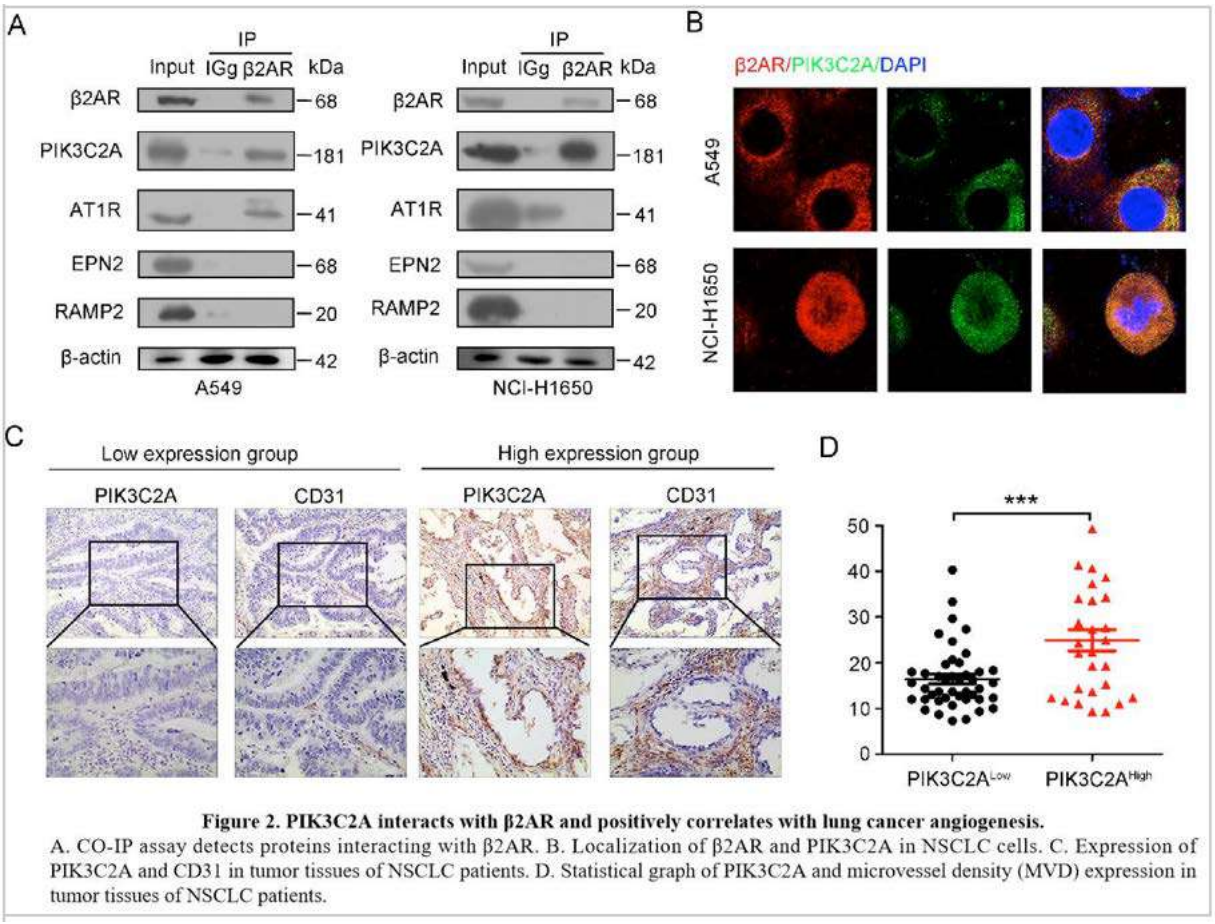

Figure 2. PIK3C2A interacts with β2AR and positively correlates with lung cancer angiogenesis.
A. CO-IP assay detects proteins interacting with β2AR. B. Localization of β2AR and PIK3C2A in NSCLC cells. C. Expression of PIK3C2A and CD31 in tumor tissues of NSCLC patients. D. Statistical graph of PIK3C2A and microvessel density (MVD) expression in tumor tissues of NSCLC patients.

EP.02B TUMOR BIOLOGY - PRECLINICAL BIOLOGY - GENOMICS
SATURDAY, SEPTEMBER 7, 2024 - 11:58 - 11:59

EP.02B.02 The Functional Roles of Intergenic ALK Fusions in NSCLC

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Introduction: ALK fusions are frequent in non-small cell lung cancer (NSCLC). The classic EML4-ALK fusions and several others have been shown to be drivers and therapeutic targets of NSCLC. However, about 15% of ALK fusions, including intergenic fusions, are variants and their biological functions and their response to ALK inhibitors remains unclear. Previously, we have discovered several new variant ALK fusions. Among them was the intergenic fusion LOC388942-ALK (LA). The patient responded but rapidly relapsed to crizotinib treatment.

Methods: To investigate the role of LA in the development and progression of NSCLC, the CRISPR-Cas9 gene editing has been applied to generate LA fusions in both NSCLC cell lines and primary lung organoids. Then these cells and organoids were transplanted into recipient mice. The tumorigenesis functions of LA were measured by cell proliferation and tumor growth in vitro and in vivo, respectively. Their response to ALK inhibitors were determined with these in vitro and in vivo models. RNA-seq was performed to investigate the molecular mechanism of LA in NSCLC.

Results: The LA fusion was successfully generated in NSCLC cell lines and primary lung organoids, verified by PCR and sanger sequencing. LA fusions led to increased levels of ALK proteins. Tumors with the LA fusion grew significantly faster than the control ones in mice. And they were resistant to ALK inhibitors. Transcriptomics analyses showed that LA significantly upregulated the EMT and TNF pathways.

Conclusions: Our study validated LA as a driver of NSCLC, which might be less responsive to ALK inhibitors. Thus, LA should be included for future NSCLC diagnosis and better treatments for these patients should be developed.

Keywords: NSCLC, Variant ALK fusions, Tumorigenesis

EP.02B TUMOR BIOLOGY - PRECLINICAL BIOLOGY - GENOMICS
SATURDAY, SEPTEMBER 7, 2024 - 11:58 - 11:59

EP.02B.03 MALAT1 And NEAT1 Contribute to Adaptive Mutability in the Transition from Drug Tolerance to Drug Resistance in Lung Cancer

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Introduction: Responses to targeted therapies are initially dramatic in patients with lung adenocarcinomas that harbour actionable mutations in EGFR or KRAS, but relapse is almost inevitable. Drug tolerant persisters (DTPs) contribute to the emergence of acquired resistance via adaptive mutability and remain a difficult clinical challenge. Long non-coding RNAs (lncRNAs) are known to contribute to several characteristics of DTPs, however their contribution to drug tolerance is unknown. Here, we investigate the role of lncRNAs in the emergence of DTPs and how lncRNAs may contribute to adaptive mutability, a process that leads to the accumulation of DNA damage and a heightened rate of acquired resistance in DTPs.

Methods: EGFR-mutant PC-9 and KRASG12C-mutant H358 cells were treated with >IC90 concentrations of osimertinib or sotorasib respectively, for 3, 7 and 19 days to induce drug tolerance. Bulk RNA-sequencing was then performed to determine DTP phenotypic changes and to identify differentially expressed lncRNAs, with changes confirmed via RT-qPCR for coding and non-coding genes, and western blotting for protein coding genes. Antisense oligonucleotides (ASOs) were used to knock down MALAT1 and NEAT1 in the presence or absence of relevant targeted therapy, and the effects of these knockdowns on the DTP phenotype was determined by proliferation assays, bulk RNA-sequencing, RT-qPCR and western blotting. Plasmid-based reporters were used to measure the functional capacity of DNA repair mechanisms to investigate the contribution of these lncRNAs to adaptive mutability. Finally, resistance assays were used to measure the emergence of acquired resistance.

Results: DTPs from both PC-9 and H358 cells expressed increased levels of the stem cell factors OCT3/4 and NANOG as well as previously described markers of minimal residual disease in patients with lung cancers, such as AQP4, SFTPC and SFTPD compared to solvent controls. DNA damage repair pathways, such as DNA mismatch repair and homologous recombination were downregulated, while levels of error-prone polymerases were also increased in the DTPs from both cell lines. Several lncRNAs were differentially expressed in DTPs compared to solvent controls, including MALAT1, NEAT1, and UFC1. MALAT1 and NEAT1 are reported to be involved in stem cycle gene regulation as well as in drug resistance, and were selected for further investigation. Combining ASO-mediated knockdown of MALAT1 and NEAT1 with targeted therapeutics for 3 and 7 days in our models also partially reversed changes to DNA repair pathways, suggesting that these lncRNAs contribute to drug resistance by inducing adaptive mutability. In proliferation assays, MALAT1 knockdown reduced the number of drug-tolerant cells in both PC9 and H358 cell lines and resulted in lower rates of late emerging (> 2 weeks) adaptive drug resistance measured by resistance assays.

Conclusions: These results represent early links between lncRNAs, drug tolerance and drug resistance in lung adenocarcinomas. This work has identified the lncRNAs MALAT1 and NEAT1 as potentially important molecules implicated in the development of acquired drug resistance that emerges from drug tolerance. Further studies are ongoing to determine whether modulating MALAT1 represents a potential approach to augment therapy in patients with lung adenocarcinomas undergoing treatment with targeted therapeutics.

Keywords: Drug Tolerant Persister, lncRNAs, NSCLC

EP.02B TUMOR BIOLOGY - PRECLINICAL BIOLOGY - GENOMICS
SATURDAY, SEPTEMBER 7, 2024 - 11:58 - 11:59

EP.02B.04 Bioinformatics & Machine Learning for Prognostic Model of LUSC by Identifying Programmed Cell Death Genes

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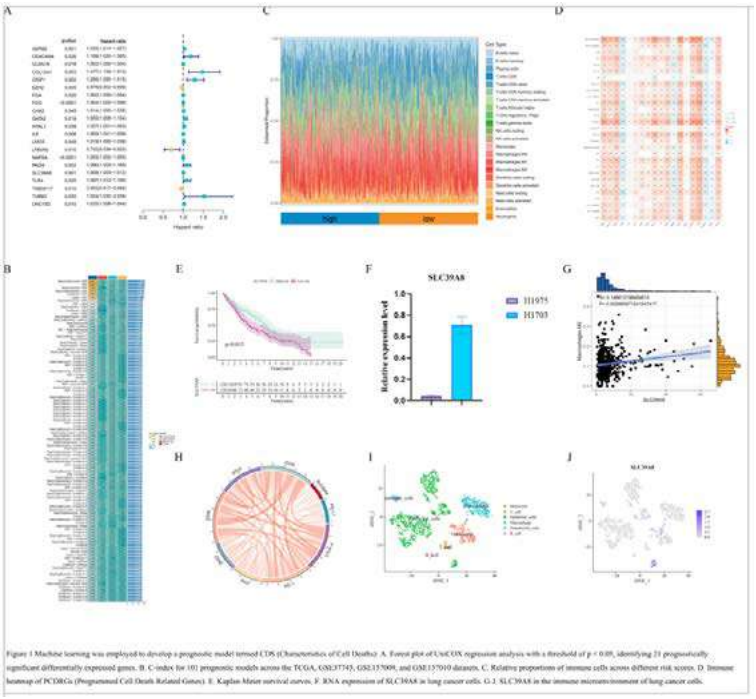
Introduction: Lung Squamous Cell Carcinoma (LUSC) is associated with significant morbidity and mortality. However, few studies have focused on programmed cell death-related genes (PCDRGs) in LUSC. Our aim was to investigate the prognostic significance of PCDRGs in LUSC using bioinformatics methods and construct a prognosis risk score model based on these genes. Additionally, our research sought to identify potential pharmaceutical inhibitors for effective alternative therapies and provided a novel theoretical basis for target and mechanism discovery in the clinical treatment of LUSC.

Methods: A predictive model named CDS was constructed by using TCGA, GSE37745, GSE157010, and GSE157009 datasets and combining with 10 different machine learning methods. To explore the correlation of PCDRGs with the tumor immune microenvironmen,Single-cell analysis was mainly employed.And RT-qPCR was used to validate the expression of PCDRGs. The top six drugs with favorable binding affinity to SLC39A8 was identified by virtual screening of 1615 FDA-approved drugs from the ZINC database via vina. Molecular interactions and binding conformations were visualized using PyMOL and MOE.

Results: The StepCox[forward] + RSF approach yielded the most effective prognostic model for PCDRGs. Patients in the low PCDRGs group exhibited improved prognosis, enhanced immune activity, immune infiltration, and tended toward an immunothermal phenotype with potential immunotherapy response. RT-qPCR confirmed abnormal expression of SLC39A8 RNAs in LUSC, with high expression correlating with poor prognosis. Additionally, small molecule inhibitors targeting SLC39A8 were identified through screening.

Conclusions: This study successfully developed a novel PCDRGs model for LUSC, and this model can be used as an important indicator for predicting the prognosis of LUSC patients and assessing their response to immunotherapy. Identifiing six active compounds with the potential to inhibit the expression of SLC39A8, which may play a role in the treatment and prevention of LUSC.

Keywords: Machine learning, Lung squamous carcinoma, Molecular docking



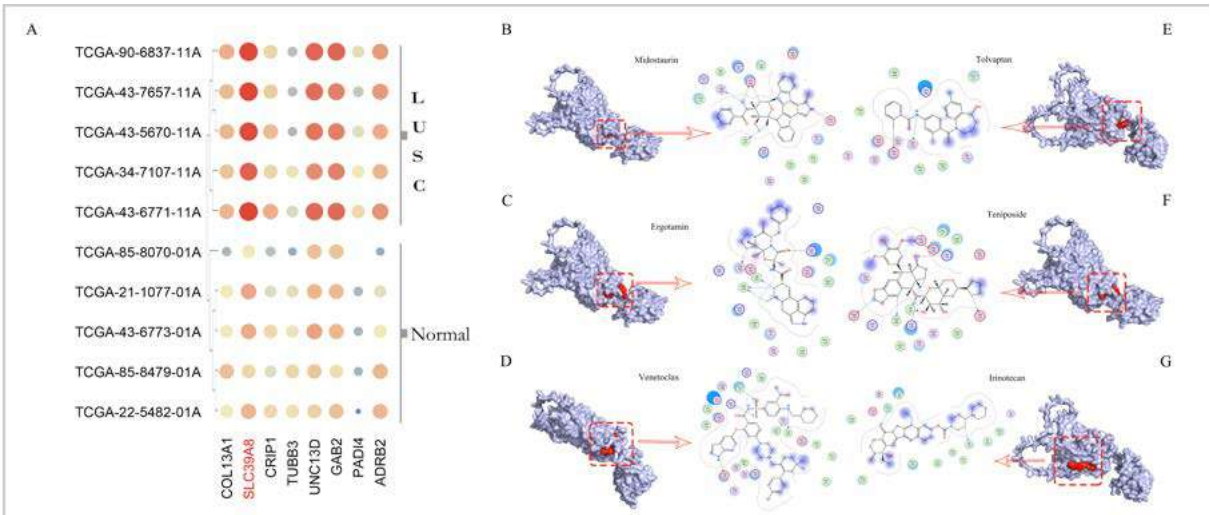


Figure 2 A. Heatmap of gene expression differential analysis in NSCLC. Blue indicates lower expression levels, while red signifies higher expression levels. The heatmap includes data from 10 NSCLC clinical samples alongside 8 targets (with 5 normal controls included for comparison). B-G. Visualization of the molecular docking results. The complexes illustrated are between SLC39A8 and various ligands: B. Midostaurin, C. Ergotamine, D. Venetoclax, E. Tolvaptan, F. Teniposide, and G. Irinotecan. Interactions are depicted with green and blue dashed lines indicating hydrogen bonds, with the bond lengths specified.

EP.02B TUMOR BIOLOGY - PRECLINICAL BIOLOGY - GENOMICS, SATURDAY
SEPTEMBER 7, 2024 - 11:58 - 11:59

EP.02B.05 XBP1s-Related Super-Enhancers Suppresses Cuproptosis via Temporally Transcription Regulation in Lung Adenocarcinoma

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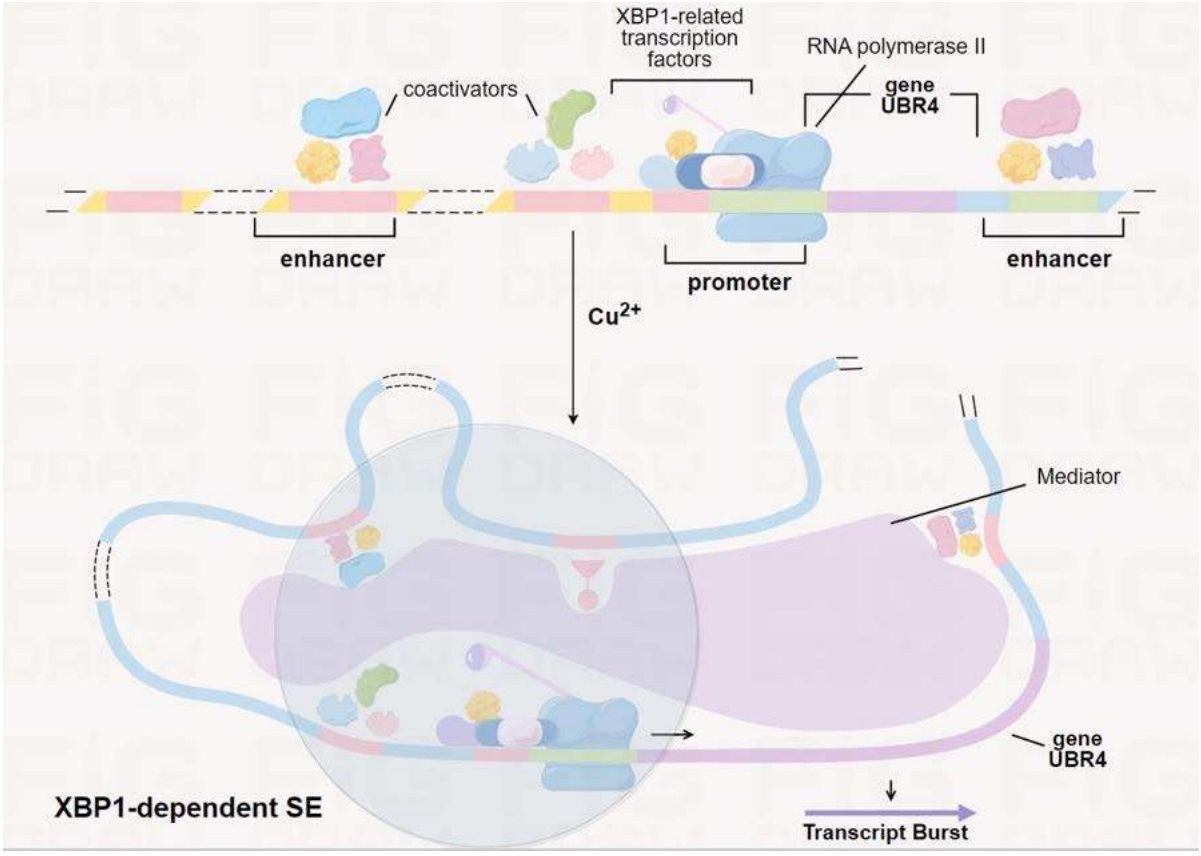
Introduction: The role of copper in tumor progression is thought to be a double-edged sword. Moderate levels of copper promote tumor progression and excess copper leads to a form of programmed cell death-cuproptosis. However, the relationship between Lung Adenocarcinoma (LUAD) and cuproptosis has not been studied.

Methods: Single-cell sequencing analysis and copper colorimetric assay identified higher pathological grade of LUAD simultaneous associated with higher copper accumulation and XBP1 expression. Then we utilized 4D-DIA proteomics to identify XBP1 promotes the degradation of LIPT1. CUT&Tag-seq and LC-MS/MS allowed us to discover that the intermediate regulatory molecules ISG15 and UBR4. Chromosome conformation capture (3C) experiment showed that XBP1s-related super-enhancers affect on the frequency of ISG15 promoter-enhancer interactions in different copper environments.

Results: Single-cell sequencing analysis and copper colorimetric assay identified higher pathological grade of LUAD simultaneous accompanied by higher copper accumulation and expression of XBP1. In addition, we confirmed that overexpression of the spliced form of XBP1 (XBP1s) negatively regulates the protein level of LIPT1 to inhibit copper ionophore induced LUAD cell death. In mouse xenograft models, co-administration of XBP1 inhibitors and copper ionophore significantly reduced tumor volume and growth rate. Additionally, XBP1s can undergo phase separation and form super-enhancers in the nucleus. This phenomenon was more intense in high copper environments and was closely related to the transcriptional regulation of XBP1s target genes. In a low copper environment, the XBP1s-related super-enhancers mainly promote the transcription of ISG15, and ISG15 interacts with LIPT1 to increase its stability. However, in a high copper environment, XBP1s reduces ISG15 transcription and increases UBR4 transcription. UBR4 can enhance the ubiquitination level of LIPT1 and ultimately leading to its degradation in the cytoplasm. Broadly, XBP1s-related super-enhancers selectively promote target gene transcription in a environment-dependent manner to protect cells from cuproptosis. On this basis, combination of copper ionophore and XBP1 inhibitors may provide a new insight into the early treatment of invasive LUAD.

Conclusions: Our study sheds light on the molecular mechanism by which XBP1s affect the cuproptosis pathway through the formation of super-enhancers in LUAD. In vivo experiment suggested the potential clinical value of the combined use of XBP1 inhibitors and copper ionophore.

Keywords: Super-enhancer, Cuproptosis, LUAD



EP.02B TUMOR BIOLOGY - PRECLINICAL BIOLOGY - GENOMICS
SATURDAY, SEPTEMBER 7, 2024 - 11:58 - 11:59

EP.02B.06 Analysis on the Correlation Between RUNX3 Mislocalization and Epigenetic Parameters in Non-Small Cell Lung Cancer

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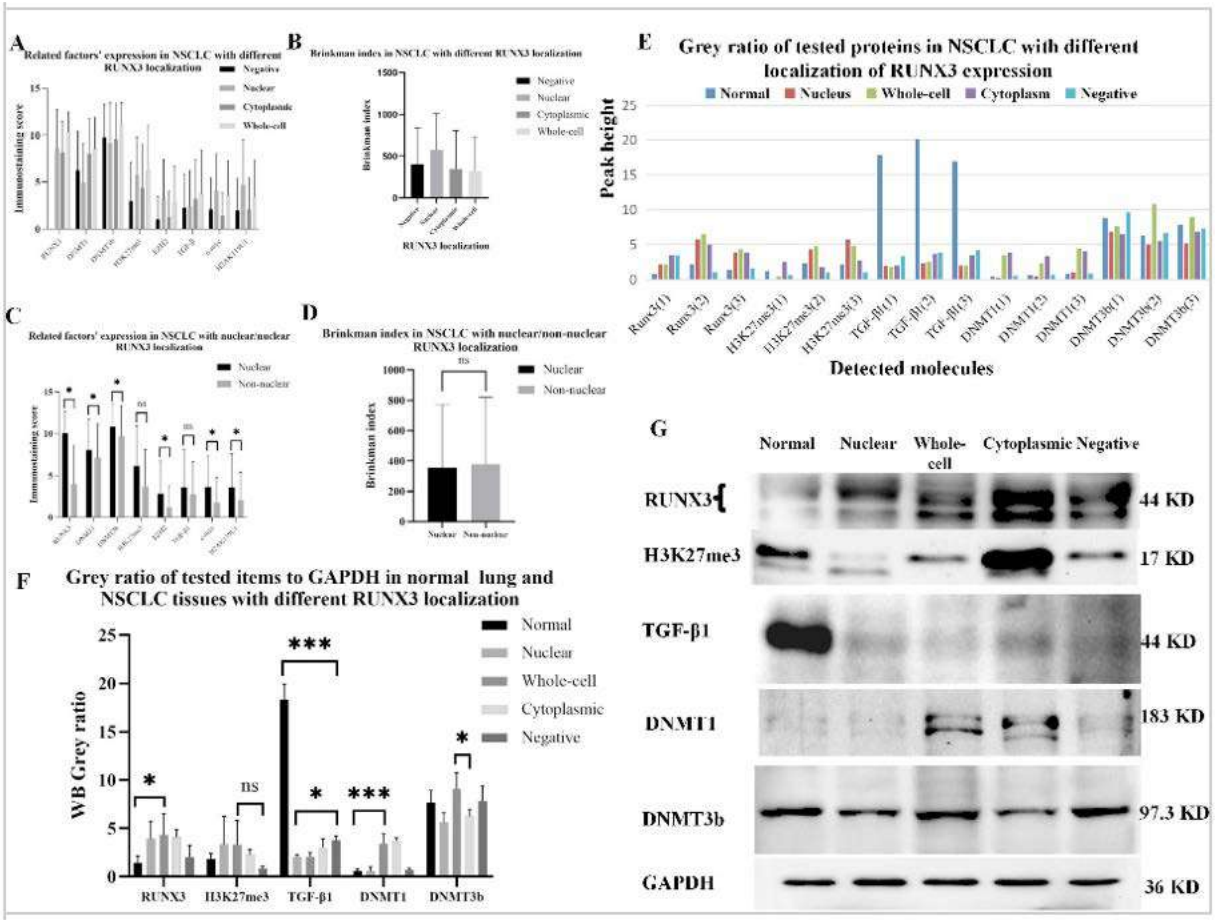
Introduction: Our previous study demonstrated different manners of RUNX3 expression in NSCLC, i.e., negative, nuclear, cytoplastic and whole-cell RUNX3 localization, and RUNX3 non-nuclear expression or mislocalization in NSCLC was associated with postoperative metastasis. Current study was to investigate the possible underlying mechanism of RUNX3 non-nuclear expression or mislocalization in terms of epigenetic aspects.

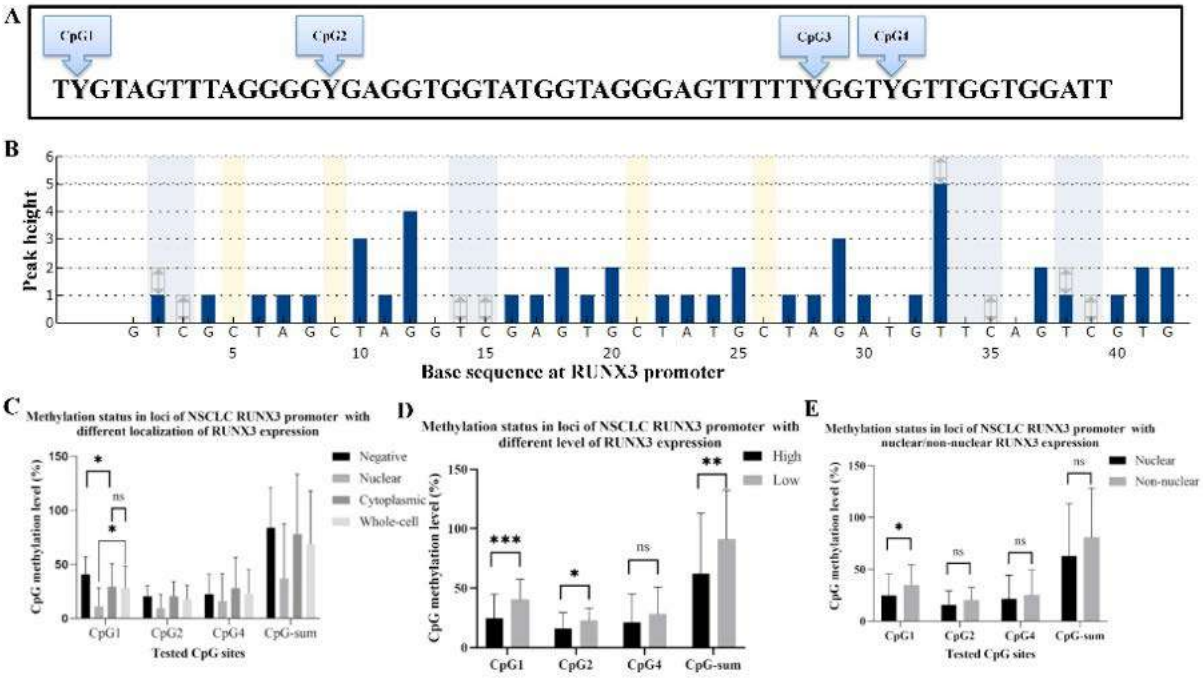
Methods: 205 NSCLC and 5 normal lung tissue were built into tissue microarrays (TMA) and detected of epigenetic parameters like H3K27me3, H2AK119U1, EZH2, DNMT1/3b, TGF-β and c-myc. Western blot was used to evaluate the protein level of RUNX3, H3K27me3, DNMT1/3b and TGF-β in different expression patterns. Methylation level at RUNX3 promoter was assessed via pyrosequencing.

Results: Among NSCLC with negative, nuclear, cytoplastic and whole-cell RUNX3 expression, epigenetic markers like H3K27me3, DNMT1/3b, H2AK119U1, EZH2 and c-myc differed significantly (all P<0.05). Non-nuclear RUNX3 localization was correlated with low H3K27me3/EZH2/H2AK119U1/c-myc/DNMT3b expression (all P<0.05). Higher methylation level on CpG1 locus affected 4/2(nuclear/non-nuclear) distribution patterns (P<0.05). Higher methylation level on CpG1/2 resulted in low RUNX3 expression and higher probability of local relapse in postoperative patients (both P<0.05).

Conclusions: Conclusively, epigenetic parameters might partially result in RUNX3 mislocalization and RUNX3 promoter hypermethylation was closely correlated with local relapse in NSCLC.

Keywords: runt-related transcription factor 3, promoter hypermethylation, non-small cell lung cancer




A
CpG1
CpG2
CpG3
CpG4
TYGTAGTTTAGGGGYGAGGTGGTATGGTAGGGAGTTTTTYGGTYGTTGGTGGATT
B
Peak height
G T C G C T A G C T A G G T C G A G T G C T A T G C T A G A T G T T C A G T C G T G
5
10
15
20
25
30
35
40
Base sequence at RUNX3 promoter
C
Methylation status in loci of NSCLC RUNX3 promoter with different localization of RUNX3 expression
CpG methylation level (%)
Negative
Nuclear
Cytoplasmic
Whole-cell
CpG1
CpG2
CpG4
CpG-sum
Tested CpG sites
D
Methylation status in loci of NSCLC RUNX3 promoter with different level of RUNX3 expression
CpG methylation level (%)
High
Low
CpG1
CpG2
CpG4
CpG-sum
E
Methylation status in loci of NSCLC RUNX3 promoter with nuclear/non-nuclear RUNX3 expression
CpG methylation level (%)
Nuclear
Non-nuclear
CpG1
CpG2
CpG4
CpG-sum
Tested CpG sites

EP.02B TUMOR BIOLOGY - PRECLINICAL BIOLOGY - GENOMICS
SATURDAY, SEPTEMBER 7, 2024 - 11:58 - 11:59

EP.02B.07 HFE as a Novel Gene Associated with Primary Lung Cancer Risk:A Mendelian Randomization and Bioinformatics Study

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Introduction: Lung cancer ranks as the foremost cause of cancer-related mortality worldwide. Despite this, the association between serum iron levels and lung cancer risk remains ambiguous. This investigation aims to elucidate the potential causal link between serum iron status and primary lung cancer risk using Mendelian randomization techniques. Additionally, it seeks to delineate the involvement of the HFE gene in lung cancer etiology through bioinformatics analyses.

Methods: Leveraging genome-wide association study data from the UK Biobank, Mendelian randomization analysis was conducted, with lung cancer as the outcome variable and serum iron, ferritin, transferrin, and transferrin saturation as exposure variables. Statistical analysis utilized MR-base software and R packages, employing a fixed-effects IVW model to evaluate genetic causality, and MR-Egger and weighted median methods for robustness testing. Furthermore, a pivotal single nucleotide polymorphism (SNP, rs1800562) linked to the HFE gene was identified, exhibiting heightened expression in both lung adenocarcinoma and squamous cell carcinoma. The investigation encompassed the exploration of HFE's associations with other proteins and functional roles, employing techniques such as protein-protein interaction networks and enrichment analysis. Additionally, HFE expression in immune cells of non-small cell lung cancer (NSCLC) was analyzed using the immune cell single-cell database and The Tumor Immune Single Cell Hub 2 (TISCH2), alongside an exploration of the correlation between HFE and various phenotypes and drug targets.

Results: Elevated serum iron, ferritin, and transferrin saturation levels were correlated with a diminished risk of squamous cell lung cancer. Notably, a major SNP (rs1800562) pertaining to the HFE gene was identified through MR analysis, demonstrating heightened expression levels in both lung adenocarcinoma and squamous cell carcinoma. High HFE expression was associated with poorer disease-specific survival in lung cancer patients. Moreover, HFE exhibited negative correlations with various immune cell types and positive correlations with tumor-infiltrating lymphocytes (TILs) abundance in squamous cell lung cancer. Two potential interacting drugs with HFE were uncovered via drug target analysis. Gene set enrichment analysis and protein-protein interaction network analysis unveiled numerous potential biological functions and mechanisms of HFE in lung cancer.

Conclusions: This study furnishes evidence of a causal link between serum iron status and squamous cell lung cancer risk utilizing Mendelian randomization techniques. Moreover, it sheds light on the putative involvement of the HFE gene in lung cancer pathogenesis. HFE may modulate lung cancer onset and progression through its impact on immune cell infiltration and regulation of iron metabolism. These insights present novel molecular targets and biological mechanisms for lung cancer prevention and treatment. Further research is warranted to validate these findings and explore the clinical utility of HFE in lung cancer management.

Keywords: Lung Cancer, Mendelian Randomization and Bioinformatics Study, HFE

EP.02B TUMOR BIOLOGY - PRECLINICAL BIOLOGY - GENOMICS
SATURDAY, SEPTEMBER 7, 2024 - 11:58 - 11:59

EP.02B.08 Interrogating Sexual Dimorphism in Lung Cell Biology and Tumourigenesis for Cancer Treatment and Prevention in Never & Smokers

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Introduction: The incidence of lung cancer in never-smokers (LCINS) is rising, and the majority of LCINS patients are female. Further, lung cancer in young people (under 54 years of age) is more common among females than males, and this increased incidence is unattributable to smoking. Although sex-based differences in LCINS incidence are evident, sexual dimorphism in lung cell biology and how it shapes lung tumourigenesis in non-smokers is largely unexplored. We interrogated published patient genomic datasets to determine if there are sex-based differences in the development of invasive mucinous lung adenocarcinoma (IMA), a subtype of lung cancer which predominantly develops in non-smoking, female people, at the transcriptional level.

Methods: Gene expression analysis of male and female IMA tumours and adjacent normal lung tissue was performed. Transcriptomic data derived from normal healthy lung cell subsets from male and female patients was also interrogated.

Results: Unique transcriptional programs are activated upon IMA development in female versus male patients.

Conclusions: These findings indicate that patient sex may shape the mechanisms underpinning IMA development at the molecular level, with implications for the design of targeted, preventative therapies for IMA and LCINS more broadly.

Keywords: Sex, IMA, transcriptomic

EP.02C TUMOR BIOLOGY - PRECLINICAL BIOLOGY - IMMUNE MODULATION
SATURDAY, SEPTEMBER 7, 2024 - 11:58 - 11:59

EP.02C.01 Investigating the Role of VISTA Immune Checkpoint in Human and Murine Mesothelioma Cell Lines

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Introduction: V-domain Ig suppressor of T cell activation (VISTA) has emerged as a key immune checkpoint regulator with implications in tumor immunity. VISTA expression on T cells normally exerts inhibitory effects on T cell proliferation. The role of VISTA expression on tumors is less clear, though it has been shown to inhibit tumor specific T cell activity as well in some models. Mesothelioma (MM) cells highly express VISTA on the cell surface though to date its role in MM biology remains unclear.PURPOSE: In this study, we aimed to understand the role of VISTA in MM biology - both in terms of what signaling pathways regulate VISTA expression as well as the effects of VISTA silencing on MM cell biology. . We hypothesized that VISTA expression is regulated by MAPK and Akt signaling pathways that are constitutively active in MM cells and that inhibition of these signaling pathways could lead to translational strategies in combination with immune checkpoint blockade. In this study, we aimed to understand the role of VISTA in MM biology - both in terms of what signaling pathways regulate VISTA expression as well as the effects of VISTA silencing on MM cell biology. . We hypothesized that VISTA expression is regulated by MAPK and Akt signaling pathways that are constitutively active in MM cells and that inhibition of these signaling pathways could lead to translational strategies in combination with immune checkpoint blockade.

Methods: Western blot analysis and flow cytometry was used to assess VISTA expression in human (2373 and HAY) and murine (40L and AB12) mesothelioma cell lines. Additionally, siRNA transfection experiments were conducted in vitro to assess the effect of VISTA knockdown on key signaling pathways involved in cell proliferation. MEK inhibitor, trametinib was used to assess the effect of MAPK inhibition on VISTA expression. Human mesothelioma cells (2373) were treated with 50 μM trametinib, 500 μM trametinib, and DMSO as a control for 24 hours. Western blot analysis was then utilized to assess the impact of trametinib treatment on VISTA, phospho-ERK1/2, total ERK1/2, phospho-AKT, and total AKT levels.

Results: Our initial western blot analysis revealed the presence of VISTA expression in both human and murine mesothelioma cells, highlighting its relevance in this malignancy. Furthermore, siRNA transfection experiments demonstrated successful VISTA suppression in human and murine mesothelioma cell lines. In HAY cells, VISTA knockdown resulted in decreased ERK1/2 and AKT phosphorylation. These results suggest that VISTA signaling may impact upon downstream signaling pathways. Trametinib treatment of H2373 cells resulted in inhibition of ERK1/2 phosphorylation as expected, however, led to increased Akt phosphorylation and marked increase in VISTA expression.

Conclusions: These data would suggest that there is interaction between VISTA expression and ERK/Akt signaling pathways. The functional significance of these interactions need to be further elucidated. Inhibition of MEK/ERK signaling pathway leads to enhanced VISTA expression and thus in mesothelioma, MEK inhibition is not likely to have a VISTA-mediated immunotherapy effect.

Keywords: mesothelioma, VISTA, MEK

EP.02C TUMOR BIOLOGY - PRECLINICAL BIOLOGY - IMMUNE MODULATION
SATURDAY, SEPTEMBER 7, 2024 - 11:58 - 11:59

EP.02C.02 Stearic Acid but Not Palmitic Acid Induces Immunomodulatory Changes that Initiate Pro-Neoplastic Processes in Lung Epithelium

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Introduction: Lung cancer (LC) detection and survival rates have steadily improved in part due to LC screening (LCS). However, a substantial number of patients need to be screened in order to detect one LC. Improving our understanding of the underlying biology of individuals who go on to develop LC is paramount.

Recent research indicates that changes in both the immune and metabolic microenvironments are critical factors for tumorigenesis. We recently demonstrated that in patients with resectable, early-stage LC, elevated levels of stearic acid (SA) and macrophage inflammatory protein 1β (MIP-1β/CCL4) were predictive of tumor-affected lung lobes. This suggests that SA might promote LC tumorigenesis via macrophage-dependent immunomodulation.

Palmitic acid (PA), the most abundant fatty acid (FA) in the human body, is structurally very similar to SA. Both PA and SA are saturated long-chain FAs, differing only in the number of carbons present. Both PA and SA are present in the lung microenvironment, with PA found at a higher concentration, and both are known to modulate innate immunity through macrophage activity. Based on our previous findings that SA is enriched in the serum of early stage LC patients, we hypothesize that SA, and not PA, is required for the immunometabolic changes that lead to the development of LC.

Methods: THP-1 monocytic cells were treated with PMA to induce differentiation into dedifferentiated macrophages. They were then stimulated with SA or PA. After 24hr both the THP-1 macrophages and the conditioned media (CM) were harvested. Expression levels of markers of macrophage differentiation were analyzed by quantitative PCR. The effect of the FA stimulated macrophage CM on cell proliferation was tested by real time IncuCyte live cell analysis using LC (H358, H2122) and immortalized non-cancerous lung epithelial (BEAS2B) cell lines. The LC and non-cancerous cell lines were also treated with SA and PA separately, and proliferation was measured by MTT assay. The effect of FA-stimulated macrophage CM on neoplastic transformation was studied using anchorage independent growth assays.

Results: THP-1 macrophages treated with SA demonstrated a pronounced upregulation of cellular markers, like Arg1 and CD206, which are specific for immunogenic macrophages, and the CM derived from these cells induced proliferation of BEAS2B cells. These effects were not observed in PA-stimulated macrophages or with the CM derived from them. Cell lines treated directly with either SA or PA did not demonstrate increased proliferation when assessed by MTT, indicating that the proliferation observed is macrophage-dependent.

Conclusions: SA promotes transformation of lung epithelial cells into a more proliferative precancerous or cancerous phenotype through an immunomodulatory pathway. However, PA does not demonstrate similar effects. Whether the observed effects are truly SA-specific or the result of FA enrichment will be the basis for future experiments. In the future, understanding the biology of FA-induced inflammation in LC may lead to the development of novel therapeutics which aim to attenuate pro-tumorigenic inflammation. Additionally, SA may be exploited as a potential biomarker of LC development, leading to novel LC detection assays and improved risk prediction modeling in high risk LCS individuals.

Keywords: tumor initiation, fatty acid, macrophage

EP.02D.01 Macrophage Migration Inhibitory Factor Promotes Invasion and Epithelial to Mesenchymal Transition in Lung Adenocarcinoma

R.R. Hudlikar, H. Wang, S.K. Gara, M.R. Zhang, D.S. Schrump, S.R. Carr, National Cancer Institute, Bethesda/MD/USA

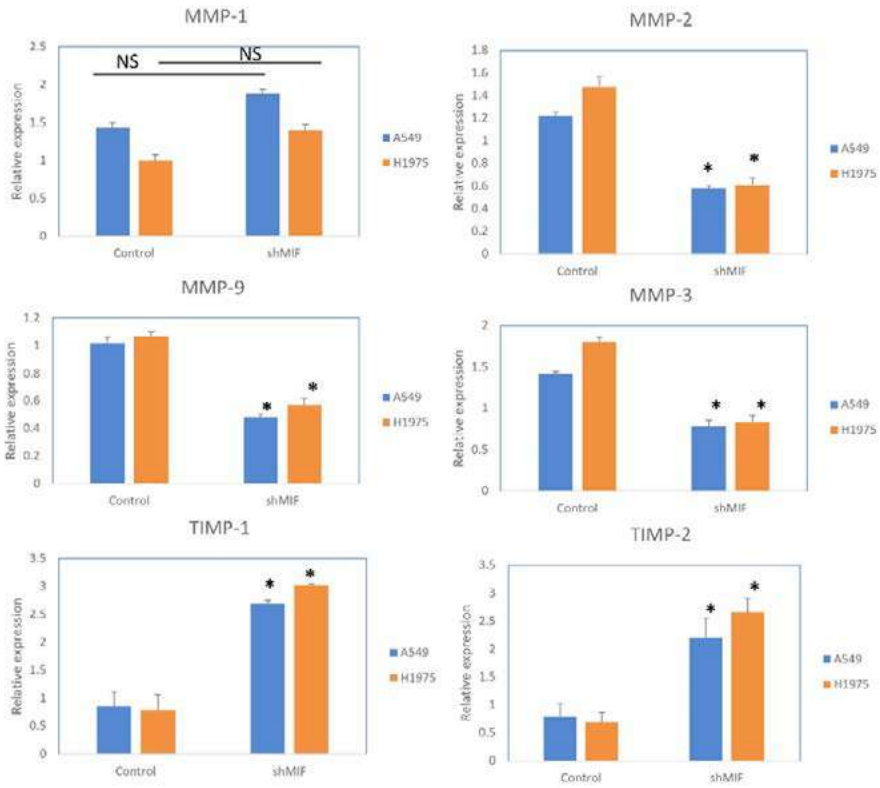
Introduction: Interventions aimed at targeting components of the tumor microenvironment (TME) have shown promise for many solid tumors yet only marginally tested for in lung adenocarcinoma (LUAD). Earlier we identified macrophage migration inhibitory factor (MIF) as an important gene associated with recurrence free survival (RFS) in LUAD. However, limited knowledge exists regarding its mechanism of action in the TME suggesting the association of MIF with RFS. Herein we investigated the role of altered MIF expression on migration, invasion, and epithelial to mesenchymal transition (EMT) in LUAD.

Methods: Gene Expression Omnibus (GEO) transcriptomic datasets from European and North American patients with LUAD were analyzed for MIF expression and correlated with recurrence. MIF expression was studied in Tissue Microarray (TMA) using immunohistochemistry and digital analysis (HALO). Immunofluorescence and immunoblotting techniques were used to evaluate MIF expression in a panel of LUAD and immortalized normal respiratory epithelial lines. MIF downregulation was induced either using Ibudilast (MIF inhibitor) or stable lentiviral transfection (shRNA) in A549 or H1975 LUAD cells, which exhibit elevated endogenous MIF. Cellular proliferation, invasion, migration, colony formation, and expression of EMT markers were assessed to elucidate effects from MIF downregulation. Further effect of downregulation of MIF on cisplatin sensitivity was also evaluated.

Results: GEO analysis demonstrated an association between elevated MIF and poor RFS in patients with LUAD. Immunohistochemical and HALO analysis of TMAs confirmed elevated MIF in LUAD compared to normal lung tissues. Downregulation of MIF significantly reduced cell proliferation; decreasing expression of phosphorylated Erk. Downregulation of MIF decreased invasion and migration with concomitant decreasing c-Jun phosphorylation by reducing the levels of MMP-2 and 9 but not MMP-1 or 3. The shRNA mediated inhibition of MIF increased the expression of TIMP-1 and 2 by regulating the levels of MMP-2 and 9 (Fig 1) and decreased N-cadherin and vimentin via modulation of snail/slug pathway, potentially promoting EMT in LUAD cells. An increased sensitivity to cisplatin was also observed with downregulation of MIF.

Conclusions: Our study demonstrated MIF promotes invasion and migration in LUAD by upregulating MMP-2 and MMP-9 via the c-Jun/slug/N-cadherin axis along with increased cisplatin resistance, which can be attenuated with a pharmacological MIF inhibitor. This opens a novel target that can potentially be leveraged in the treatment of LUAD.

Keywords: Lung Adenocarcinoma, Macrophage Migration Inhibitory Factor



EP.02E TUMOR BIOLOGY - PRECLINICAL BIOLOGY - NOVEL MODELS/NOVEL TECHNOLOGIES
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EP.02E.01 Development of Patient-Derived and Xenograft-Derived Organoids for Lung Adenocarcinoma Study

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Introduction: Lung adenocarcinoma (LUAD) presents a significant global health challenge, characterized by complex genetic aberrations within tumors. However, the inherent differences between primary tumors and many in vitro models have hampered advancements in elucidating LUAD pathogenesis. Directly generated from human tissues, the LUAD organoids preserve the genetic, transcriptomic, and phenotypic traits of originating patient tumor. Our research aims to develop advanced preclinical models for future LUAD studies.

Methods: Written consent was obtained from enrolled LUAD patients. Fresh lung and LUAD cells were isolated from nontumoral lung and LUAD tissues. After being embedded in Matrigel, the lung and LUAD organoids were cultured according to different mediums shown in Table 1. Tumor cells were injected into NSG mice for the generation of patient-derived xenografts (PDX). In parallel, xenograft cells were also isolated from PDX and cultured into xenograft-derived organoids. A schematic diagram of tissue culture was presented in Figure 1A. Pathohistological analysis and next-generation sequencing were performed on established organoids and matched patient tissues for characterization.

Table 1: Overview of culture medium components for lung and LUAD organoids

Results: Morphologically, lung organoids exhibited cystic structures with a single-layer compartment, whereas LUAD organoids manifested as densely packed spheroids with significantly thickened walls (Figure 1B). The lung organoids recapitulated the phenotype feature with the expression of alveolar type II cell markers (SFTPC and SFTPB) and alveolar type I cell marker (AQP5). LUAD organoids demonstrated distinct immunomarker expression profiles of TTF-1 and Napsin A. Whole-exome sequencing and transcriptome revealed genetic patterns and dominant mutational changes in organoids that are consistent with matched parental tissues.

Conclusions: Our lab has developed nontumoral lung and LUAD organoids directly from patients and PDX, whereby we provide robust experimental models for future studies. The comprehensive investigation into the phenotypic and genetic profiling of these organoids holds substantial promise for facilitating translational and individualized therapeutic strategies in the management of LUAD patients.

Keywords: organoid, lung adenocarcinoma

Lung organoid medium		**LUAD organoid medium**	
Components	Concentration	Components	Concentration
AIM-V medium	500 ml	Advanced DMEM/F12 medium	500 ml
L-Glutamine	2 mM	L-Glutamine	2 mM
B27	50x diluted	B27	50x diluted
Noggin	25 ng/ml	Noggin	25 ng/ml
N-Acetyl-L-cysteine	1 mM	N-Acetyl-L-cysteine	1.25 mM
Insulin-Transferrin-Selenium	100x diluted	HEPES	10 mM
Pen-Strep	0.35 U/ml	Antibiotic-Antimycotic	100 U/ml
Wnt3a-conditioned medium	30%	A-83-01	0.5 µM
R-spondin1-conditioned medium	10%	Y-27632	10 µM
N2 supplement	100x diluted	CHIR99021	250 µM
MEM Non-Essential Amino Acids	100x diluted	SAG	100 µM
Nicotinamide	10 mM		
recombinant human EGF	100 ng/ml		
recombinant human FGF10	100 ng/ml		
recombinant human HGF	25 ng/ml		
Leu-15-GastrinI human	10 nM		
Forskolin	10 mM		
A8301	3 µM		

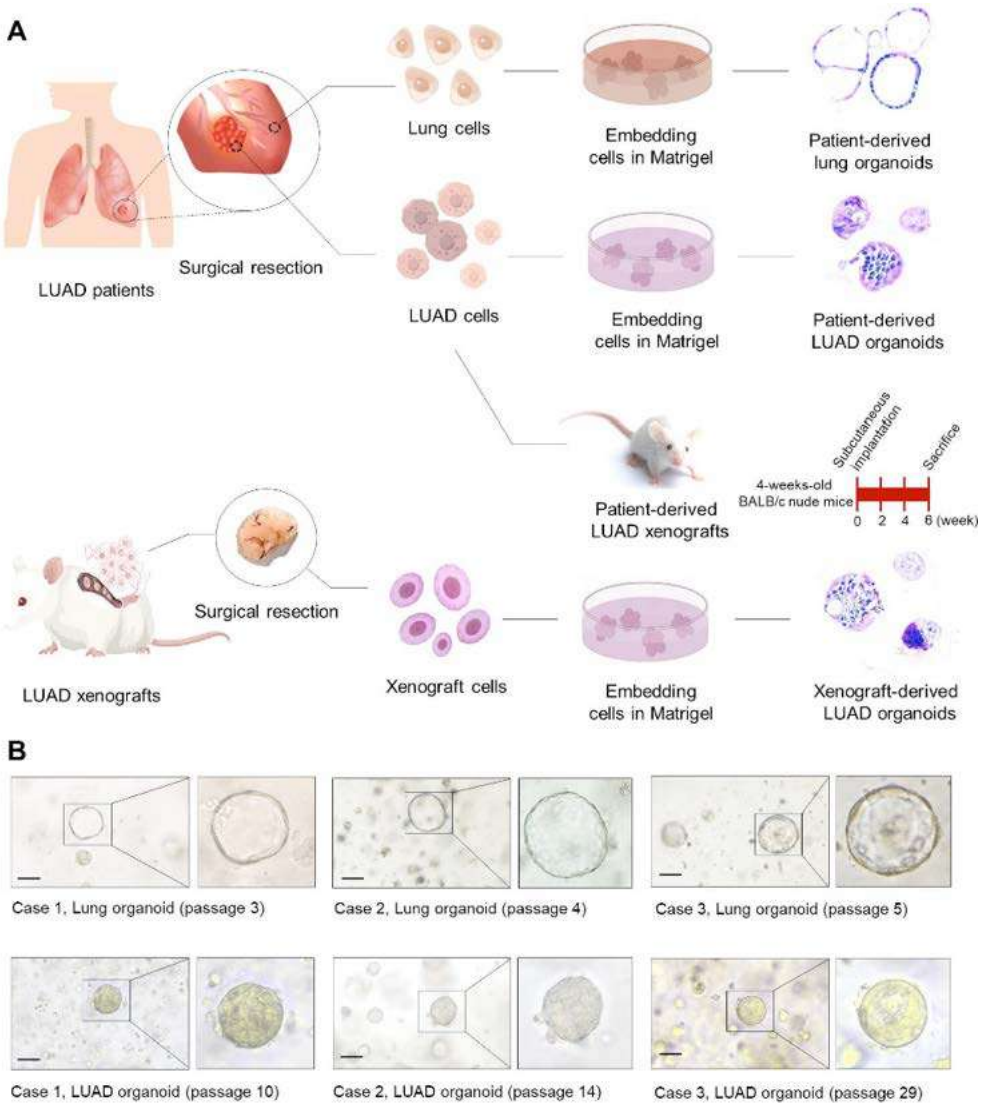

Figure 1: A. Schematic diagram of tissue culture of lung and LUAD organoids; B. Morphology of lung and LUAD organoids. Scale bar, 200μm.

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EP.02F.01 Berberine and Osimertinib Inhibit Progression of EGFR-TKI Primary and Acquired Resistant NSCLC Cells by a Multimodal Intervention

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Introduction: Lung cancer is a prevalent malignancy in the world, leading to significant mortality rates. The emergence of acquired resistance to EGFR-TKIs poses a challenge in treating NSCLC patients effectively. Osimertinib (Osi), a third-generation EGFR-TKI, is commonly used but resistance development limits its long-term efficacy. Berberine (BBR), a natural compound, exhibits diverse anti-cancer properties. The aims of this study is to elucidate the inhibitory mechanism of combined Osi with BBR in treatment of NSCLC and evaluate the effectiveness of nano-drugs carrying these agents for treating Osi-resistant cells.

Methods: EGFR wild-type NSCLC cells (A549 and H460) and EGFR mutant NSCLC cells (H1975 OR and HCC827 OR) were utilized. The synergistic effects of Osi and BBR on NSCLC cells were assessed through colony formation, EdU staining, cell cycle, and apoptosis. Metastasis-related phenotypes were examined using wound healing, transwell, adhesion, and tube formation assays, along with cytoskeleton staining. Western Blot analysis was conducted to detect changes in proteins associated with cell cycle, apoptosis, and tumor metastasis. The synergistic effects of Osi and BBR were also investigated by xenograft models in nude mice and lung cancer organoids. Finally, liposomes encapsulating Osi and/or BBR, loaded with EGF as a targeting peptide and fluorescently labeled with FITC, were synthesized to create a new nano-drugs. The anticancer mechanism of nano-drugs was preliminarily explored through experiments.

Results: The combination of BBR and Osi synergistically inhibited the proliferation and metastasis of EGFR-TKI primary and acquired resistant cells and resulted in inhibited proliferation and colony formation, as well as decreased migration, invasion and adhesion ability of tumor cells. Meanwhile, formation of vascular-like structures of HUVEC and tumor cells was inhibited. Morphology of microtubules and microfilaments related to cytoskeleton was changed and apoptosis was increased after treatment with Osi combined BBR. Moreover, Osi and BBR combination inhibited the growth of NSCLC in nude mice and lung cancer organoids. Targeted nano-drugs carrying Osi and/or BBR selectively accumulated in NSCLC cells with high EGFR expression. Compared to nano-drugs carrying single agents, nano-drugs carrying Osi and BBR exhibited significant effect of inhibited proliferation and metastasis of tumor cells.

Conclusions: The combination of BBR and Osi synergistically inhibited the proliferation of EGFR-TKI primary and acquired resistant NSCLC cells, induced cell cycle arrest and apoptosis. The combination of two drugs inhibits tumor metastasis by inhibiting tumor migration, invasion, cell adhesion, decreasing tumor angiogenesis and changing the structure of microtubules and microfilaments. Targeted nano-drugs carrying Osi and/or BBR could selectively enriched in NSCLC cells with high EGFR expression and significantly inhibited the proliferation and metastasis of tumor cells in vitro and in vivo.

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EP.02F.02 Individual and Combined Effects of Annonacin and 2-Deoxy-D-Glucose on Non-Small Cell Lung Cancer Cells

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Introduction: Non-Small Cell Lung Cancer (NSCLC) is the most common type of cancer, accounting for approximately 81% of all lung cancer cases, and remains a leading cause of cancer-related mortality worldwide. Despite advancements in cancer treatment, the five-year survival rate of NSCLC is low, warranting the urgent need for innovative and effective therapeutic approaches to treat it. The aberrant energy metabolism, which is a hallmark of cancer, including NSCLC, known as the Warburg effect, makes it a potential target for therapeutic interventions. Annonacin, a natural compound, has shown promise in targeting key metabolic pathways, inhibiting mitochondrial complex I, and exploiting the altered energy dynamics of cancer cells. In contrast, 2-Deoxy-D-Glucose (2DG) is a glucose analog, that has been widely studied for its ability to target the glycolytic pathway of energy metabolism. This investigation tests both glycolytic inhibitor and mitochondrial complex I inhibitor individually and in combination to target energy metabolism to inhibit A549 cell growth and explore their potential as novel antitumor agents and to treat NSCLC therapeutically.

Methods: The study was carried out in an in vitro model system using the A549 NSCLC cell line, where the NL20 Bronchial Epithelium cell line was used as a parallel control. Cells were treated with 0 μM, 2 μM, 4 μM, and 6 μM concentrations of Annonacin and 0 mM, 2.5 mM, 5 mM, and 10 mM concentrations of 2DG, both individually and in combination in triplicate experimental design with control. The MTT assay was employed to determine immediate cell viability and to assess the cytotoxic effects of applied treatments. The DNA damage induced by treatments was evaluated using a Comet Assay also called Single Cell Gel Electrophoresis. The oxidative stress in treated and control cells was determined through assays of superoxide dismutase and glutathione peroxidase. Furthermore, the long-term proliferative capacity of the cells post-treatment was examined using a colony-forming assay.

Results: Preliminary results indicate that both Annonacin and 2DG when used individually, exhibit a dose-dependent inhibitory effect on the viability of A549 cells. The combined application of 2DG and Annonacin showed a synergistic effect, resulting in a significant reduction in cell viability compared to individual applications. The Comet Assay revealed increased DNA damage in cells treated with the combination of Annonacin and 2DG, suggesting enhanced genotoxic stress. In addition, treated cells exhibited alterations in the activities of glutathione peroxidase and superoxide dismutase, indicating changes in the oxidative stress response. The colony-forming assay revealed a decrease in the long-term proliferative capacity of cells treated with the combination of Annonacin and 2DG.

Conclusions: The combination of Annonacin and 2DG has a synergistic effect on inhibiting the growth of A549 cells. The observed increase in DNA damage and alterations in the oxidative stress response further support the potential of this combined treatment as an effective therapeutic strategy for NSCLC. These findings need further investigation to elucidate the detailed underlying mechanisms and explore the in vivo and clinical applicability details for the combined administration of Annonacin and 2DG's use in NSCLC treatment.

Keywords: Cell viability, DNA damage, Oxidative stress

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EP.02F.03 Elucidating the Role of XRCC6BP1 In Mitochondrial Bioenergetics and Metabolism in Non-Small Cell Lung Cancer

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Introduction: X-Ray Repair Cross Complementing 6 Binding Protein 1 (XRCC6BP1) plays a key role in DNA double-stranded break (DSB) repair. Recent studies in our group identified XRCC6BP1 as a prognostic marker in patients with non-small cell lung cancer (NSCLC). The relationship between mitochondrial bioenergetics and DNA damage repair remains unclear. In this study, we explored the potential link between DNA damage repair, mitochondrial function and metabolism in NSCLC.

Methods: Stable transfected NSCLC cell lines (H460, A549, SKMES-1), representing large cell carcinoma, adenocarcinoma and squamous cell carcinoma histology, were generated using XRCC6BP1 shRNA and control lentivirus particles. The effect of XRCC6BP1 knockdown on the expression of 84 genes involved in mitochondrial biogenesis and function was assessed using human Mitochondria RT^2 Profiler PCR Arrays. These comprised of regulators and mediators of mitochondrial molecular transport, ions required for maintaining mitochondrial membrane polarization, ATP synthesis, in addition to intrinsic apoptosis pathway genes activated by intracellular damage signaling. Genes that were significantly upregulated or downregulated in response to XRCC6BP1 knockdown were validated by qPCR. Gene expression was also examined in an isogenic panel of matched parental and cisplatin resistant A549 and SKMES-1 NSCLC cells. Tumor cell apoptosis was assessed using Annexin V/propidium iodide staining by flow cytometry in the presence or absence of the DNA damaging agent, cisplatin (IC50). Cell metabolism and key parameters of mitochondrial function were examined using the SeahorseXF24 Cell Mito Stress Test kit in XRCC6BP1 shRNA and control shRNA lung cancer cells.

Results: Relative to control shRNA cells, 19 genes involved in mitochondrial function were significantly altered in XRCC6BP1 shRNA transfected A549 NSCLC cells compared to 5 genes in SKMES-1 cells. Two genes (AIP and UCP2) were upregulated in both cell lines while one gene (SLC25A12) was increased in A549 cells but decreased in SKMES-1 cells. Of interest, when data from similar arrays were assessed for H460 cells, UCP2 was found to be upregulated in all three lung cancer cell lines. Validation of these findings confirmed a significant increase ($p<0.001$) in UCP2 gene expression in XRCC6BP1 shRNA A549 cells relative to shRNA controls. Expression was also significantly increased ($p<0.01$) in cisplatin resistant A549 cells relative to their parental (sensitive) counterparts. Cisplatin induced significant apoptosis of XRCC6BP1 shRNA A549 and XRCC6BP1 shRNA SKMES-1 cells treated with cisplatin (IC50). These were comparable to levels of apoptosis observed in control cells. There were no significant differences between XRCC6BP1 shRNA A549 or XRCC6BP1 shRNA SKMES-1 cells relative to their control shRNA counterparts when baseline extracellular acidification rate, coupling efficiency, proton leak, non-mitochondrial oxygen consumption and spare respiratory capacity were examined. Basally, oxygen consumption rate (OCR) was significantly higher in A549 cells, while SKMES-1 cells had a significantly increased spare respiratory capacity ($p<0.01$) and diminished proton leak ($p<0.05$).

Conclusions: Our data show that UCP2 is upregulated in different NSCLC subtypes in response to XRCC6BP1 knockdown. Significant differences in the levels of proton leak and spare respiratory capacity between NSCLC cell lines highlights the different metabolic phenotypes that exist between adenocarcinoma and squamous cell lung cancers.

Keywords: DNA repair, Metabolism, Mitochondria

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EP.02F.04 Development and Validation of an ADRB2-based Prognostic Model for Non-Small Cell Lung Cancer

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Introduction: ADRB2 (β2-adrenergic receptor) is upregulated in various malignant tumors, including non-small cell lung cancer (NSCLC), and associated with unfavorable disease advancement. Developing an ADRB2-based clinical score will facilitate the discovery of novel prognostic biomarkers and prospective targets for NSCLC.

Methods: Dysregulated genes associated with ADRB2 were identified by differential expression analysis of NSCLC from the TCGA database. Then, biological processes and signaling pathways involved in these genes were explored. An ADRB2-based clinical score model was constructed, and its relationship with immune checkpoint genes or immune cell infiltration was calculated by the CIBERSORT algorithm. Potential upstream regulatory mechanisms and therapeutic targets associated with the ADRB2-related genes were investigated using multi-omics data. A global network regulation model was developed.

Results: 5270 differentially expressed genes (DEGs) and 93 differentially expressed miRNAs (DemiRNAs) were identified as factors affected by ADRB2 in NSCLC. Dysregulated genes associated with ADRB2 were involved in the JAK-STAT signaling pathway and cytokine-cytokine receptor interactions, important for angiogenesis. High ADRB2 expression significantly positively correlated with immune checkpoint genes and infiltration of immune cells.

Conclusions: The ADRB2-based score clinical model has been develop, which predicts the prognosis of NSCLC patients and suggests possible therapeutic targets.

Keywords: ADRB2, Immune microenvironment, Prognosis

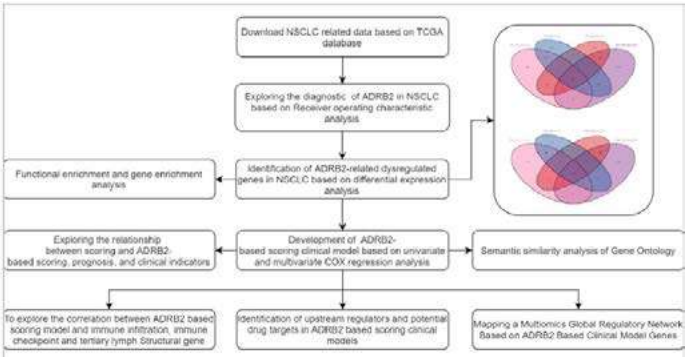

Figure 1. Flow chart of this study. Wayne diagram described DEGs and DEmiR. TCGA: The Cancer Genome Atlas; DEG: Differentially Expressed Gene; DEmiR: Differentially Expressed miRNA

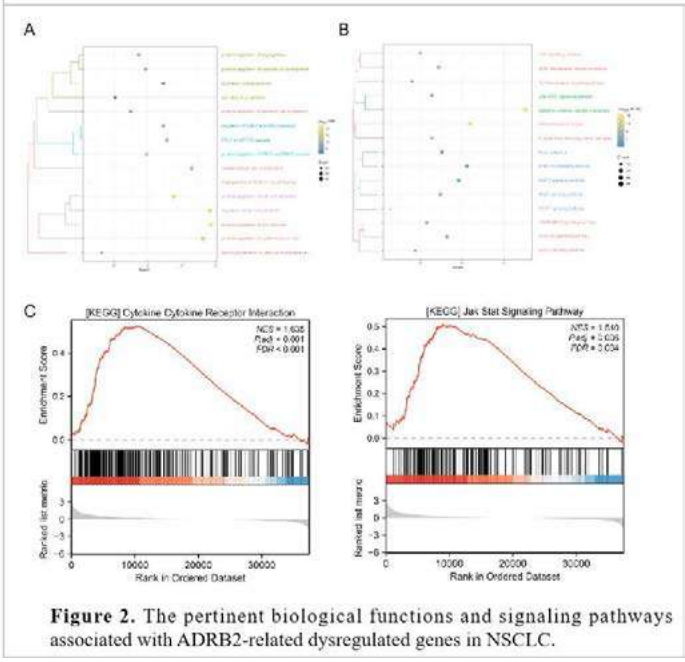

Figure 2. The pertinent biological functions and signaling pathways associated with ADRB2-related dysregulated genes in NSCLC.

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EP.02F.05 Lysosomal Calciumrelease via TRPML3 Enhances Drug Sensitivity of Gefitinib-resistance NSCLS Cells

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Introduction: Lysosomes have recently gained prominence as pivotal signaling hubs implicated in drug resistance within cancer cells. However, the precise role of Transient receptor potential mucolipin 3 (TRPML3), an endo-lysosomal calcium-permeable channel known to regulate lysosomal trafficking during endocytosis and autophagy, remains enigmatic in the context of cancer progression. This study aimed to elucidate the involvement of TRPML3 in modulating exosomal release triggered by lysosomal exocytosis during the development of gefitinib resistance in non-small cell lung cancer (NSCLC).

Methods: Exosomal counts and cell-cycle analysis were conducted by flow cytometry and western blot analysis. Ratiometric assays and enzymatic activity assessments were performed to investigate calcium signaling, lysosomal pH, and lysosomal exocytosis

Results: Our finding revealed that gefitinib-resistant NSCLC cells, HCC827/GR, exhibited significantly higher basal exosomal release and lysosomal exocytosis compared to gefitinib-sensitive NSCLC cells, HCC827. This difference was associated with an increased expression of TRPML3 in HCC827/GR cells. Furthermore, we observed a close correlation between the elevated exosomal release and lysosomal exocytosis and the upregulation of TRPML3 expression. Notably, the triggering of lysosomal calcium release through TRPML3 was facilitated by gefitinib-induced elevation of lysosomal pH. Our investigation demonstrated that deficiency of TRPML3 resulted in gefitinib-induced cell death, as indicated by the accumulation of Sub-G0 population, hindered cell proliferation, and facilitated poly (ADP-ribose) polymerase cleavage.

Conclusions: In summary, our data demonstrate the emerging role of TRPML3 as a molecular factor in anti-cancer drug resistance. By effectively sensing lysosomal pH acidification, TRPML3 orchestrates lysosomal calcium release, subsequently influencing lysosomal trafficking, exocytosis, and exosomal release. This study contributes to comprehending the defense mechanisms that developed by acquired drug resistance to tyrosine kinase inhibitor gefitinib in NSCLC cells.

Keywords: gefitinib, drug sensitivity, lysosomal calcium

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EP.02F.06 Suppression of Chemotherapy Induced Antiviral Signaling by YAP/TAZ in Lung Cancer

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Introduction: Chemotherapy is widely used to treat lung cancer (LC) and initially induces tumour regression in most patients; however, chemoresistance inevitably develops. Thus, an improved understanding of the biology driving chemoresistance is needed to enhance chemotherapeutic efficacy in patients. YAP and TAZ are transcriptional regulators whose overactivation is well-documented to promote LC chemoresistance. Interestingly, some chemotherapies induce antiviral signaling in tumours, which contributes to their anti-cancer effects. Moreover, recent studies suggest that YAP/TAZ antagonize antiviral immunity by suppressing induction of type I interferons and interferon stimulated genes (ISG). Therefore, we hypothesize that YAP/TAZ-mediated suppression of antiviral signaling induced by chemotherapy represents a previously unrecognized mechanism of LC chemoresistance. Here, we investigated whether YAP/TAZ suppress chemotherapy-induced antiviral signaling in LC models as the first step in testing this hypothesis.

Methods: qPCR was used to assess gene expression of the type I interferon, IFNβ, in several lung adenocarcinoma (LUAD) cell lines with different levels of YAP/TAZ protein expression under basal conditions. LUAD lines with high (H1299, H2030) and low YAP/TAZ expression (H2122) were transfected with siRNA to knockdown YAP and/or TAZ, or a non-targeting control siRNA (siNTC). Cells were then treated with chemotherapies including cisplatin, doxorubicin and paclitaxel for 48 hours; or Poly(I:C) for 4 hours as a positive control for inducing antiviral signaling. qPCR was used to measure expression of IFNβ and the ISGs, OASL and CCL5 as readouts of antiviral signaling.

Results: Basal IFNβ expression was negatively correlated with YAP/TAZ expression in a panel of 7 LUAD cell lines, consistent with YAP/TAZ suppression of antiviral signaling. Poly(I:C) stimulation of H1299 cells (YAP/TAZ high) with YAP or TAZ knockdown led to a 2-3-fold increase in IFN-β expression, while combined YAP/TAZ depletion induced a 5-fold increase in IFN-β relative to cells transfected with siNTC. These results provide functional evidence that YAP/TAZ suppress antiviral signaling in LC cells. Similarly, chemotherapy treatment of H1299 cells with YAP or TAZ knockdown led to a 2-3 fold increase, and combined YAP/TAZ depletion induced a 4-6 fold increase in CCL5 and OASL relative to siNTC. Another YAP/TAZ high model, H2030, showed similar results with chemotherapy treatment. In contrast, H2122 cells with low basal YAP/TAZ expression showed little to no change in CCL5 and OASL expression upon chemotherapy treatment and little to no change in IFN-β expression with Poly(I:C) treatment when YAP and/or TAZ were depleted.

Conclusions: Our results suggest that YAP/TAZ suppression of chemotherapy induced antiviral signaling could contribute to chemoresistance. We plan to complement these knockdown experiments with YAP/TAZ overexpression and studies to determine whether YAP/TAZ-mediated suppression of antiviral signaling affects the sensitivity of LC models to chemotherapy. Our work illuminates a new putative mechanism for YAP/TAZ-mediated chemoresistance that could rationalize the use of YAP/TAZ inhibitors or drugs that augment antiviral signaling to enhance the efficacy of chemotherapy in LC.

Keywords: YAP/TAZ, Antiviral Signaling, Chemoresistance

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EP.02F.07 Targeting NRAS Increases Lung Adenocarcinoma Sensitivity to Paclitaxel Chemotherapy

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Introduction: This project investigates the role of NRAS in the resistance of lung adenocarcinoma to paclitaxel. By combining transcriptome data analysis and in vitro experiments, it aims to propose a new strategy for improving the treatment outcomes of lung adenocarcinoma.

Methods: Initially, transcriptome data from The Cancer Genome Atlas (TCGA) and several other genomic databases were analyzed. We also investigated NRAS expression in various stages of LUAD to assess its correlation with disease progression. Subsequently, Gene Set Enrichment Analysis was utilized to identify genes and pathways associated with NRAS. Vitro experiments were also performed, which involved culturing various LUAD cell lines and using siRNA to knock down NRAS in these cell lines. Functional assays such as cell viability tests and scratch assays were then employed to confirm changes in drug sensitivity following NRAS knockdown.

Results: Our extensive analysis revealed a striking up-regulation of NRAS in LUAD tissues compared to normal lung tissues. This over-expression was more pronounced in advanced stages of LUAD. Importantly, higher levels of NRAS expression were correlated with poorer patient outcomes. Furthermore, patients with high NRAS expression exhibited decreased sensitivity to paclitaxel, indicating a potential mechanism of drug resistance. The GSEA highlighted significant enrichment of NRAS-related genes in pathways involved in the cell cycle, DNA damage response, and repair mechanisms. This suggests that NRAS may contribute to paclitaxel resistance through these pathways. In vitro experiments, LUAD cell lines with NRAS knockdown demonstrated markedly increased sensitivity to paclitaxel. This was evident in reduced cell proliferation and increased apoptosis rates upon treatment with the drug, compared to control cell lines.

Conclusions: Targeting NRAS, therefore, emerges as a promising therapeutic strategy. By inhibiting NRAS, it may be possible to enhance the efficacy of paclitaxel, thereby improving treatment outcomes for patients with LUAD.

Keywords: NRAS, Paclitaxel Chemotherapy, Sensitivity

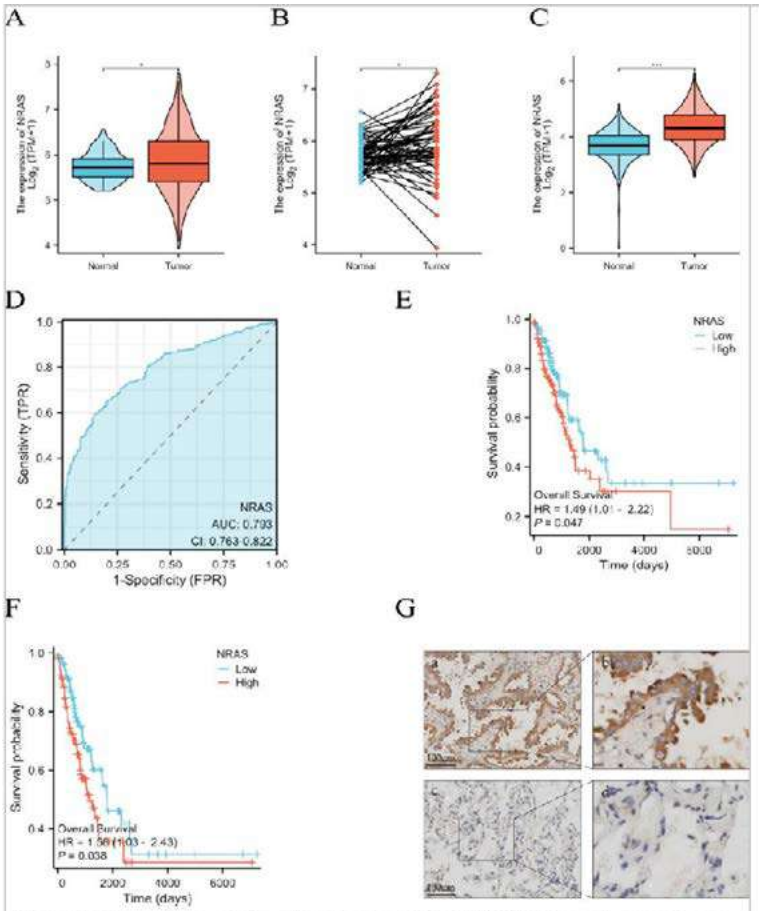

Figure 1: Expression analysis and survival analysis of NRAS in lung adenocarcinoma. A. Relative mRNA expression of NRAS in the TCGA-LUAD database. b. Relative mRNA expression of NRAS in LUAD tissues and their paired normal tissues in the TCGA database. c. Relative mRNA expression of NRAS in the TCGA-LUAD+GTEx database. d. ROC curves of the LUAD prognostic model. e, f. Relative survival analyses of NRAS in the TCGA associated with the survival analysis associated with NRAS high and low expression groups.G. NRAS expression in LUAD tissue (a, b) and normal lung tissue (c, d) in LUAD tissue microarray (TMA). (*P < 0.05, **P < 0.01, ***P < 0.001).

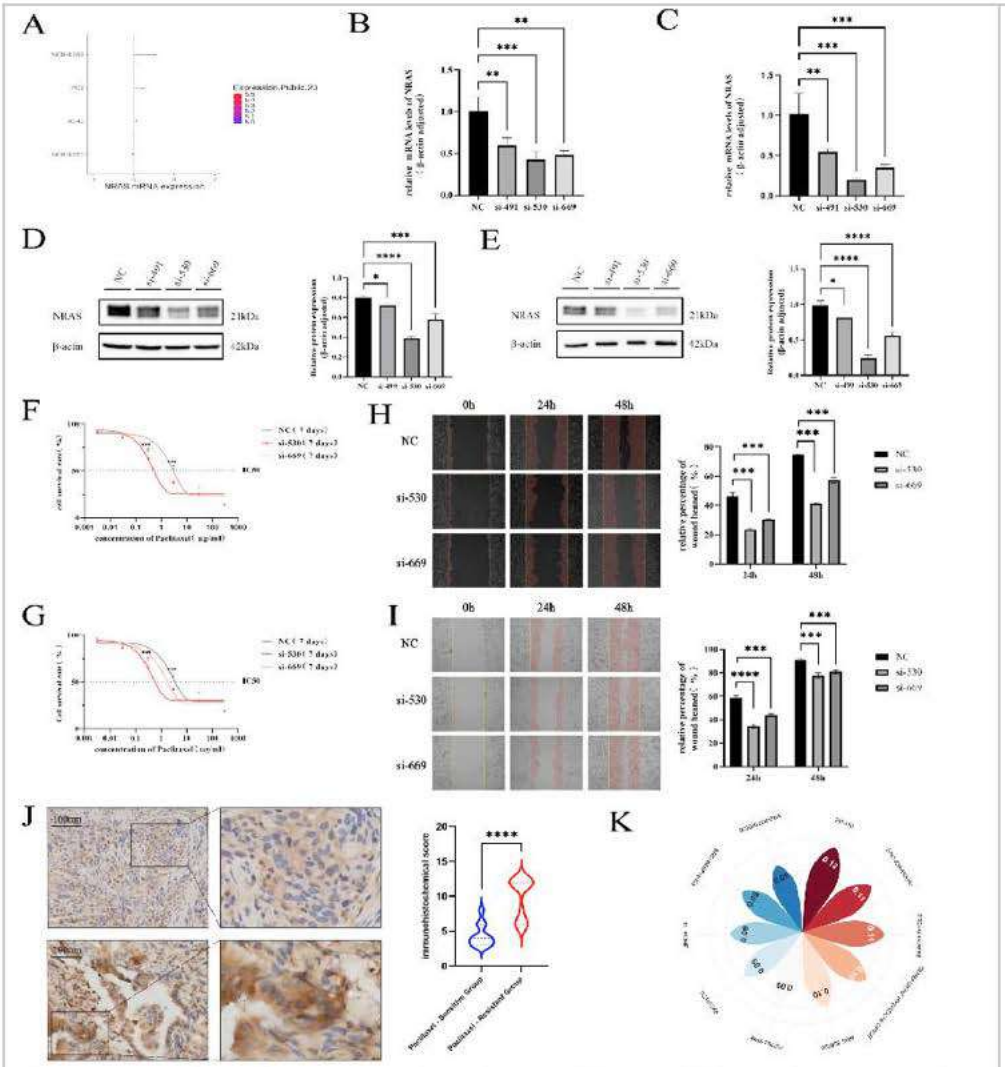

Figure 2: Expression and functional analysis of NRAS in different cell lines and assessment of sensitivity and resistance to paclitaxel .

A. Gene expression levels of NRAS in multiple cell lines were analyzed in the CCLE database. b, D. Validation of NRAS knockdown using 3 siRNAs in H1299 cell line by q-PCR (B) and Western Blot (D). c, E. Validation of NRAS knockdown using 3 siRNAs in PC9 cell line by q-PCR (C) and Western Blot (E).F. Cell survival was assessed in H1299 cell line using CCK8 assay with IC50 of 3.038ug/ml in NC group, 0.509ug/ml in Si-NRAS-530 group and 1.525ug/ml in Si-NRAS-669 group.G. CCK8 assay was used in PC9 cell line to To assess cell survival, the IC50 was 3.415ug/ml in the NC group, 0.584ug/ml in the Si-NRAS-530 group, and 1.739ug/ml in the Si-NRAS-669 group.H. Data from three representative wound healing migration experiments in the H1299 cell line (each group was treated with 3ug/ml paclitaxel).I. PC9 Data from three representative wound healing migration experiments in cell lines (each group was treated with 3.5ug/ml paclitaxel). J. Immunohistochemical detection of NRAS expression in paclitaxel-sensitive and paclitaxel-resistant groups.K. Petaloid plots of drug prediction. (*P < 0.05, **P < 0.01, ***P < 0.001, ****P < 0.0001).

EP.02G TUMOR BIOLOGY - PRECLINICAL BIOLOGY - TUMOR MICROENVIRONMENT
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EP.02G.01 Differentiation and Metabolic Phenotypes of Lung Squamous Cell Carcinoma Organoids are Modified by the Tumor Microenvironments

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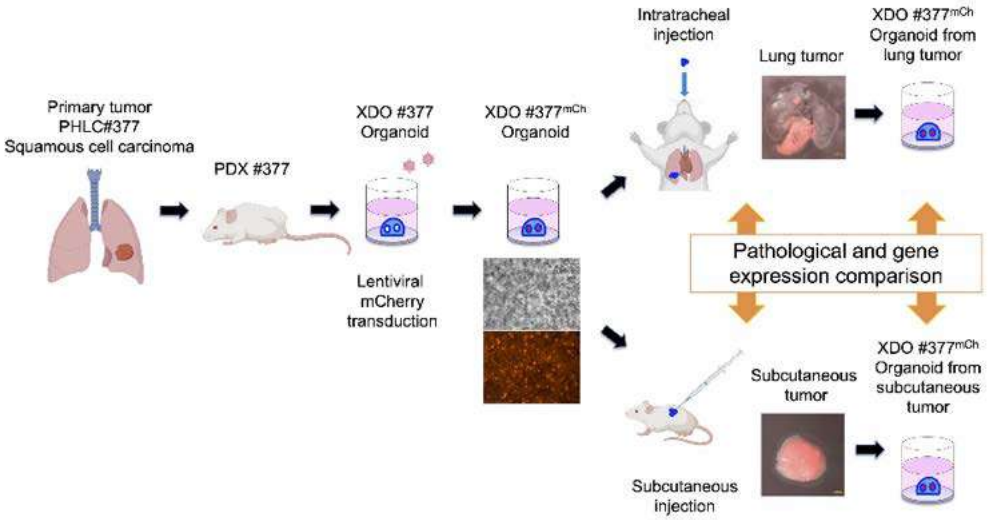
Introduction: Cancer organoids are recognized as a novel preclinical model retaining genetic and transcriptomic characteristics of the original tumors. In this study, we aimed to investigate the influence of the microenvironment on lung squamous cell carcinoma (SqCC) organoids.

Methods: We established a lung squamous cell carcinoma xenograft-derived organoid (XDO) model under organoid culture condition from a patient-derived xenograft (PDX) PHLC377 tumor. Lentivirus was used to transduce mCherry into XDO377 (referred to as XDO377mCh). We injected XDO377mCh subcutaneously and intratracheally into the lung of non-obese severe combined immunodeficient gamma (NSG) mice. We compared the pathology and gene expression profiles XDO377mCh-derived subcutaneous and lung tumors. Additionally, we established cancer organoids from both XDO377mCh-derived subcutaneous and lung tumors and compared their pathology and gene expression profiles with the parental XDO377mCh organoid (Figure).

Results: Pathological examination revealed a poorly differentiated non-keratinizing phenotype in the orthotopic lung tumors in mice, whereas the subcutaneous tumors and the parental tumor exhibited a moderately differentiated keratinizing SqCC. Immunohistochemistry showed stronger positivity for SqCC markers (P40, P63, SOX2) in the subcutaneous tumors compared to the lung tumors. RNA sequencing confirmed these findings, showing elevated expression of SqCC markers in the subcutaneous tumors compared to the lung tumors. GSEA hallmark analysis revealed significant upregulation of pathways related to “MTOR1 signaling”, “glycolysis”, and “hypoxia” in the subcutaneous tumors compared to the lung tumors. No significant differences in pathology or gene expression profiles were observed among the newly established cancer organoids derived from subcutaneous and lung tumors and the parental XDO377mCh.

Conclusions: Our findings suggest that the differentiation and metabolic status of lung squamous cell carcinoma are reversibly influenced by the tumor microenvironment. Cancer organoids can contribute to our understanding of the molecular mechanisms of tumor plasticity that is regulated by the microenvironment.

Keywords: lung cancer, cancer organoid, cancer microenvironment



EP.03A TUMOR BIOLOGY - TRANSLATIONAL BIOLOGY - BIOMARKERS
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EP.03A.01 Lung Cancer: Artificial Intelligence, Synergetics, Complex System Analysis, Statistics and Simulation of Alive Supersystems.

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Introduction: 5-survival (5YS) and life span after radical surgery for non-small cell lung cancer (LC) patients (LCP) (T1-4N0-2M0) - alive supersysems was analyzed. The importance must be stressed of using complex system analysis, artificial intelligence (neural networks computing), simulation modeling and statistical methods in combination, because the different approaches yield complementary pieces of prognostic information.

Methods: We analyzed data of 782 consecutive LCP (age=57.6±8.3 years; tumor size=4.1±2.4 cm) radically operated and monitored in 1985-2024 (m=670, f=112; upper lobectomies=282, lower lobectomies=179, middle lobectomies=18, bilobectomies=46, pneumonectomies=257, mediastinal lymph node dissection=782; combined procedures with resection of trachea, carina, atrium, aorta, VCS, vena azygos, pericardium, liver, diaphragm, ribs, esophagus=198; only surgery-S=626, adjuvant chemoimmunoradiotherapy-AT=156: CAV/gemzar + cisplatin + thymalin/taktivin + radiotherapy 45-50Gy; T1=326, T2=258, T3=137, T4=61; N0=525, N1=133, N2=124, M0=782; G1=199, G2=248, G3=335; squamous=422, adenocarcinoma=310, large cell=50; early LC=218, invasive LC=564; right LC=420, left LC=362; central=294; peripheral=488. Variables selected for study were input levels of 45 blood parameters, sex, age, TNMG, cell type, tumor size. Regression modeling, clustering, SEPATH, Monte Carlo, bootstrap and neural networks computing were used to determine significant dependence.

Results: Overall life span (LS) was 2252.1±1742.5 days and cumulative 5-year survival (5YS) reached 73.2%, 10 years - 64.8%, 20 years - 42.5%. 513 LCP lived more than 5 years (LS=3124.6±1525.6 days), 148 LCP - more than 10 years (LS=5054.4±1504.1 days).199 LCP died because of LC (LS=562.7±374.5 days). 5YS of LCP after bi/lobectomies was significantly superior in comparison with LCP after pneumonectomies (78.1% vs.63.7%, P=0.00001 by log-rank test). AT significantly improved 5YS (66.3% vs. 34.8%) (P=0.00000 by log-rank test) only for LCP with N1-2. Cox modeling displayed that 5YS of LCP significantly depended on: phase transition (PT) early-invasive LC in terms of synergetics, PT N0—N12, cell ratio factors (ratio between cancer cells- CC and blood cells subpopulations), G1-3, histology, glucose, AT, blood cell circuit, prothrombin index, heparin tolerance, recalcification time (P=0.000-0.038). Neural networks, genetic algorithm selection and bootstrap simulation revealed relationships between 5YS and PT early-invasive LC (rank=1), PT N0—N12 (rank=2), thrombocytes/CC (3), erythrocytes/CC (4), eosinophils/CC (5), healthy cells/CC (6), lymphocytes/CC (7), segmented neutrophils/CC (8), stick neutrophils/CC (9), monocytes/CC (10); leucocytes/CC (11). Correct prediction of 5YS was 100% by neural networks computing (area under ROC curve=1.0; error=0.0).

Conclusions: 5YS of LCP after radical procedures significantly depended on: 1) PT early-invasive cancer; 2) PT N0--N12; 3) cell ratio factors; 4) blood cell circuit; 5) biochemical factors; 6) hemostasis system; 7) AT; 8) LC characteristics; 9) LC cell dynamics; 10) surgery type: lobectomy/pneumonectomy; 11) anthropometric data. Optimal diagnosis and treatment strategies for LC are: 1) screening and early detection of LC; 2) availability of experienced thoracic surgeons because of complexity of radical procedures; 3) aggressive en block surgery and adequate lymph node dissection for completeness; 4) precise prediction; 5) adjuvant chemoimmunoradiotherapy for LCP with unfavorable prognosis.

Keywords: lung cancer, surgery, prediction

EP.03B TUMOR BIOLOGY - TRANSLATIONAL BIOLOGY - GENOMICS
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EP.03B.01 The Genomic Scarring Score as a Biomarker for the Use of PARP Inhibitors in Early-Stage Non-Small Cell Lung Cancer

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Introduction: Tumours with Homologous Recombination Deficiency (HRD) frequently arise due to germline or somatic BRCA1 or BRCA2 mutations and respond favourably to PARP inhibitors (PARPi). "Genomic scars" are the consequence of HRD and is measured using available diagnostic tools, which grade the tumours with a genomic scarring score (GSS). However, HRD may occur beyond the presence of genomic alterations in BRCA1, BRCA2 or any other homologous recombination repair (HRR) gene alteration. In this work, we sought to evaluate the GSS of operable non-small cell lung cancer (NSCLC) tumours and examine whether high GSS tumours can be successfully treated with PARPi independently of the presence of HRR gene mutations.

Methods: Using the available diagnostic panels (Amoy Dx®), we measured the GSS score and evaluated the HRR (germ line and somatic) gene alterations of 136 early-stage NSCLC tumours. HR deficiency was confirmed via staining for the formation of RAD51 foci. Patient-derived xenografts (PDX) were used to compare the response of HRD versus HRP (homologous recombination proficient) tumours to cisplatin or PARPi.

Results: High (>50) GSS was observed in 39 (28.5%) of the tumours and were considered to be HRD but only 13 (30%) of them harboured pathogenic/likely pathogenic (P/LP) germ line/somatic mutations; at the same time, 11 out of 97 patients (11.3%) with low GSS also carried P/LP HRR mutations, indicating that mutations in HR genes alone cannot explain the genomic instability phenotype in NSCLC. The incidence of pathogenic TP53 mutations was significantly higher in the HRD compared to HRP cohort (85% vs 50% respectively, p=0.001), while variant allele frequency of the TP53 mutations also showed a highly significant correlation (r=0.5648) with the GSS. Administration of PARPi significantly delayed tumour growth in high GSS but not in low GSS PDXs; moreover, the HR repair of cisplatin-induced double strand breaks, as evaluated by RAD51 foci formation, was also hampered in high GSS PDXs. Finally, there is a non-statistically significant trend for longer median DFS and OS for hGSS compared to lGSS patients, presumably because of the limited number of patients currently comprising the cohort and the incomplete patients' follow up

Conclusions: In this study, we present evidence that molecular traits compatible with HRD are evident in early-stage NSCLC. Preclinical data in PDXs indicate that these tumors might respond favourably to PARPi. Moreover, HRR gene mutations alone cannot account for all NSCLC cases that present a high GSS score, accompanied by reduced frequency, that would benefit from PARPi therapies. This study paves the way for the introduction to the clinic of PARPi in NSCLC for a subgroup of patients not necessarily defined by HRR gene mutations.

Keywords: non small cell lung cancer, homologous recombination deficiency, PARP inhibition

EP.03B TUMOR BIOLOGY - TRANSLATIONAL BIOLOGY - GENOMICS
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EP.03B.02 Association of Pre-Existing Conditions with Major Driver Mutations and Immune Contextures in Non-Small Cell Lung Cancer

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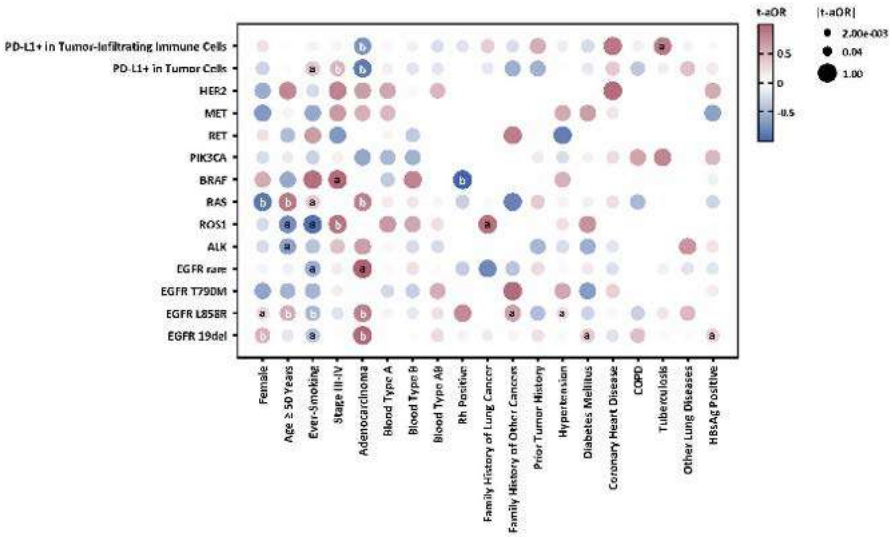
Introduction: The paradigm of therapies for non-small cell lung cancer (NSCLC) has evolved significantly with the advent of genetic profiling and the elucidation of immune landscapes, such as the expression of programmed cell death-ligand 1 (PD-L1). These factors contribute to the heterogeneous biological behaviors observed in NSCLC. Despite advancements, the influence of pre-existing conditions, including blood types, family history of cancers, and comorbid diseases, on the genetic and immunological landscape of NSCLC remains inadequately explored. This study aims to elucidate these correlations, thereby filling a gap in the current understanding.

Methods: A cross-sectional study was conducted at our institution, encompassing patients who underwent surgical resection for NSCLC from January 2014 to July 2018. Targeted next-generation sequencing (NGS) was deployed to detect somatic mutations in nine pivotal oncogenes, coupled with immunohistochemical staining to assess PD-L1 expression. Logistic regression analysis was utilized to examine the associations between pre-existing conditions and the occurrence of specific driver mutations or levels of PD-L1 expression.

Results: The cohort included 5,507 patients, all of whom underwent NGS, with 1,839 also evaluated for PD-L1 expression. Notable associations were identified: ROS1 mutations closely associated with a family history of lung cancer (OR: 5.356, 95%CI: 0.798-21.225, P = 0.035). EGFR L858R mutations were prevalent in patients with a family history of non-lung cancers (OR: 2.089, 95%CI: 1.029-4.135, P = 0.037) and hypertension (OR: 1.252, 95%CI: 1.001-1.562, P = 0.048). Pre-existing conditions such as diabetes (OR: 1.468, 95%CI: 1.042-2.047, P = 0.026) and hepatitis B surface antigen positivity (OR: 1.373, 95%CI: 1.012-1.847, P = 0.038) were correlated with EGFR exon 19 deletions. RhD negativity showed potential ties to BRAF mutations (OR: 0.009, 95%CI: 0.001-0.228, P = 0.001). A history of tuberculosis linked to increased PD-L1 expression in immune cells (OR: 3.597, 95%CI: 1.295-14.957, P = 0.034).

Conclusions: This comprehensive, large-scale study reveals significant associations between pre-existing conditions and specific genetic and immunological alterations in NSCLC. These findings underscore the importance of considering patients' medical histories when developing personalized treatment strategies, highlighting the potential for more tailored therapeutic approaches based on individual genetic and immunological profiles.

Keywords: non-small cell lung cancer (NSCLC), driver mutations, comorbid diseases



Notes:
-aOR Transformation: Displayed odds ratios (t-aOR) are log-transformed to correct skewness, followed by tan-transformation for distribution normalization, ensuring clear visualization.
-Color Coding: Red bubbles represent actual aORs > 1, indicating increased odds; Blue bubbles represent actual aORs < 1, indicating decreased odds.
-Significance Levels: (a) P = .002 to < .05; (b) P ≤ .002.

EP.03B TUMOR BIOLOGY - TRANSLATIONAL BIOLOGY - GENOMICS
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EP.03B.03 Whole Genome Analysis in Resected Adenocarcinoma and Squamous Cell Carcinoma of the Lungs

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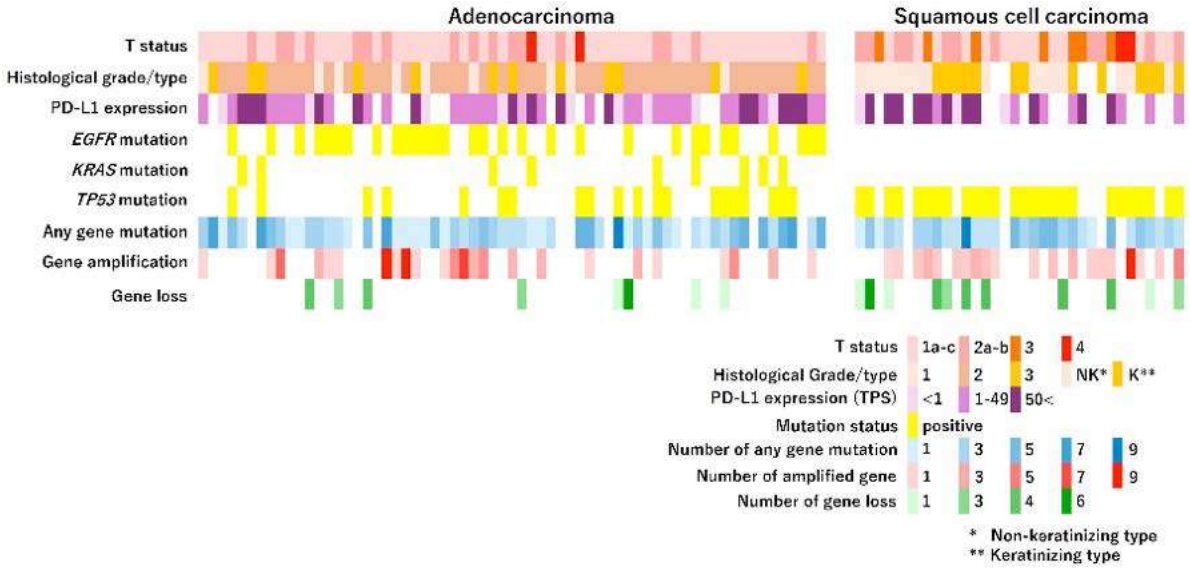
Introduction: A comprehensive genetic profile is essential for the development of therapeutic strategies for lung cancer. Genetic status is a predictor of response to targeted therapy and immune checkpoint inhibitors. There are limited data regarding the whole-genome profiles of lung adenocarcinoma and squamous cell carcinoma. Whole-genome sequencing can be used to detect features that are potentially therapeutically targetable or diagnostic markers.

Methods: A whole-genome analysis of resected primary lung cancer was performed. Genetic alterations (mutations including substitutions in intron, deletions, amplifications, and losses), homologous recombination deficiency, and tumor mutation burden (TMB) were evaluated. We evaluated the differences between adenocarcinoma and squamous cell carcinoma and their specific profiles. Clinicopathological backgrounds specific to the genetic features were also explored.

Results: Sixty-five adenocarcinoma and 34 squamous cell carcinoma cases were analyzed after cases with non-/minimally invasive, variant-type adenocarcinoma, or cases after preoperative treatment were excluded. In patients with adenocarcinoma, cases with an EGFR mutation harbored significantly lower TMB compared to EGFR wild-type cases (median: 1.59/Mb [range: 0.09-6.98; IQR: 1.1575-2.14] vs. median 3.84/Mb [range: 0-25.78; IQR: 1.03-8.92], p = 0.0289). Cases with a TP53 mutation harbored higher TMB (median: 7.5/Mb [range: 0.75-25.78; IQR: 2.615-11.5625] vs. median: 1.41/Mb [range: 0-10.64; IQR: 0.85-2.43]; p < 0.001). No significant differences in TMB were found with respect to T status, histological type, or PD-L1 expression in adenocarcinoma or squamous cell carcinoma cases. TP53 mutations were more frequent in patients with squamous cell carcinoma than those with adenocarcinoma (30.8% [20/65] vs. 76.5% [26/34]; p < 0.001). The number of cases with amplification and the number of amplified genes per case were significantly higher in patients with squamous cell carcinoma (incidence of cases with amplification: 37.5% [24/65] vs. 58.8% [20/34]; p = 0.0373; median number of amplified genes per case: 1.5 [range: 0-34; IQR: 0-3.75] vs. 0 [range: 0-6; IQR: 0-1]; p = 0.00428). Gene loss is significantly more frequent in patients with squamous cell carcinoma. (incidence of cases with gene loss: 12.3% [8/65] vs. 32.4% [11/34]; p = 0.0327; median number of lost genes per case: 0 [range: 0-6; IQR: 0-0] vs. 0 [range: 0-4; IQR: 0-1]; p = 0.00220).

Conclusions: TMB was significantly lower and higher in EGFR and TP53 mutant cases in patients with adenocarcinoma, respectively. Squamous cell carcinoma cases are characterized by a higher incidence of TP53 mutations, with a higher frequency and number of gene amplifications and losses compared to adenocarcinoma cases.

Keywords: whole genome sequence, early stage, squamous cell carcinoma



EP.03B TUMOR BIOLOGY - TRANSLATIONAL BIOLOGY - GENOMICS
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EP.03B.04 Clinicopathological Features of Lung Cancers with RICTOR Gene Amplification

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Introduction: The patients with lung cancer harboring amplification of the RICTOR (rapamycin-insensitive companion of mTOR) gene have been proposed as a subset of patients who may benefit from mTORC1/2 inhibitors (Cheng H, et al,. Cancer Discov 2015). However, only a few studies have been performed thereafter. Therefore, we aimed to determine the incidence and clinicopathologic features of lung cancer with RICTOR gene amplification.

Methods: We analyzed data from 142 lung cancer patients who received surgical resection between June 2022 and June 2023, and participated in a clinical study that performed next-generation sequencing (NGS) analysis of the tumors. The Fisher's Exact test and the Mann-Whitney U-test were used to analyze the correlations between the presence of the RICTOR gene amplification and categorical variables or continuous variables, respectively.

Results: Among 142 lung cancer patients, RICTOR gene amplification was detected in 15 patients (11%). The prevalence of the RICTOR gene amplification was highest in small cell lung cancer and large cell neuroendocrine carcinoma (LCNEC) (33%, 3/9 cases) followed by squamous cell carcinoma (11%, 4/35 cases), and lung adenocarcinoma (9%, 8/86 cases). None of 12 lung cancers of other histologies such as adenosquamous cell carcinoma harbored RICTOR amplification. Among 8 lung adenocarcinoma patients with RICTOR gene amplification, 3 had concurrent EGFR mutation (L858R, G719A, and exon 20 insertion) but none had KRAS mutation. In the analysis of clinical factors, all patients with RICTOR gene amplification but one were smokers. The presence of the RICTOR gene amplification was not associated with sex and age of the patients. TP53 mutation was numerically more frequent in patients with RICTOR gene amplification (60%) than those without (47%, p=0.42).

Conclusions: RICTOR gene amplification was present in 11% of lung cancer, and may be associated with smoking-related lung cancer with neuroendocrine features.

Keywords: Driver mutaion, Small cell lung cancer, Squamous cell carcinoma

EP.03B TUMOR BIOLOGY - TRANSLATIONAL BIOLOGY - GENOMICS
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EP.03B.05 Construction and Validation of a Prognostic Model Using Loratadine-Related Genes in NSCLC Patient with Tumor Microenvironment.

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Introduction: This study aimed to investigate the association between loratadine use and lung cancer patients' survival and to develop a risk score formula for lung adenocarcinoma (LUAD) patients based on gene expression profiles and clinical features.

Methods: Utilizing the least absolute shrinkage and selection operator (LASSO) Cox regression, we developed a 5-gene prognostic signature related to loratadine's mechanism of action in LUAD, drawing from The Cancer Genome Atlas (TCGA) cohort and a Gene Expression Omnibus (GEO) dataset. We evaluated gene expression, immune infiltration, and animal experiments to confirm the functional significance of the identified risk genes in mice.

Results: A risk score formula of loratadine use was established incorporating five genes (ABCC2, NUPR1, KCNH2, ABCB1, NR0B2) to classify LUAD patients into high-risk and low-risk groups with different survival probabilities, confirmed by Kaplan-Meier curves and validated by time-dependent ROC analysis (AUCs for 1, 3, and 5 years: 0.677, 0.640, 0.644, respectively). Multivariate regression analysis identified pathological subtyping and the risk model as independent prognostic factors. Additionally, immune profiling revealed differential expression of immune cells and checkpoints between risk groups, with the low-risk group showing a favorable immune environment. In vivo experiments demonstrated the same conclusion. Finally, we conducted immunohistochemistry to validate the function of the risk genes. The results revealed significant differences in the expression of the KCNH2 and NR0B2 gene between the treatment group (receiving loratadine) and the control group (not receiving loratadine), which suggests that the use of loratadine may influence the survival of LUAD patients by affecting the expression of the KCNH2 and NR0B2 gene.

Conclusions: Our study introduces a loratadine-based risk score model for LUAD. The model, coupled with immune profiling, offers insights into the molecular and immunological landscape of LUAD, presenting implications for personalized medicine and targeted therapies.

Keywords: Prognostic Model, NSCLC Patient, Loratadine

EP.03C TUMOR BIOLOGY - TRANSLATIONAL BIOLOGY - IMMUNE MODULATION
SATURDAY, SEPTEMBER 7, 2024 - 11:58 - 11:59

EP.03C.01 The Impact of Systemic Inflammatory Markers on EGFR Mutant Non-Small Cell Lung Cancer (NSCLC)

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Introduction: High prevalence of EGFR-mutant (EGFRm) lung cancer was found in the Asian population, especially in non-smoker. Preclinical data has demonstrated that inflammatory cytokines activated by PM2.5 affected the expansion of EGFRm clone in patients. Here, we explored the pathogenesis and the correlation between inflammatory markers and EGFRm NSCLC.

Methods: Resected NSCLC patients treated at Ramathibodi Hospital during 2016-2023 were enrolled. Tumor tissues and blood serum were retrieved from Ramathibodi tumor biobank. Del19 and L858R mutation were performed by real time-PCR in the cancerous tissue and digital PCR in the normal tissue of resected tumor in the same patient. NF-Kb and STAT3 protein signaling were measured by InstantOne ELISATM assays in both cancerous and normal tissue of resected tumor. Cytokines including of IL-1ß, IL-6, IL-8, IL-10, IL-12 and TNF-α were explored in baseline serum by flow cytometry (BD Cytometric Bead Array). Association factor between EGFR status and inflammatory cytokines determined by Logistic regression. P-value < 0.05 was defined as statistical significance.

Results: One-hundred and forty resected NSCLC patients were enrolled. The majority of NSCLC patients were female (65%), non-smokers (74%), stage 1 (64%), and treated with lobectomy (91%). The prevalence of EGFRm in cancerous tissue was 58% (Del19=30% and L858R=28%). Whereas, the normal tissue of resected tumor, EGFRm was found only 5% in EGFRm NSCLC. NF-Kb protein signaling was statistically higher in cancerous tissue compared to normal tissue [median OD=0.82 (IQR; 0.07-2.82) vs 0.32 (IQR; 0.05-2.48, P<0.001] (Figure 1). STAT3 protein signaling was also higher in cancerous tissue compared to normal tissue [median OD=0.32 (IQR; 0.10-1.58) vs 0.17 (IQR; 0.06-1.29, P<0.001]. Furthermore, STAT3 was significantly increased in EGFRm patients compared to EGFRwt patients in the cancerous tissue [median OD=0.36 (IQR; 0.234-0.592) vs 0.23 (IQR; 0.158-0.409), odds ratio=11.09 (95% CI; 2.17-56.58), P=0.004]. Serum TNF and IL-10, together with STAT3 in cancer cell were statistically significant higher in EGFRm compared to EGFRwt patients (P=0.003, 0.008, and <0.001, respectively). None of the cytokines was statistically different between EGFRm and EGFRwt patients in univariable analysis, only STAT3 in cancer cell, PD-L1 and smoking status were statistically significant difference by EGFR mutational status (P=0.004, 0.05, and 0.008). However, only STAT3 in cancer cells and non-smoker were associated with EGFRm NSCLC in multivariable analysis.

Conclusions: Inflammation could be pathway of both NSCLC and EGFRm lung cancer pathogenesis as we demonstrated in our pilot study. STAT3 is a potentially important inflammatory-predictive biomarkers. Larger cohort is needed.

Keywords: EGFRm lung cancer, Cytokines, STAT3

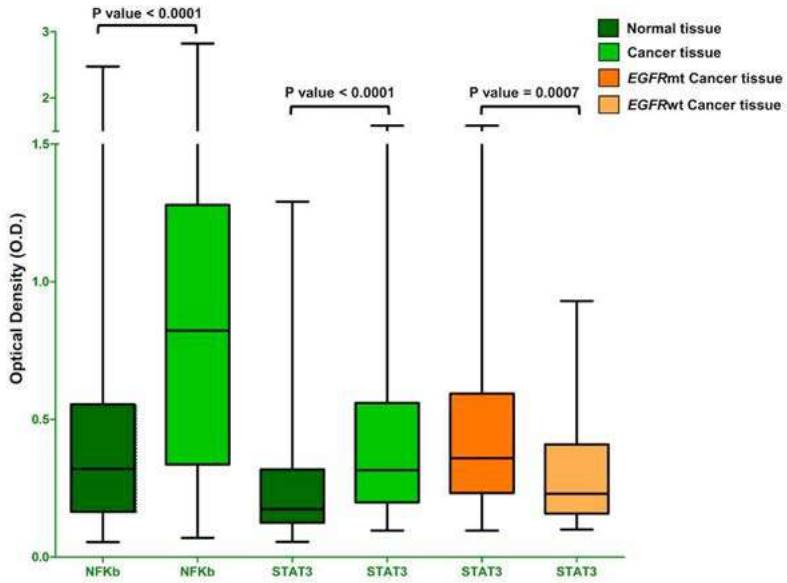

Figure 1: Boxplot showed significant difference of NFKb, STAT3 in lung cancer

EP.03C TUMOR BIOLOGY - TRANSLATIONAL BIOLOGY - IMMUNE MODULATION
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EP.03C.02 The Potential of Fluoropyrimidine to be an Immunologically Optimal Partner of Immunotherapy for Thoracic Malignancies

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Introduction: Chemo-immunotherapy, a combination therapy of cytotoxic chemotherapy with immune checkpoint inhibitor (ICI), is a current standard regimen in the treatment of thoracic malignancies. Chemotherapy is known to induce not only direct cytotoxic effects on tumor cells but also immune modulating effects, such as stimulating immunogenic cell death (ICD) or depleting immune suppressive cells, such as myeloid derived suppressor cells (MDSCs). These effects are thought to be a rationale of combining chemotherapy with ICI. Either pemetrexed (PEM) or taxane plus platinum are the standard regimens in the combination with ICI for thoracic malignancies, however, it is still unknown that whether they are immunologically optimal partners. We then performed the immunological analyses to determine the optimal chemotherapy to be combined with ICI for thoracic malignancies.

Methods: We used four human NSCLC cell lines (PC9, A549, H226, and H2170) and one murine malignant mesothelioma cell line (AB1-HA). To evaluate the immune modulating effects of chemotherapeutic agents that are clinically administered for thoracic malignancies, we used 5-fluorouracil (5-FU), tegafur-gimeracil-oteracil potassium (S-1), PEM, paclitaxel (PTX), docetaxel (DTX), vinorelbine (VNR), gemcitabine (GEM), cisplatin (CDDP), and carboplatin (CBDCA). The induction of ICD in vitro was evaluated with cell-surface expression of calreticulin (CRT) and ATP secretion. The immunogenicity of ICD-induced tumor cells was evaluated with vaccination assay in mice. The number of tumor-infiltrating MDSCs was evaluated by flow cytometry and immunohistochemistry. The anti-tumor effects of several chemo-immunotherapies were evaluated with ABI-HA bearing mice.

Results: Among the several chemotherapeutic agents, 5-FU induced cell-surface expression of CRT on tumor cells tested more efficiently than others in vitro. 5-FU also enhanced the secretion of ATP from tumor cells. The efficiency of 5-FU in the induction of CRT was enhanced when combined with platinum. The vaccination with dying-AB1-HA cells treated with 5-FU, but neither PEM nor PTX, induced robust anti-tumor immune response in vivo. Furthermore, 5-FU and its oral formulation S-1, but not others, inhibited the accumulation of MDSCs in AB1-HA bearing mice through suppression of tumor-derived chemotactic factors for MDSCs, such as Bv8 and S100A8. Lastly, in comparison with PEM, administration of S-1 improved the synergistic anti-tumor efficacy of ICI in mice.

Conclusions: These results suggest that fluoropyrimidine can be an immunologically optimal partner of ICI through stimulating ICD of tumor cells and depleting MDSCs from tumor microenvironment for thoracic tumors.

Keywords: fluoropyrimidine, immunogenic cell death, myeloid derived suppressor cells

EP.03C TUMOR BIOLOGY - TRANSLATIONAL BIOLOGY - IMMUNE MODULATION
SATURDAY, SEPTEMBER 7, 2024 - 11:58 - 11:59

EP.03C.03 Development of a Novel Immunotherapy for ICI Resistant KRAS-Mutantlung Cancer

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Introduction: Immune checkpoint inhibitors (ICIs) have proven to be effective in patients with advanced-stage lung cancer and have shown high efficacy in KRAS-mutant lung cancer. However, the efficacy of ICIs in KRAS-mutant lung cancer varies, and the presence of "co-mutations" is an important predictor of efficacy. Approximately 30% of KRAS lung cancer subtypes do not respond to ICIs, particularly KRAS-mutant lung cancers with co-mutations in LKB1 (KL lung cancer). This study aimed to present a novel treatment for ICI-resistant KRAS-mutant lung cancers.

Methods: We analyzed The Cancer Genome Atlas Program (TCGA) and the Cancer Cell Line Encyclopedia (CCLE) to investigate the association between co-mutations and our target molecule, protein X, in KRAS lung cancer. We validated its dual function as both a therapeutic target and a biomarker. The antitumor immune response was evaluated through in vitro immune cell co-culture experiments using KL lung cancer cell lines with forced expression of protein X. Furthermore, the effect of overexpressing protein X on tumor shrinkage was validated in vivo using a syngeneic tumor transplantation model. Additionally, immunohistochemistry (IHC) for LKB1 and protein X was performed on samples from 57 patients with KRAS lung cancer at Asahikawa Medical University Hospital to confirm the association between their expression levels.

Results: Co-culture experiments with immune cells showed that KRAS-mutant lung cancer cells overexpressing protein X showed enhanced immune response. Furthermore, when protein X-overexpressing KRAS-mutant lung cancer cell lines of syngeneic origin were generated and subcutaneously administered to immunocompetent mice, the tumor size decreased compared to that in the control group. Additionally, IHC results for LKB1 and protein X in KRAS lung cancer patient samples showed a correlation between the expression of these two molecules.

Conclusions: Protein X may serve as a novel therapeutic target for ICI-resistant KRAS-mutant lung cancers. Furthermore, induction of protein X expression could lead to novel immunotherapy approaches.

Keywords: non-small cell lung cancer, KRAS, Immune checkpoint inhibitors

EP.03D.01 Mechanistic Study of 5-Hydroxytryptamine-Mediated Promotion of Non-Small Cell Lung Cancer Metastasis by Regulation of RPL24

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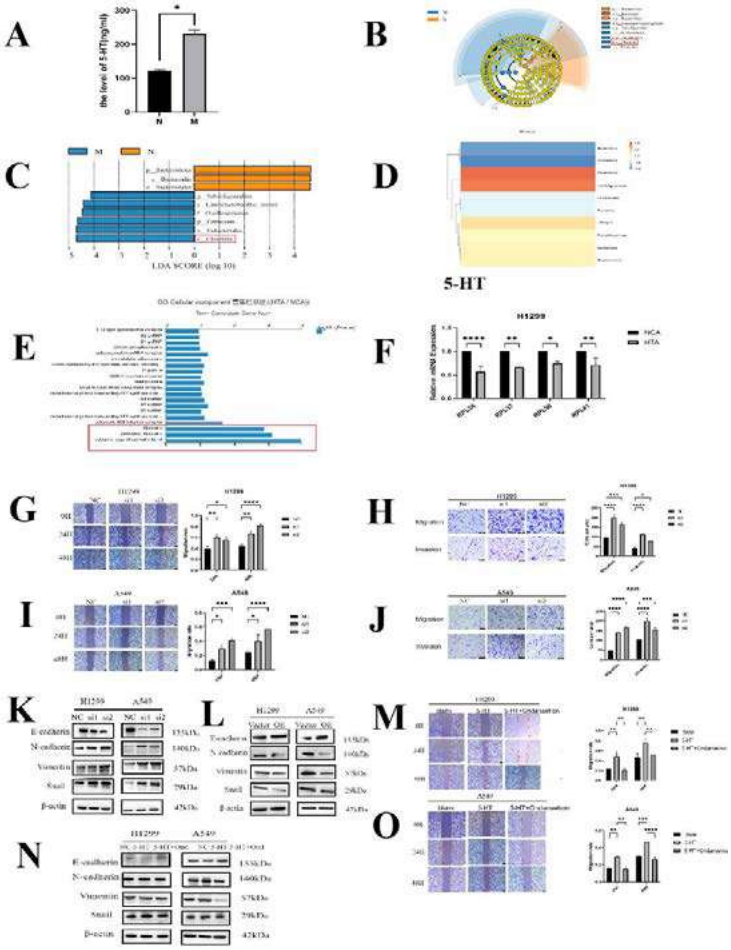
Introduction: Non-small cell lung cancer (NSCLC) is one of the most common and aggressive types of lung cancer. The gut microbiota can directly or indirectly influence host 5-HT levels. Previous experiments from our research group have shown that 5-HT can promote the migration and invasion of lung cancer cells.

Methods: In this study, we measured peripheral blood 5-HT levels in NSCLC patients with distant metastases (28 cases) and without distant metastases (20 cases) using ELISA kits. Simultaneously, we conducted metagenomic analysis of the gut microbiota in both groups of patients and correlated it with peripheral blood 5-HT levels. Next, we performed whole-genome sequencing of H1299 cells treated with 5-HT to identify differential genes. We assessed the impact of the differential molecule RPL24 on the migration and invasion ability of NSCLC cells through Western blotting, Transwell assays, and scratch assays. We predicted potential receptors of 5-HT using the GEPIA2 database. We measured the mRNA expression levels of 5-HT receptor genes in cells using qRT-PCR. We evaluated the effects of 5-HT and 5-HT receptor antagonists on the migration and invasion ability of NSCLC cells and on the EMT pathway using Transwell assays, Western blotting, and scratch assays.

Results: Peripheral blood 5-HT levels were significantly higher in NSCLC patients with distant metastases than in those without distant metastases. NSCLC patients with distant metastases had higher species richness and diversity of gut microbiota, and the abundance of the differential bacterium Clostridium difficile was positively correlated with peripheral blood 5-HT levels. Transient silencing of RPL24 promoted the migration and invasion of H1299 and A549 cells and facilitated EMT. The expression of the 5-HT receptor HT3A was higher in primary NSCLC tissues than in adjacent non-tumor tissues, and the mRNA expression of HTR3A in H1299 and A549 cells was higher than in lung epithelial cells. Partial reversal of the migratory and invasive ability of 5-HT was observed after treatment with 5-HT combined with ondansetron, indicating that HTR3A is the receptor mediating the role of 5-HT in regulating RPL24 to promote NSCLC migration and invasion.

Conclusions: NSCLC patients with distant metastases have higher peripheral blood 5-HT levels. These patients exhibit a unique gut microbiota profile, with the abundance of Clostridium difficile positively correlated with 5-HT levels. 5-HT downregulates RPL24 through the HT3A receptor, activates the EMT pathway, enhances the migration and invasion ability of NSCLC cells, and promotes NSCLC metastasis.

Keywords: Non-small cell lung cancer, 5-hydroxytryptamine, metastasis



EP.03D TUMOR BIOLOGY - TRANSLATIONAL BIOLOGY - METASTASIS/TUMOR PROGRESSION
SATURDAY, SEPTEMBER 7, 2024 - 11:58 - 11:59

EP.03D.02 HNRNPC-Regulated PA2G4 Promotes Proliferation and Metastasis of LUAD Cells

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Introduction: HNRNPC is a RNA-binding protein, which takes part in pre-mRNA processing. In our previous research, HNRNPC was identified to high-expressed in lung adenocarcinoma (LUAD) tissue with poor-prognosis. Moreover, HNRNPC has known as to extend PA2G4 mRNA and change its polyadenylate (PolyA) site. This research aims to explore the role and mechanism of HNRNPC/PA2G4 in LUAD.

Methods: Transcripts with different polyA site in PA2G4 mRNA 3'UTR are confirmed by 3'RACE-electrophoresis. The binding between HNRNPC protein and PA2G4 mRNA is confirmed by RNA pulldown, RNA binding protein immunoprecipitation (RIP) assays and luciferase reporter experiment. Gene expressions are detected by qRT-PCR experiment and western blotting. Transcription inhibitor Actinomycin D (ActD) is used to evaluate the RNA stabilization. Cell proliferation is evaluated by CCK8 assay and colony formation assay. Cell cycle is analyzed by flow cytometry assay. Cell migration and invasion are detected by Transwell assay

Results: PA2G4 mRNA has two transcripts with different PolyA sites, PA2G4-L and PA2G4-S. HNRNPC overexpression increases PA2G4-T level, while PA2G4-L level has no significant changes, which means that PA2G4-S is increased. Conversely, HNRNPC inhibition decreases PA2G4-T level and increases PA2G4-L level, which means that PA2G4-S is decreased. Moreover, HNRNPC overexpression promotes PA2G4 mRNA stabilization and HNRNPC inhibition have an adverse effect. The binding between HNRNPC protein and PA2G4 mRNA is further confirmed. After transfected with overexpression plasmids, PA2G4 mRNA and protein level are increased. ActD treatment shows that PA2G4-S is more stable than PA2G4-L. Furthermore, both PA2G4-L and PA2G4-S overexpression promotes LUAD cells proliferation and metastasis, but PA2G4-S overexpression has a better effect than PA2G4-L.

Conclusions: HNRNPC binds to PA2G4 mRNA, induces an advance PolyA site and shortened PA2G4 mRNA, which results in a stabilization of PA2G4 mRNA and promotes proliferation and metastasis of LUAD cells.

Keywords: LUAD, Proliferation, metastasis, HNRNPC, PA2G4

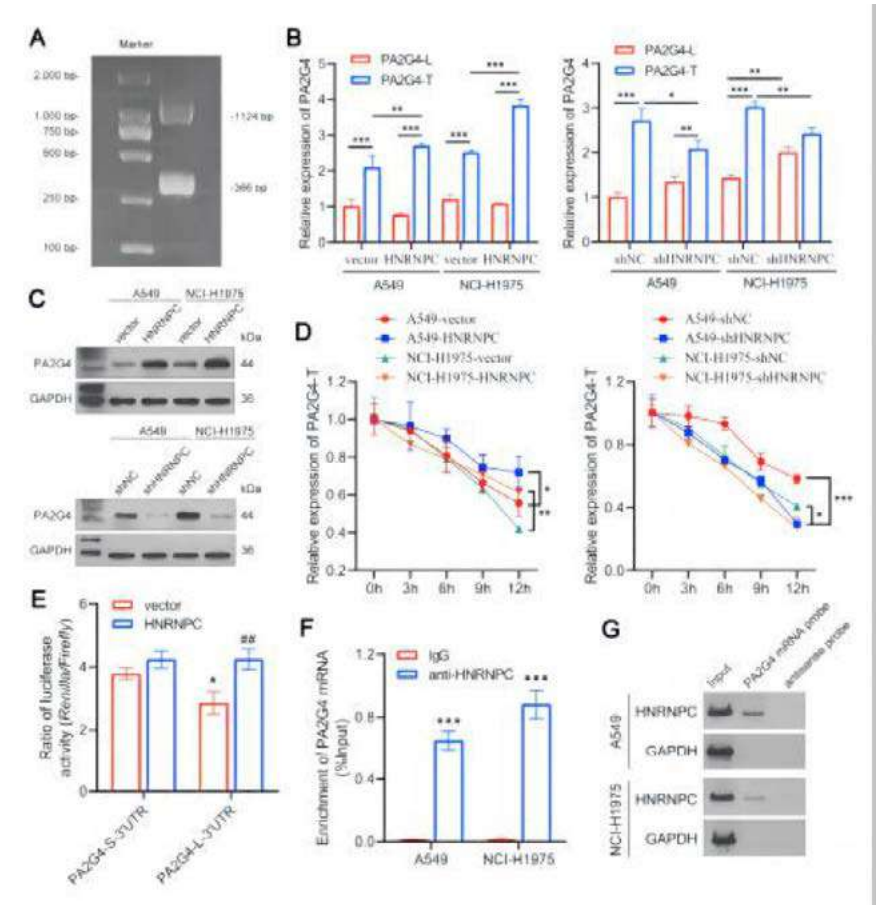

Figure1. HNRNPC binds to PA2G4 mRNA and regulated its stabilization. (A) Transcripts with different polyA site in PA2G4 mRNA 3'UTR are confirmed by 3'RACE-electrophoresis. (B) PA2G4 mRNA level detected by qRT-PCR. (C) PA2G4 protein level detected by western blotting. (D) PA2G4 mRNA stabilization detected by using transcription inhibitor Actinomycin D. (E-G) The binding between HNRNPC protein and PA2G4 mRNA confirmed by luciferase reporter experiment, RNA binding protein immunoprecipitation (RIP) assay and RNA pulldown assay.

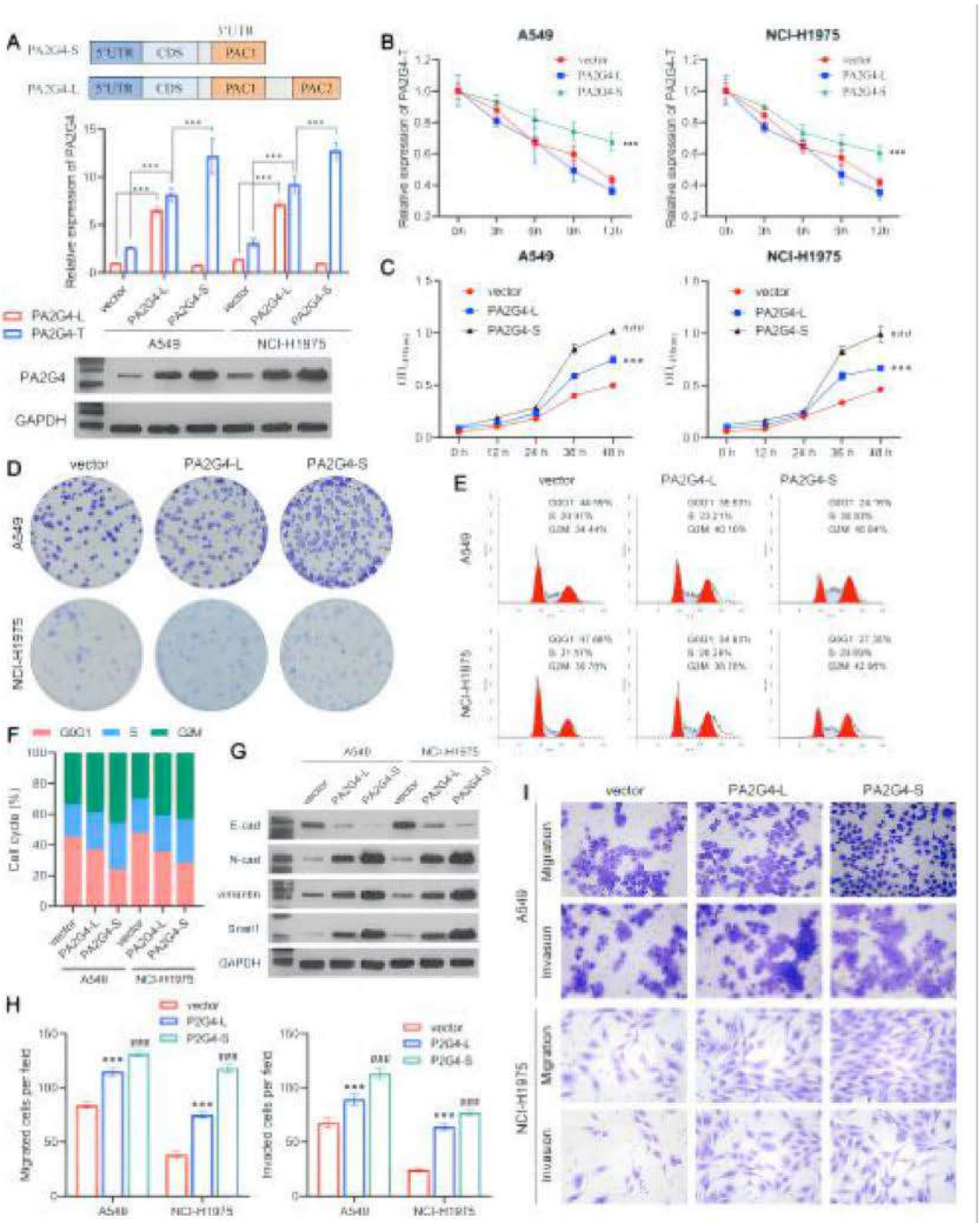

Figure 2. PA2G4 overexpression promotes LUAD cells proliferation and metastasis. (A) PA2G4 level detected by qRT-PCR and western blotting assay. (B) PA2G4 mRNA stabilization detected by using transcription inhibitor Actinomycin D. (C) Cell viability detected by CCK8 assay. (D) Cell proliferation detected by colony formation assay. (E-F) Cell cycle analyzed by flow cytometry assay. (G) Metastasis- related proteins detected by western blotting. (H-I) Cell migration and invasion detected by Transwell assay.

EP.03D TUMOR BIOLOGY - TRANSLATIONAL BIOLOGY - METASTASIS/TUMOR PROGRESSION
SATURDAY, SEPTEMBER 7, 2024 - 11:58 - 11:59

EP.03D.03 Genomic and Disease-specific Hallmarks of Extrachromosomal Circular DNAs in Lung Cancer and Its Potential Role in Cancer Progression

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Introduction: Extrachromosomal circular deoxyribonucleic acids (eccDNAs) carrying random genomic segments widely present in various cancers and participate in tumorigenesis and tumor progression, which are a newly discovered hallmark of cancer. However, their molecular functions and mechanisms in non-small cell lung cancer (NSCLC) are rarely known.

Methods: In this study, we comprehensively characterized and analyzed the circulome-associated genome heterogeneity in 34 NSCLC patients using Circle-Seq and RNA-Seq. 34 surgically NSCLC tissues, 34 matched normal adjacent tissues (NAT), and 23 matched recurrent cancer tissues (RCT) were used as study objects. All patients had complete prognostic information. qRT–PCR was used to verify the expression level of eccDNA.

Results: The eccDNA abundance in NSCLC tissues was aberrantly higher than that of NAT and that of RCT. The eccDNAs of NSCLC tissues and RCT are GC-rich. Analysis of the genomic distribution of eccDNAs shows that eccDNAs of NSCLC tissues and RCT are found on all chromosomes but enriched on chromosomes 7 and 19 with a high density of protein-coding genes, 5'Untranslated Regions and exon regions. Moreover, eccDNA with miRNA genes is highly enriched in NSCLC tissues and RCT. The eccDNA derived from CILP2 was upregulated in RCT and patients with eccDNAs derived from CILP2 was upregulated in RCT were associated with worse outcomes.

Conclusions: The cancerous eccDNAs could influence genome-wide gene expression and increased oncogene dosage of NSCLC. CILP2 promoting metastasis of NSCLC and CILP2 identified by eccDNA sequencing acts as an oncogene and might be a new biomarker for NSCLC diagnosis and prognosis evaluation.

Keywords: extrachromosomal circular DNAs, lung cancer, CILP2

EP.03D TUMOR BIOLOGY - TRANSLATIONAL BIOLOGY - METASTASIS/TUMOR PROGRESSION
SATURDAY, SEPTEMBER 7, 2024 - 11:58 - 11:59

EP.03D.04 SOX2 Inhibits Ferroptosis by Regulating FOXM1 Transcription Through Phase-Separation Recruitment of Coactivators

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Introduction: SOX2 is an oncogenic transcription factor that activates transcription by regulating promoter linkage. Intrinsic disordered regions (IDRs) in the transactivation domain of SOX2 are essential for the formation of phase separation droplets. Liquid-liquid phase separations (LLPS) are Intrinsic disordered regions (IDRs) of various proteins (including transcription factors, chromatin regulators, and RNA-binding proteins) that form dynamic liquid droplets or gel-like phase separation condensates through multivalent and weak interactions, thereby affecting organelle formation and countless biological processes. These include transcription, X chromosome inactivation, DNA damage, tumorigenesis, autophagy, etc. However, how SOX2 regulates transcription via phase separation to promote lung cancer progression remains unclear.

Methods: We analyzed the role of SOX2 in lung adenocarcinoma by bioinformatics. Then, we overexpressed or knocked down SOX2 in A549 and H1299 cell lines to detect ferroptosis-related indicators, proliferation, invasion and migration abilities. By analyzing the 317 amino acid sequence encoding SOX2, three major intrinsic disordered regions were identified. The ability of SOX2 to phase separation in cells was demonstrated by in vitro and in vivo droplet assay, fluorescence recovery after photobleaching (FRAP) assay and droplet fusion assay . The co-localization of SOX2 with transcriptional coactivators (P300, Med1, CDK9) and gene activation histone markers was verified by immunofluorescence. The binding sites were verified by luciferase reporter and Chip experiments. Stable cell lines with both overexpression and knockdown of SOX2 were successfully generated and confirmed in in vivo experiments.

Results: SOX2 promotes lung adenocarcinoma proliferation and inhibits ferroptosis. And has the ability of phase separation. It regulates transcription through phase separation recruitment coactivator to activate FOXM1 to initiate transcription and inhibit ferroptosis, thus affecting the progression of lung adenocarcinoma.

Conclusions: SOX2, through the IDR region of its trans-activation domain, undergoes phase separation, recruits coactivators and histone markers to regulate transcription to inhibit ferroptosis and promote lung adenocarcinoma progression. This provides new ideas and methods for the treatment of lung cancer.

Keywords: Phase separation, Transcription, Lung adenocarcinoma

EP.03E TUMOR BIOLOGY - TRANSLATIONAL BIOLOGY - NOVEL MODELS/NOVEL TECHNOLOGIES
SATURDAY, SEPTEMBER 7, 2024 - 11:58 - 11:59

EP.03E.01 Patient-Derived Organoids Can Predict Response to Chemotherapy and Targeted Therapy in Lung Cancer Patients

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Introduction: Lung cancer is a challenging disease with significant inter-individual heterogeneity, numerous options for clinical therapeutic agents, and a clear and unmet clinical need for biomarkers that predict responsiveness to cancer chemotherapy and targeted therapies. Here, we evaluated the ability of patient-derived organoids (PDOs) to predict the functional consequences of clinical drug response and tumor heterogeneity.

Methods: Lung cancer cells isolated from patients were cultured, after which pathohistologic validation, next-generation sequencing, and drug sensitivity testing were done to determine the sensitivity of each patient to specific drugs. We evaluated the utility of such testing, including: success rate in generating organoids, time to culture the organoids, reproducibility and heterogeneity of the drug testing, and correlation of the test results with clinical efficacy.

Results: We successfully generated and validated from 90% (54/60) of patients undergoing standard care. In this study, we generated 54 lung cancer organoids (LCO) from 60 patients, all derived from CT-guided lung puncture or bronchoscopic biopsy samples. These LCOs were cultured in a relatively short period of time and included four major histological subtypes of lung cancer and multiple mutation types that were consistent with parental tumor tissue.The in vitro drug sensitization correlated with the clinical outcome of the patients, both untreated and clinically treated. Importantly, PDOs display inter- and intrapatient drug response heterogeneity to chemotherapy and targeted drugs. The drug sensitization results correlated with the clinical outcome and progression free survival (PFS) of the patients.

Conclusions: Our research imply that PDOs can predict LC patients responses in the clinic and may represent a companion diagnostic tool in lung cancer treatment, complementing genetic testing and helping to develop personalized treatment strategies, and adding to our understanding of the heterogeneity of genetic and drug responses.

Keywords: lung cancer, organoids, personalized treatment strategies

EP.03E TUMOR BIOLOGY - TRANSLATIONAL BIOLOGY - NOVEL MODELS/NOVEL TECHNOLOGIES
SATURDAY, SEPTEMBER 7, 2024 - 11:58 - 11:59

EP.03E.02 Elucidation of Trastuzumab-Deruxtecan Resistance Mechanisms using in Vivo Xenograft Model Reflecting Pharmacokinetics

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Introduction: Trastuzumab-deruxtecan (T-Dxd) is an antibody-drug conjugate, which has been approved for HER2-low expressing breast cancer, HER2-positive breast cancer, HER2-positive gastric cancer, and HER2 mutation-positive NSCLC, in many countries. T-Dxd is effective against these cancers, almost all patients experience relapse due to resistance. In vivo pharmacokinetics is an important factor which affects emergence of acquired resistance. Therefore, we used human HER2-positive-breast cancer, -gastric cancer, and -NSCLC cell lines to induce T-Dxd resistance in a xenograft model that can reflect in vivo pharmacokinetics, and investigated the resistance mechanism.

Methods: We inoculated gastric cancer cell line (N87) subcutaneously into immunodeficient mice, and treated the mice with T-Dxd (5 mg/kg) intravenously three times every 1 to 2 months when tumors regrew. Then, the enlarged tumor was recovered, and the resistant tumor cells (N87 T- Dxd AR) was established. For NSCLC and breast cancer, where central nervous system (CNS) metastasis is a clinical problem, we inoculated luciferase gene-introduced cancer cell lines (Calu-3, BT474) into leptomeningeal space of immune deficiency mice. We monitored tumor progression in CNS by luminescence after luciferin administration, and administered T-Dxd (5mg/kg) three times every 1 to 2 months when tumors regrew. Then, the enlarged tumors were collected, and resistant tumor cells (Calu-3 LMC T-Dxd AR, BT474 LMC T-Dxd AR) were established.

Results: Compared to the parental cells, all three resistant tumor cell lines were resistant to T-Dxd and Dxd, but sensitive to DTX and eribulin, in vitro. In addition, the three resistant tumor cell lines expressed HER2 at the same level as each parental cell line, and were sensitive to afatinib and lapatinib, which have HER2 kinase inhibitory activity. ABC-G2 (BCRP1) expression was increased in N87 T-Dxd AR cells compared to the parental cells. Furthermore, combined use of ABC-G2 inhibitors (Ko143 or KS176) restored T-Dxd sensitivity. On the other hand, ABC-G2 expression was not increased in Calu-3 LMC T-Dxd AR, and T-Dxd sensitivity was not restored even when ABC-G2 inhibitor was used in combination.

Conclusions: These results suggest that the mechanism of T-Dxd resistance differs depending on the cancer type. We are currently conducting studies to further elucidate the resistance mechanism of T-Dxd in order to develop treatments to overcome resistance.

EP.03E TUMOR BIOLOGY - TRANSLATIONAL BIOLOGY - NOVEL MODELS/NOVEL TECHNOLOGIES
SATURDAY, SEPTEMBER 7, 2024 - 11:58 - 11:59

EP.03E.03 Next Step for R1 Resection of Tracheal/Bronchial Malignant Tumor - Organoids Predict Adjuvant Therapy Response

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Introduction: Currently, there is no acknowledged guideline for adjuvant therapy in tracheal malignancies. This pilot prospective study with the goal of determining whether patient-derived organoids (PDOs) can model or predict postoperative outcomes for tracheal/bronchial cancers with positive resection margins (R1 resection).

Methods: Patients with R1 resection of tracheal/bronchial malignancy were enrolled to establish PDOs from surgical specimens. PDOs were verified by histological staining, of which interests were analyzed through drug and radiation sensitivity tests. Utilizing a comparative analysis in cellular viability pre- and post-exposure, alongside morphological observations via light field illumination, sensitivities were categorized into distinct tiers: highly sensitive (Grade A), moderately sensitive (Grade B), mildly sensitive (Grade C), or non-sensitive (Grade D). The most discerning therapeutic regimen was subsequently selected for implementation in patient's adjuvant treatment. The assessment of adjuvant treatment efficacy adhered to the RECIST version 1.1 criteria, thereby facilitating a comprehensive appraisal of the viability of PDO-based detection therapy sensitivity.

Results: 6 patients received surgeries, with distinct pathological types. PDOs cultures were successfully established, including nuclear protein testis carcinoma (NUT-C) (1/6), mucoepidermoid carcinoma (MEC) (2/6), adenoid cystic carcinoma (ACC) (2/6) and squamous cell carcinoma (SCC) (1/6). NUT-C showed high sensitivity to chemotherapy and SCC revealed mildly sensible to immunotherapy, while the others exhibited high sensitivity to radiotherapy. All patients received adjuvant therapies. Repeated computed tomography (CT) scans and surveillant bronchoscopy were performed for therapeutic evaluation. For the patients who underwent respective adjuvant treatment regimens, the median follow-up time was 4.5 months (ranging from 3 to 8 months), and neither lesion recurrences nor metastases, with a noticeable improvement in the quality of life compared to preoperative state.

Conclusions: Tracheal/Bronchial malignancy PDOs may be feasible for prediction of adjuvant therapeutic sensitivity and have clinical benefits to reduce the recurrence risk and improve prognosis for R1 resection cases. The prediction by PDOs will inform larger trials designed to further investigate the accuracy on the forecast of outcomes as well as strategies for airway cancers.

Keywords: Tracheal/Bronchial Malignant Tumor, Organoids, Adjuvant Therapy Response

EP.03E TUMOR BIOLOGY - TRANSLATIONAL BIOLOGY - NOVEL MODELS/NOVEL TECHNOLOGIES
SATURDAY, SEPTEMBER 7, 2024 - 11:58 - 11:59

EP.03E.04 Establishment of a Cancer Orgnoid Model for Personalized Drug Selction

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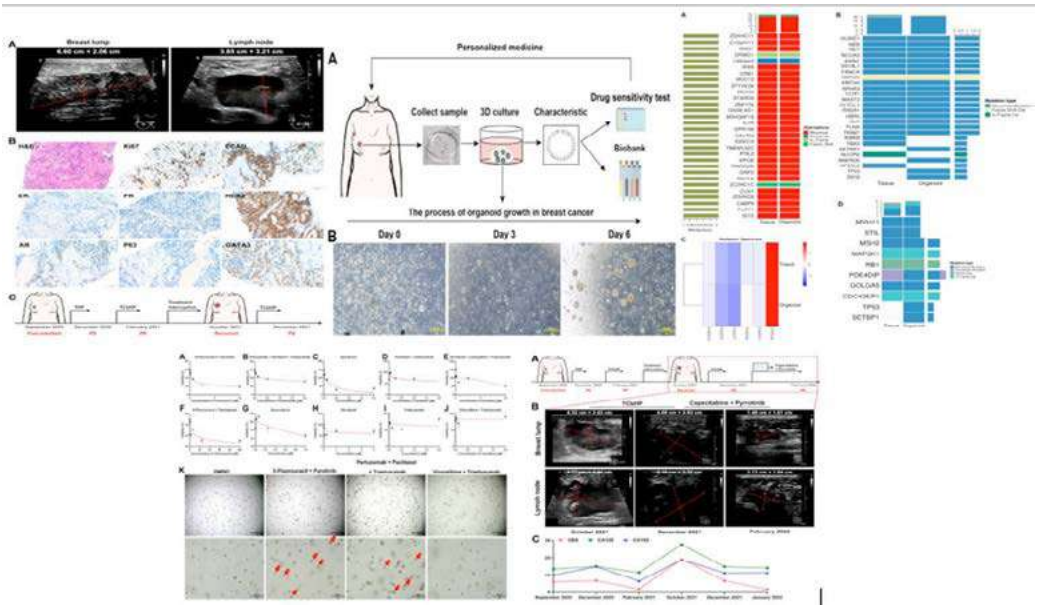
Introduction: Recently, the development of HER2 targeted therapy has improved the treatment efficacy on HER2 positive breast cancer, but the overall situation is still unsatisfying due to the complex pathology and tumorigenesis. So far, organoid model derived from BC patients has a good potential in becoming a promising in-vitro tool for personalized treatment and preclinical research. A breast cancer organoid model was established from the patient's tumor punch biopsy sample, which reproduced the morphological and molecular characteristics of the original tumor. Selecting drugs based on tumor organoid models can improve therapeutic efficacy.This study revealed that patient derived tumor organoid model could retain the tumor heterogeneity and contribute to the in-vitro drug testing for precision therapy.

Methods: Patients And Human SamplesFour puncture biopsies were obtained from a 51-year-old female patient with a breast tumor and collected with an 18G needle.The samples were used for organoid construction. Patient-derived Organoids ModelGenomic AnalysisBreast cancer tissue samples and cultured organoids were used to extract genomic DNA and perform whole-exome sequencing (WES) analysis,respectively. ImmunohistochemistryDrug ScreeningOrganoids were dissociated into single cells according to the passaging procedure described above. The collected cells were resuspended in appropriate amount of MasterAimTM Breast Cancer Organoid Complete Medium (AimingMed Hangzhou, China) with 5% Matrigel.After 48 hours, 6 concentrations of 5-fluorouracil, Pyrotinib, Pertuzumab, Docetaxel, Carboplatin, Trastuzumab, Paclitaxel, Epirubicin, Doxorubicin, Vinorelbine (Selleck) as well as DMSO controls were added in triplicates. After 4 days,The luminescence values were read on a multifunctional enzyme marker (Tecan).Clinical applicationSelect the clinical medication scheme according to the drug sensitivity results of Organoid

Results: A breast cancer organoid model was established from the patient's tumor punch biopsy sample, which reproduced the morphological and molecular characteristics of the original tumor. Drug sensitivity tested by organoids model suggested that the patient was not sensitive to the guideline recommended by first-line therapy, while combination of pyrotinib and 5-fluorouraeil showed highest tumor cell inhibition. After 2 cycles of combination of capecitabine and pyrotinib, the significant reduction of breast lumps and axillary lymph nodes were shown on ultrasound, with the decrease of tumor markers, and efficacy assessment of partial response (PR).

Conclusions: This study revealed that BCOs derived from advanced recurrent and TCbHP-resistant BC patient could retain the tumor heterogeneity and contribute to the in-vitro drug testing for precision therapy.

Keywords: Organoid, Resistant, Transformation



EP.03F TUMOR BIOLOGY - TRANSLATIONAL BIOLOGY - TARGETED THERAPY/NOVEL THERAPY
SATURDAY, SEPTEMBER 7, 2024 - 11:58 - 11:59

EP.03F.01 Modeling the Relationship of Clinical Safety Profile of EGFR Inhibitors with Wild-Type EGFR Inhibition in Cellular Model

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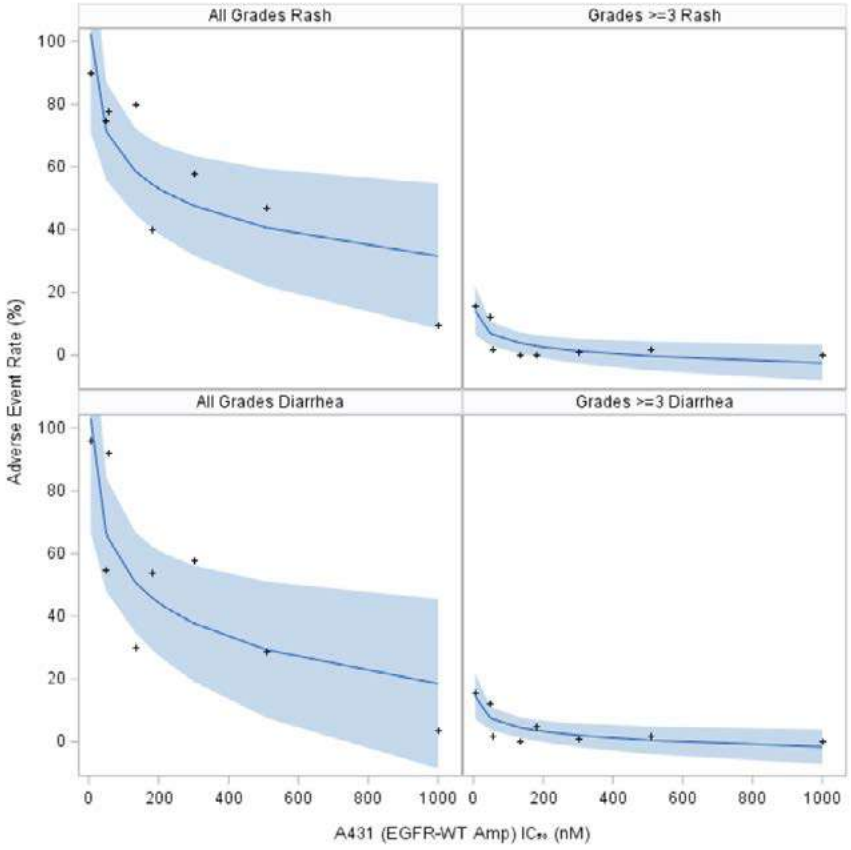
Introduction: EGFR inhibitors are established therapies for EGFR mutant NSCLC. Rash and diarrhea are well characterized adverse events (AE) associated with this class attributed to inhibition of wild-type (WT) EGFR. Systematic quantification of the relationship of nonclinical potency against WT EGFR with the reported clinical safety profile may help to better predict the potential clinical safety of novel drugs targeting this pathway. The study objective is to systematically evaluate the relationship between the reported rates and grades of rash and diarrhea across multiple clinical EGFR inhibitors with their inhibitory activity against WT EGFR.

Methods: Nonclinical inhibitory activities of EGFR inhibitors against WT EGFR were measured by deriving IC50 concentrations from cell proliferation assays in A431 cells carrying EGFR-WT gene amplification. The EGFR inhibitors include commercially available proxy compounds of gefitinib, afatinib, osimertinib, mobocertinib, sunvozertinib, zipalertinib, BLU-945, BDTX-1535, etc. Clinical safety data are obtained from drug labels or publications, including all grades AEs and Grades ≥3 rash and diarrhea. To assess correlations between A431 IC50 values and clinical data, Pearson correlation test was used. The relationship between AE rates and A431 IC50 data was modelled using linear regression model. With event count data and their sample sizes, a logistic regression model was also built. Its goodness-of-fit was assessed by the Hosmer and Lemeshow test.

Results: Highly statistically significant correlations of A431 cell IC50 values with All Grades rash (correlation coefficient r=-0.86, p=0.0027), with Grades ≥3 rash (r=-0.82, p=0.0067), with All Grades diarrhea (r=-0.84, p=0.0091), and with Grades ≥3 diarrhea (r=-0.82, p=0.012), respectively, were observed. Linear regression and logistic models adequately fit rash and diarrhea data, supported by the Hosmer and Lemeshow goodness-of-fit test results. The fitted regression line of clinical safety rates with 95% confidence limits against the A431 cell IC50 values together with the reported AE rates for rash and diarrhea are shown in the figure.

Conclusions: The relationship of clinical adverse event rates of rash and diarrhea with nonclinical inhibitory activity against WT EGFR in A431 cell proliferation assay is robustly described by regression modeling as determined by a systematic approach. The potency of inhibition of WT EGFR in a uniform nonclinical assay strongly correlated with overall rates and severity of rash and diarrhea observed in the clinical setting. These results may be useful in enhancing the understanding of the potential clinical safety profile of novel EGFR targeted therapies at the nonclinical development stage.

Keywords: EGFR inhibitor, cellular model, rash



EP.03F TUMOR BIOLOGY - TRANSLATIONAL BIOLOGY - TARGETED THERAPY/NOVEL THERAPY
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EP.03F.02 Exploration of Acquired Resistance Mechanisms to the 4th-Generation EGFR-TKI in EGFR-Mutated Lung Cancer - An in Vitro Study

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Introduction: In patients with lung cancer harboring activating EGFR mutation, the emergence of acquired resistance to EGFR tyrosine kinase inhibitors (TKIs) is almost inevitable even after a remarkable clinical response. Secondary mutations such as T790M or C797S are important mechanisms responsible for acquired resistance to the 1st / 2nd generation TKIs and 3rd generation TKIs, respectively. Novel EGFR-TKIs, the 4th generation EGFR-TKIs, are under early clinical development to overcome both the T790M and C797S mutations. However, even with these new drugs, it is anticipated that the cancer cells will develop resistance. In this study, we explored such acquired resistance mechanisms to the 4th generation TKI, BI-4020.

Methods: HCC4006, H1975, H3255, PC9, and HCC827 lung cancer cell lines, all of which harbor EGFR mutation, were exposed to increasing concentrations of BI-4020. After establishing cell lines that can grow in the presence of 2000 nM of BI-4020, the mechanisms for the resistance were explored by direct sequencing of the EGFR, copy number analysis of candidate genes, Western blotting, phospho-RTK array, and RNA sequencing.

Results: We successfully established acquired resistant cell lines from all cell lines used but H3255. None of the resistant cells harbor any secondary EGFR mutations. We found that HCC827 resistant to BI-4020 (HCC827BIR) had MET gene amplification (2.97 times) and that it was sensitive to a combination of capmatinib (MET-TKI) and BI-4020. On the other hand, HCC4006BIR and H1975BIR developed epithelial to mesenchymal transition as shown by reduced expression of E-cadherin, increased expression of vimentin, and morphological change. PC9BIR showed increased MET phosphorylation without MET copy number gain, however, capmatinib did not restore sensitivity to BI4020.

Conclusions: The on-target resistance through the secondary EGFR mutation was not detected. Instead, MET gene alterations and EMT known for the mechanisms to 1st - 3rd generation EGFR-TKIs, were recurrently observed.

Keywords: BI4020, lung cancer cell lines, acquired resistance mechanisms

EP.03F TUMOR BIOLOGY - TRANSLATIONAL BIOLOGY - TARGETED THERAPY/NOVEL THERAPY
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EP.03F.03 Orally Bioavailable Cyclin A/B RxI Macrocycle has Antitumor Effect in SCLC & NSCLC Cell Line Derived (CDX) & Patient Derived Xenograft (PDX) Models

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Introduction: Currently, there is no approved therapy targeting Rb/E2F pathway deregulation, which occurs in the majority of small cell lung cancer (SCLC) tumors. Complexes between cyclins and cyclin-dependent kinases (Cdk) regulate the activity of RB1 and E2F to drive cell cycle progression. Key substrates and modulators of Cyclin/Cdk complexes bind to the cyclin hydrophobic patch (HP) through their conserved RxL motif. CID-078, an orally bioavailable, passively cell permeable, potent, and selective macrocycle binds the HP of cyclins A and B and blocks the interaction of E2F1 with cyclin A-Cdk2 and Myt1 with cyclin B-Cdk1. CID-078 has been shown to have potent and selective antiproliferative activity in multiple cancer cell lines, including tumor regression in SCLC xenografts and triple negative breast cancer (TNBC) PDX models with high E2F targets hallmark pathway. Here we show that elevated E2F targets and G2M checkpoint hallmark pathway scores and elevated levels of cyclin B1 and p-separase (S1126) are associated with response to cyclin A/B RxL inhibition in SCLC xenografts. These activities are consistent with the proposed mechanism of action for cyclin A/B RxL inhibition which leads to DNA damage, blocks progression at G2M, and leads to apoptotic tumor cell death.

Methods: CID-078 drug response was evaluated in 46 SCLC and 104 NSCLC cell lines. Hallmark pathway scores were calculated from RNAseq data by Gene Set Variation Analysis method using the MSigDB hallmark collection. Based on the significant association of high E2F hallmark pathway score, several CDX and PDX models were selected to evaluate response. NCI-H446 (SCLC CDX) was treated with CID-078 at 50 and 100 mg/kg BID and 25 and 100 mg/kg TID for 14 days. LUX083 (SCLC PDX), NCI-H23 (NSCLC CDX), NCI-H2106 (NSCLC CDX), and CTG-0860 (NSCLC PDX model with low E2F targets hallmark pathway score included as a negative control) were treated at 100 mg/kg BID and TID for 28 days. Post-CID-078 treatment and vehicle control samples from NCI-H446 were analyzed by multiplex IHC for protein level changes in E2F1, cyclin B1, mitotic specific marker p-separase, and DNA damage marker ATM.

Results: CID-078 induced antiproliferation activity in SCLC and NSCLC cell lines. Tumor models with high E2F and G2M hallmark pathways scores and/or elevated levels of cyclin B1 and gene expression levels for separase (ESPL1) showed tumor growth inhibition and/or regression at 100 mg/kg BID and TID (NCI-H446, LUX-083, NCI-H23, NCI-H2106). NCI-H446 tumor IHC analysis at day 6 post treatment showed an increase in p-separase and colocalization of p-separase and cyclin B1. CTG-0860, exhibited modest tumor growth inhibition, but no tumor regression.

Conclusions: As shown previously in TNBC PDX models, CID-078 treatment of SCLC and NSCLC models with high E2F hallmark pathway scores led to tumor regression. Interfering with RxL-mediated interactions between cyclins A and B with their substrates and modulators, including E2F1 and Myt1 by CID-078 may be a new treatment option for patients with SCLC, NSCLC, or TNBC. This hypothesis will be explored in the CID-078 first-in-human trial CID-AB1-24001 beginning later this year.

Keywords: Cyclin, SCLC, NSCLC

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EP.03F.04 Treatment of Non-Small Cell Lung Carcinoma (NSCLC) Cells with Tumor Treating Fields (TTFields) And DNA-Dependent Protein Kinase (PK) Inhibitors

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Introduction: Double-stranded breaks (DSBs) are considered the most deleterious form of DNA damage and can be repaired in cells through three main repair pathways: homologous recombination (HR), non-homologous end-joining (NHEJ), and microhomology-mediated end-joining (MMEJ). Tumor Treating Fields (TTFields) are non-invasive electric fields that disrupt cellular processes critical for cancer cell viability and tumor progression. Recent research showed that TTFields downregulate expression of proteins from the Fanconi Anemia-BRCA pathway, thus lowering the cell's repair capacity via the HR pathway, leading to replication stress and DNA damage. Nedisertib and CC-115 are potent inhibitors of DNA-PK, a main protein mediating the repair of DSBs through the NHEJ pathway. CC-115 also inhibits mTOR, which regulates cell proliferation and survival. The current study examined the potential of the concomitant treatment of TTFields and DNA-PK inhibitors to impair DSBs repair and whether this effect can promote accumulation of DNA damage, triggering cancer cell death.

Methods: A549 and H1299 non-small cell lung carcinoma (NSCLC) cells were treated with TTFields (1 V/cm RMS, 150 kHz, 72 h), alone or with the addition of different concentrations of DNA-PK inhibitors (nedisertib or CC-115). Efficacy was measured by analyzing cell count, colony formation, and apoptosis induction. The overall effect was calculated by multiplying cell count with colony formation. To determine the type of TTFields-drug interaction, the expected additive effect was calculated from the effects of the individual treatments and compared to the actual measured value for treatments co-application (using the Bliss independence method). In addition, cell cycle distribution at different time points was performed for each treatment alone and for the concomitant treatments.

Results: Co-application of TTFields and nedisertib or CC-115 showed a synergistic interaction in A549 cells, which was somewhat higher for CC-115. In H1299 cells, the concomitant treatment of TTFields and nedisertib showed additive interaction and the concomitant treatment of TTFields and CC-115 showed synergistic interaction in cytotoxicity and an additive overall effect. The concomitant treatment of TTFields and nedisertib or CC-115 also resulted in G1 arrest of both cell lines.

Conclusions: Our results suggest a potential advantage for TTFields concomitant with DNA-PK inhibitors. The stronger interaction between TTFields and CC-115 compared to that with nedisertib seen in both cell lines, may possibly be attributed to the dual inhibitory effect of CC-115. In addition, the lower effect of both drugs in H1299 cells compared to A549 cells may be explained, at least in part, by the fact that H1299 cells have an amplification mutation in PRKDC, the catalytic subunit of DNA-PK. Future studies will test whether treatment with TTFields plus DNA-PK inhibitors may sensitize cancer cells to irradiation, a treatment modality that induces DSBs.

Keywords: TTFields, PNA-PK inhibitors, DNA damage

EP.03F TUMOR BIOLOGY - TRANSLATIONAL BIOLOGY - TARGETED THERAPY/NOVEL THERAPY
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EP.03F.05 A Dose-Effect Relationship of a Novel Bronchoscopy Guided Endobronchial Radiofrequency Ablation for Peripheral Lung Tumors

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Introduction: Bronchoscopy-guided radiofrequency ablation (RFA) represents a promising technique for treating peripheral lung tumors, and a predictive dose-effect relationship of RFA is crucial for its clinical application. Here, we present finding on the dose-effect relationship of our novel bronchoscopy-guided endobronchial RFA technique for peripheral tumors.

Methods: In this preclinical study, we employed a novel bronchoscopy-guided RFA procedure utilizing a specially designed balloon catheter (CAROL catheter) and an injectable bronchial electrode based on a medical grade liquid metal (E-GaIn) in porcine lungs. We evaluated the correlation between the volume of E-GaIn and the diameter of the ablation zone. Additionally, we utilized a pseudotumor model created by artificially injecting a mixture of beef meat and contrast dye to validate the efficacy of this novel bronchoscopy-guided RFA technique.

Results: Sixteen temperature-time controlled mode bronchoscopic RFA experiments were conducted, and we found a close correlation between the volume of E-GaIn and the size of the ablation zone (Table 1). This dose-effect relationship of RFA was well-established when the volume of E-GaIn was less than 0.5 ml (R2=0.63, Figure 1). However, achieving homogenous ablation with bronchial electrodes containing more than 0.5 ml of E-GaIn appeared unlikely. In the confirmatory pseudotumor model, all tumors (n=5, mean tumor volume 15,069.6 ± 9,624.3 mm3) were successfully ablated (mean ablation volume 165,441 ± 89,998.5 mm3) using this novel bronchoscopic RFA technique. The mean volume of infused E-GaIn was 0.58 ± 0.16 ml, and the mean ablation time was 464 ± 252.9 seconds.

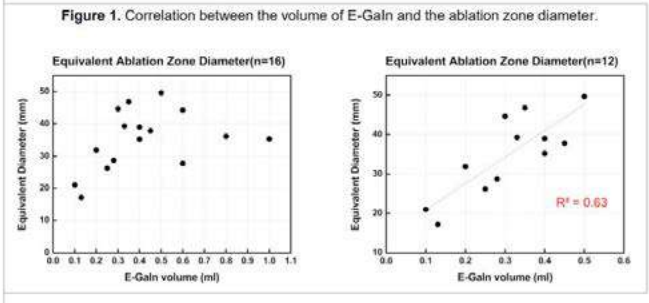
Conclusions: Our study demonstrated that the novel concept of bronchoscopy-guided endobronchial RFA exhibited an excellent dose-effect relationship when the volume of medical-graded liquid metal was less than 0.5ml. These promising preclinical findings strongly advocate for the translation to human application.

A Dose-effect Relationship of Novel Bronchoscopy Guided Endobronchial Radiofrequency Ablation(CAROL)

Keywords: Bronchoscopic Radiofrequency Ablation, Dose-effect Relationship, Peripheral Lung Tumor

E-GaIn volume [ml]	Controlled mode	Duration [min]	Total Energy [W]	Equivalent Ablation Zone Diameter [mm]
0.1	Temp 80°C	6	10000<	20
0.2	Temp 80°C	7	20000<	27
0.3	Temp 80°C	8	30000<	34
0.4	Temp 80°C	9	40000<	41
0.5	Temp 80°C	10	50000<	48
0.5>	Energy 140W	15>	50000>	

Figure 1. Correlation between the volume of E-GaIn and the ablation zone diameter.



EP.03G.01 Comparison of Tumor Immune Microenvironments Between Primary and Metastatic Sites in Non-Small Cell Lung Cancer

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Introduction: The tumor immune microenvironment (TIME) plays a key role in tumor progression and response to immune checkpoint inhibitors (ICIs). Additional analysis of the TIME across sites of disease may help inform future clinical trial designs and identify unique processes to exploit through novel combinatorial approaches. Here, we investigated differences in the TIME of primary and common metastatic sites in patients with NSCLC.

Methods: We retrospectively analyzed de-identified next-generation sequencing data from unique patients with metastatic NSCLC (n=6,534) in the Tempus Database. Tumors from primary lung (n=3,823), liver (n=937), CNS, brain and meninges (n=1,035) and bone (n=739) were sequenced with the Tempus xT DNA (648-gene panel) and xR whole transcriptome RNA assays. Demographics, clinical characteristics, PD-L1 expression, tumor mutational burden (TMB), and proportions of B, T (CD4+, CD8+), NK cells and macrophages were compared across all 4 sites. Pairwise comparisons were performed using Pearson's Chi-squared, Kruskal-Wallis rank sum, and Dunn's tests, and the FDR method was used to correct for multiple comparisons.

Results: The cohort (median age at metastatic diagnosis=67, IQR 61-75, Male=50%) comprised a diverse population (White, 79%, Black/African American, 12%, Asian, 4.0%, Other, 5.8%). The immune biomarker composition varied in primary lung tumors as compared to metastatic sites. Liver, CNS, and bone sites had lower percentage of total immune cells, CD8+ T cells, CD4+ T cells and B cells, and higher percentage of macrophages as compared to primary lung tumors (Table 1) (q-values <0.001). PD-L1 positive status was lower in liver, CNS, and bone compared to lung (q<0.001, q<0.01, q<0.01 respectively). When compared to lung, TMB-H status was modestly higher in patients with CNS metastasis (q<0.001), while TMB-high status was unchanged in patients with liver or bone metastasis (q>0.05).

Conclusions: In this large, real world analysis of patients with metastatic NSCLC, we observed a less immunogenic TIME in liver, CNS, and bone sites of disease compared to primary lung tumors. Our findings are hypothesis generating and further research is warranted to understand how the immune composition of metastatic sites alters the efficacy of ICI in patients with NSCLC.

Table 1. Immune cell quantification in primary and metastatic NSCLC

Characteristics	Lung (L)N=3,823[1]	Liver (LV)N=937[1]	CNSN=1,035[1]	Bone (B)N=739[1]	L vs. LVq-value[2]	L vs. CNS q-value[2]	L vs. B q-value[2]
% IC of all cells	21 (13, 28)	14 (6, 21)	17 (8, 26)	13 (6, 21)	<0.001	<0.001	<0.001
% B cells of all IC	18 (10, 28)	7 (3, 14)	11 (4, 24)	6 (2, 14)	<0.001	<0.001	<0.001
% CD4 cells of all IC	23 (17, 29)	18 (12, 26)	19 (11, 26)	16 (10, 23)	<0.001	<0.001	<0.001
% CD8 cells of all IC	7 (2.3, 10.9)	1.6 (0, 8.8)	4.5 (0, 10.9)	0 (0, 7.9)	<0.001	<0.001	<0.001
% Macrophages of all IC	35 (26, 45)	53 (43, 64)	42 (30, 57)	57 (43, 68)	<0.001	<0.001	<0.001
% NK cells of all IC	12 (7, 18)	12 (8, 17)	14 (9, 20)	12 (7, 20)	>0.05	<0.001	>0.05

IC = immune cells[1]Median (IQR)
[2]Dunn's test with FDR correction

Keywords: Non-small cell lung cancer, Tumor microenvironment, Metastatic sites

EP.03G.02 Molecular and Immune Landscape of Invasive Mucinous Adenocarcinoma (IMA) Of the Lung and Its Survival Outcome

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Introduction: IMA constitutes a rare subset of lung adenocarcinomas. Due to its low incidence, the IMA's biology and prognosis remain poorly understood. In this study, we analyzed the tumor microenvironment, gene expression, and clinical outcomes of IMA patients.

Methods: A retrospective cohort of de-identified records of patients with primary lung cancer were identified in the Tempus database and stratified into IMA or non-IMA. Clinical, biopsy, and molecular characteristics were assessed. Normalized RNA-seq data were used to test for differential gene expression (DGE). Real-world overall survival (OS) was compared by histological subgroup using Kaplan-Meier curves and Cox proportional hazards models using a prospective-like approach. Immune cell infiltration measures were estimated using the quanTIseq algorithm.

Results: The overall cohort consisted of 20,071 patients, with 699(3.5%) in IMA and 19,372(96.5%) in non-IMA. IMA demonstrated significantly lower tumor mutational and neoantigen burdens(3.1 vs. 4.2 mutations/Mb and 7 vs. 9 neoantigens/Mb; p<0.001) with fewer positive PD-L1 status(28% vs. 59%; p<0.001). The tumor microenvironment in IMA patients had higher infiltration of M2 macrophages, regulatory T cells, and NK cells(Table 1). DGE analysis highlighted significant upregulation in genes such as ERVW-1, REG4, TFF2, and TM4SF4 and significant downregulation in IL36RN, NAT8L, and LIN28B in IMA compared to non-IMA. Additionally, hundreds of additional genes were differentially expressed in IMA vs. non-IMA. OS for IMA patients was significantly worse compared to that of non-IMA(Fig 1, HR 1.46, [95% CI 1.07-2.01], p=0.018).

Conclusions: Our study demonstrates the unique pathological and molecular characteristics of IMA vs. non-IMA. IMA showed significantly worse overall survival compared to non-IMA. Our findings warrant further prospective investigation.

Keywords: mucinous adenocarcinoma, microenvironment, tumor biology

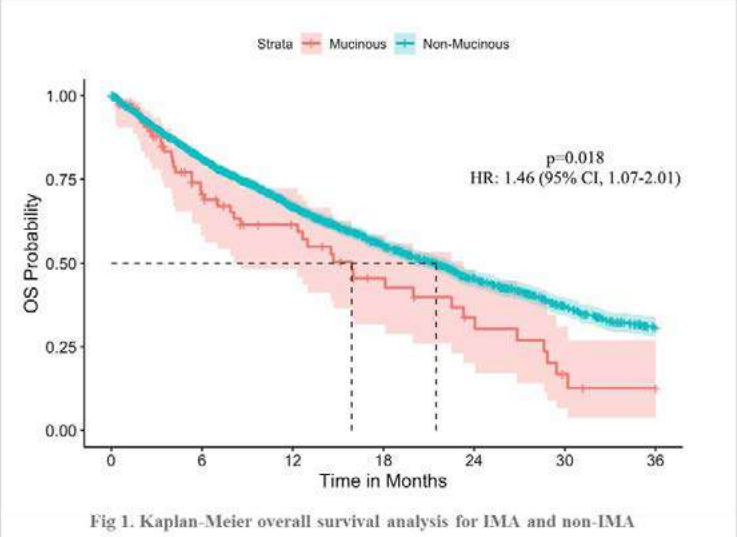

Fig 1. Kaplan-Meier overall survival analysis for IMA and non-IMA

Table 1. Tumor microenvironment according to histology types

Immune cell type, median (Q1, Q3)	IMA	Non-IMA	p-value
B cell	5.9 (4.4, 8.0)	4.5 (3.1, 7.3)	<0.001
M1 macrophage	8 (6,10)	9 (6, 13)	<0.001
M2 macrophage	7.1 (5.0, 9.5)	6.3 (3.8, 8.9)	<0.001
Neutrophils	7.9 (6.2, 10.0)	8.4 (6.4, 10.8)	0.005
CD8 T cell	0.73 (0.19, 1.52)	0.87 (0.17, 2.02)	0.009
NK cell	2.90 (2.33, 3.63)	2.80 (2.11, 3.62)	0.013
Treg cell	5.87 (4.01, 7.77)	4.86 (3.08, 7.28)	<0.001

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EP.03G.03 Tumor Treating Fields (TTFields) Induce Pro-Inflammatory Phenotype Skewing of Macrophages

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Introduction: Tumor Treating Fields (TTFields) are low intensity electric fields that disrupt cellular processes critical for cancer cell viability. Downstream to their antimitotic effect, TTFields have been shown in preclinical models to induce immunogenic cell death of cancer cells and elicit a systemic anti-cancer immune response. Co-application of TTFields with an immune checkpoint inhibitor (ICI) has recently demonstrated benefit in a phase 3 study in non-small cell lung carcinoma. The current research examined possible effects of TTFields on macrophage phenotype regulation.

Methods: Bone marrow-derived macrophages (BMDMs) were generated from the femurs and tibias of 5-8-week-old Balb\C mice. To induce M1 and M2 polarization, BMDMs were exposed to LPS+IFN-γ or IL-4, respectively. The polarized BMDMs were then treated for 24 h with 150 kHz TTFields, followed by flow cytometry examination of surface expression of the F4/80 macrophage biomarker. The treated macrophages were also tested for expression of the following activation markers: CD80, major histocompatibility complex class II (MHC II), inducible nitric oxide synthase (iNOS), CD206, and ARG-1. The supernatants of the treated cells were collected and analyzed for secretion levels of CXCL1 (KC), IL-18, IL-23, IL-12p70, IL6, TNF-γ, IL-12p40, TGγ1, CCL22 (MDC), IL-10, IL-6, G-CSF, CCL17 (TARC), and IL-1 γ using a multiplexed secretion assay. The lysates of treated cells were examined for RhoA activation using an appropriate kit and GEF-H1, c-Jun, and p65 phosphorylation levels by Western blot analysis.

Results: Following TTFields exposure BMDMs demonstrated elevated expression of CD80+ and MHC IIhigh pro-inflammatory M1 markers, and decreased expression of CD206 and ARG-1 M2 markers. The secretion pattern was pro-inflammatory, with increased levels of CXCL1, IL-18, IL-23, IL-12p70, TNF-γ, IL-12p40, CCL22, G-CSF, CCL17 and IL-1 γ. TTFields treatment induced activation of RhoA, and phosphorylation of GEF-H1, c-Jun and p65.

Conclusions: This study reveals a novel immunomodulatory role for TTFields, promoting in vitro pro-inflammatory macrophage polarization, possibly via transcriptional response driven by the GEF-H1/RhoA/ROCK pathway.

Keywords: TTFields, Immunomodulation, Macrophages

EP.03G TUMOR BIOLOGY - TRANSLATIONAL BIOLOGY - TUMOR MICROENVIRONMENT
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EP.03G.04 High SLFN11 Expression Predicts Response but is not Required to Confer Sensitivity to Lurbinectedin

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Introduction: Lurbinectedin (Zepzelca®) received accelerated approval from the US FDA as monotherapy in June 2020 for the treatment of adults with metastatic small cell lung cancer (SCLC) with disease progression on or after platinum-based chemotherapy. Lurbinectedin binds to the GC-rich triplets in the promoters of protein-coding genes, blocks RNA polymerase II, and induces its degradation resulting in double-stranded DNA breaks and DNA damage that leads to cellular apoptosis. Schlafen 11 (SLFN11), a putative DNA/RNA helicase, irreversibly binds to DNA replication forks in response to stress and blocks replication. SLFN11 is an emerging predictive biomarker of response to therapeutics that elicit DNA damage including cisplatin, topoisomerase I/II, and poly(ADP-ribose) polymerase (PARP) inhibitors.

Methods: In vitro studies: Cytotoxicity assays were performed on cancer cell lines and patient-derived non-SCLC organoids. Lurbinectedin (100 nM-0.01 nM) was used and cell viability was determined by measuring intracellular ATP. SLFN11 expression was retrieved as RNAseq values from DepMap database. RNAseq value of >2 was assigned as SLFN11 high, and value of <2 was assigned as SLFN11 low. The significance of the difference in log10(IC50) between SLFN11 high and low lines was determined using the Mann-Whitney test. SLFN11 was knocked down (KD) using siRNA in 2 cervical (CA Ski and C-33 A) and 2 SCLC (NCI-H1048 and DMS79) cell lines. In vivo studies: Lurbinectedin response was evaluated in 3 SCLC xenograft models (NCI-H1048, NCI-H889, and NCI-H69) at doses of 0.06, 0.12, or 0.18 mg/kg IV Q3W. Tumor-bearing mice were randomly allocated to treatment and control groups (n=8) once tumors reached a volume of 100-150 mm3. Protein expression assays: SLFN11 protein was detected using Western blot (sc-374339) and quantified by image analysis. Immunohistochemistry was used to detect SLFN11 protein on xenograft tissues. The intensity of positive staining on tumor cells was scored at 4 levels: 0 (negative), 1+ (weak), 2+ (medium), and 3+ (strong). The percentages at each intensity were used to assign an H-Score (0-300).

Results: High SLFN11 models are 3-4-fold more sensitive to lurbinectedin compared with low SLFN11. SLFN11 RNA and protein show a strong correlation (r2=0.924). The in vivo efficacy shows the NCI-H1048 model is significantly more responsive with 90% tumor growth inhibition compared with 35% in NCI-H889 and NCI-H69 at 0.18 mg/kg dose (p-value=0.006). An H-score of 111.86 (NCI-H1048) and 0 (NCI-H889 and NCI-H69) was observed. Western blot confirmed ~95% protein loss in KD cells. SLFN11 KD did not affect lurbinectedin response in CA Ski, C-33 A, and NCI-H1048 cells. SLFN11 KD in DMS 79 cells had a modest 2-fold decrease in sensitivity to lurbinectedin.

Conclusions: Cell viability and in vivo studies confirm that high SLFN11 models are more sensitive to lurbinectedin. SLFN11 RNA and protein expression show strong correlation. Loss of SLFN11 does not affect sensitivity to lurbinectedin, suggesting it is a biomarker of response but not necessary for sensitivity. Some low SLFN11 models are sensitive to lurbinectedin, suggesting a role of other genes in determining drug response. Further proteomics and genomics work is needed to define additional response biomarkers.

Keywords: SLFN11, Lurbinectedin, biomarker

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P.03H TUMOR BIOLOGY - TRANSLATIONAL BIOLOGY - CLINICAL TRIALS IN PROGRESS
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EP.03H.01 Detection of PAX5 Gene Mutations in Patients with East Asian Non-Small Cell Lung Cancer Patients

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Introduction: PAX5 is one of the most frequently mutated genes in B-cell acute lymphoblastic leukemia (B-ALL), and children with inherited preleukemic PAX5 mutations are at a higher risk of developing the disease. The aim of this study is to investigate mutations and prognosis of non-small cell lung cancer (NSCLC) harboring PAX5 mutations.

Methods: A total of 602 patients with non-small-cell lung cancer were recruited between July 2012 and December 2018. The status of PAX5 mutations and other genes were detected by next generation sequencing.

Results: PAX5 gene mutation rate was 0.83% (5/602) in non-small cell lung cancer, including T251I(1 patient), E113D(1 patient), H318L(1 patient), T386N(1 patient) and S134F(1 patient), and median overall survival (OS) for these patients was 22.0 months. Among them, all patients were PAX5 gene with co-occurring mutations. Briefly, patients with (n=2) or without (n=3) co-occurring ALK mutations had a median OS of 3.0 months and 24.0 months respectively (P=0.04); patients with (n=13) or without (n=1) co-occurring SMARCA4 mutations had a median OS of 15.5 months and 22.0 months respectively (P=0.64); patients with (n=2) or without (n=3) co occurring KEAP1 mutations had a median OS of 24.0 months and 5.0 months respectively (P=0.20); patients with (n=3) or without (n=2) co-occurring CREBBP mutations had a median OS of not up to now and 11.5 months respectively (P=0.30).

Conclusions: Althoght ALK, SMARCA4, KEAP1, CREBBP gene accompanied may have less correlation with PAX5 mutation in NSCLC patients, predict which patients may harbor PAX5 mutations, could have implications in triaging toward PAX5 variant identification for potential future targeted therapy. These data have implications for the identification of therapeutic target candidates.

Keywords: non-small-cell lung cancer, PAX5 mutation, prognosis

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EP.04A.01 Lung Cancer Nurse Consultant-Led Pulmonary Nodule Assessment and Surveillance Clinic: Multidisciplinary Team Evaluation

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Introduction: In July 2025, Australia will introduce a national Lung Cancer Screening Program. The assessment of pulmonary nodules and subsequent patient management are Program aspects anticipated to have major workforce implications.

This implementation project aimed to 1) demonstrate safe, advanced practice nursing relative to pulmonary nodule assessment, surveillance, and patient management, 2) promote the scope of the advanced practice nurse role in this service context, and 3) improve capacity in respiratory physicians to attend to high-risk cases in a timelier manner.

Methods: Early 2023, clinical redesign of a regional public out-patients respiratory medicine specialist service in New South Wales included: streamlined general practice referral pathways, nurse-led triage, rapid access pathway and pulmonary nodule assessment and surveillance for high-risk patients, consistency in diagnostic radiology reporting and, new standardised documentation. Two lung cancer nurse consultants were up-skilled via a mentor program in image review and reporting.

During April to July 2023, nurses evaluated incidentally found pulmonary nodules against evidence-based guidelines, provided recommendation for nodule management with governance review by a respiratory physician, and communicated the plan to patients and their primary care practitioner. The nurses assessed and managed up to 10 surveillance patients each at any one time, with each patient potentially requiring two to three images for review. The Evaluating the Nurse Practitioner Role: Multidisciplinary Team Questionnaire, a 22-item validated Likert scale (1=Strongly Disagree to 5=Strongly Agree) was adapted to elicit multidisciplinary team members' perceptions of the contribution and value of this nurse-led clinic to patients, the team and broader out-patients service (14 items), and perceptions of the abilities of the advanced practice role to deliver the clinic safely (8 items). Free text capability is also provided. Descriptive analyses generated sentiment scores reflecting the level of respondent's perceptions of a) the clinic and b) the advanced practice role. Qualitative content analysis helped to interpret some neutral and mildly negative sentiments.

Results: Eighteen respondents completed the questionnaire (August to September 2023). Of respondent's perceptions of the clinic, a sentiment score of 4.7 (out of a possible 5) suggests team members are very positive about the contribution and value of the clinic to patients, team functioning and service efficiency. This score was affected by mildly negative responses to item 1 ('I fully understand the Specialist Lung Cancer Nurse Pulmonary Nodule Surveillance Clinic'). Of respondent's perceptions of the advanced practice role to deliver the clinic, a sentiment score of 4.6 (out of a possible 5) indicates team members are highly confident in the lung cancer nurse consultant role to deliver the clinic service in a safe and appropriate manner. Informed by the content analysis, the 12-week pilot phase was considered too short, impacting time needed for team members to fully understand the scope of both the clinic and role in this important area of practice. This influenced neutral scoring, particularly across items centred on the advanced practice role.

Conclusions: This project highlights the critical importance of rigorous definition in the lung cancer nurse consultant role relative to Australia's imminent national Lung Cancer Screening Program.

Keywords: Nurse-led pulmonary nodule assessment, Advanced practice nurse, Pulmonary nodule surveillance

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EP.04A.02 Automated Reading May Improve the Safety of Triennial Lung Cancer Screening Intervals for Low-Risk Subjects

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Introduction: Lung cancer (LC) screening with low dose computed tomography (LDCT) can reduce mortality in high-risk individuals, but the optimal screening interval has still to be defined. The BioMILD trial tested the feasibility and safety of triennial LDCT screening in subjects with a negative baseline LDCT, showing a limited risk of late diagnosis.

Methods: We re-assessed the diagnostic efficacy and safety of a prolonged LDCT interval by automated second reading of all negative baseline LDCTs, using an artificial intelligence (AI) software (Coreline AVIEW). Lung cancers detected before the scheduled triennial LDCT were analysed according to the AI LungRADS classification, to explore any avoidable risk of late diagnosis.

Results: Of the 3450 BioMILD participants with negative baseline LDCT, automated AI reading classified 423 (12.3%) as LungRADS 3 and 172 (5%) as LungRADS 4. A total of 3 LCs were detected in the re-classified subsets (0.5%), 2 in LungRADS 3 (at 25-31 months from baseline) and 1 in LungRADS 4 (at 28 months). The type and stage distribution (SCLC, stage III-IV) does not suggest a potential clinical benefit achievable by shorter LDCT intervals. Nonetheless, some of the LungRADS 4 subjects could have been more safely sent to 3-6 months and LungRADS 3 to annual or biennial LDCT, upon evaluation of the radiologist.

Conclusions: Automated AI reading can reduce the number of false negative baseline LDCTs and improve the selection of longer screening intervals, based on the individual LC risk. AI software represents a useful instrument in the hands of dedicated radiologists.

		AI Coreline			
	Total	LungRADS 1	LungRADS 2	LungRADS 3	LungRADS 4
Negative baseline LDCT	3450	986 (28.6%)	1869 (54.2%)	423 (12.3%)	172 (5%)
Lung Cancers within 3 years	9 (0.3%)	1 (0.1%)	5 (0.3%)	2 (0.5%)	1 (0.6%)
SCLC	4	1	0	2	1
NSCLC stage III-IV	2		2		
NSCLC stage I-II	3		3		

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EP.04A.03 Quality Implementation of Lung Cancer Screening using the QUILSTM System: Baseline Data from Ten Programs in Kentucky

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Introduction: Lung cancer screening (LCS) using low-dose computed tomography (LDCT) has emerged as an evidence-based approach to detect lung cancer early and reduce lung cancer mortality when conducted among individuals at high risk. Despite robust evidence supporting LCS implementation and a favorable insurance coverage climate due to established guidelines and recommendations, national LCS implementation has encountered a host of multilevel barriers, including incomplete LCS awareness among clinicians, limited engagement among eligible individuals, suboptimal adherence to the screening algorithm, and lack of integration into healthcare system operations. To address barriers and optimize LCS delivery, the Kentucky LEADS Collaborative developed a comprehensive system (QUILSTM System 1.0: Quality Implementation of Lung Cancer Screening) to evaluate LCS delivery, with a focus on supporting rural and low-resource LCS programs. The purpose of this study was to implement the QUILSTM System 1.0 in ten LCS programs to evaluate quality of LCS delivery in diverse settings.

Methods: A multidisciplinary development team created the QUILSTM Index 1.0, an evaluation system to assess quality LCS program operations across six domains: (1) Screening Eligibility, (2) Clinical Radiology Operations, (3) Interdisciplinary Team Operations, (4) Lung Cancer Prevention Efforts, (5) Patient Education, Counseling, and Support, and (6) Community Outreach. Each domain included multiple quality elements, creating 16 scored elements and a total score ranging from 0 to 75. The score was normalized to a range of 0 to 100% quality points. Ten LCS programs at academic, private, and rural community hospitals across Kentucky were evaluated using the QUILSTM Index 1.0. Three data sources contributed to calculating the QUILSTM Index 1.0, including: surveys and interviews conducted with LCS program navigators and medical directors and site-level LCS implementation data.

Results: Overall quality scores ranged from 55% to 87%, with an average score of 69% (SD=9%) across the ten sites evaluated. LCS Programs consistently received high scores on elements involving (1) Screening Eligibility Policy, (2) Screening Frequency & Duration Policy, (3) LDCT Performance, (4) Lung Nodule Identification, and (5) Provider Outreach with most programs receiving optimal scores. LCS Programs scored consistently low on several other elements, including (1) Team Review of Radiology Results, (2) Tobacco Treatment Interventions, (3) Tobacco Treatment Targets, and (4) Shared Decision Making.

Conclusions: Quality LCS implementation will be an essential component to achieving optimal individual and population health benefits promised by rigorous efficacy trials of LDCT. Across ten sites evaluated with the QUILSTM System 1.0, LCS programs performed well under the Screening Eligibility and Clinical Radiology Operations domains but demonstrated opportunities for improvement in the Interdisciplinary Team Operations and Lung Cancer Prevention Efforts domains. Despite the heterogeneity of sites, all ten LCS programs demonstrated areas for potential improvement. Next steps included delivering feedback to the sites using the QUILSTM Audit and Feedback process, and providing access to the QUILSTM Resource Portal and QUILSTM Coaching and Technical Assistance components to help LCS programs improve service quality. Longitudinal evaluations will also be conducted to assess change in service delivery and quality outcomes.

Keywords: Lung Cancer Screening, Quality, Implementation Science

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EP.04A.04 Real-World Data of LDCT Lung Cancer Screening Implementation in a Public Healthcare System: Quebec Three 3-Year Experience

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Introduction: Studies have shown that Low Dose Computed Tomography (LDCT) lung cancer screening decreases lung cancer mortality. However, only few jurisdictions worldwide with public healthcare system have implemented formal screening program. Cost is a concern but many other challenges might be obstacles to moving forward. Real-world data from experiences in this setting can provide some answers not available in randomized trials. Here, we present the three-year experience in Quebec, Canada.

Methods: Public LDCT lung cancer screening started in June 2021, implemented in a limited number of hospitals. The process involved an evaluation phase before a decision was made on whether to extend the program to the entire province. The objective was to enroll 3000 participants and analyze the data after two annual rounds of screening. A public communication campaign was launched at the outset but was not repeated thereafter. All referrals and self-referrals were centrally evaluated at the coordination center (IUCPQ) and LDCT scans were conducted at one of the designated hospitals nearest to the participant residence. Quebec decided to offer lung cancer screening to individuals aged 55 to 74 who were current or former smoker (with cessation ≤ 15 years), had a smoking history of 20 years or more, and a PLCOm2012norace score ≥ 2%. The Lung-RADS classification system was used. A standardized report template was used by all participant radiologists. All reports were forwarded to the coordinating center, which was responsible for communicating with participants and prescribing physicians and ensure proper follow-up. Smoking cessation interventions with the participants were also integrated.

Results: After 18 months, the coordination center received 8212 referrals, of which 4318 were deemed eligible and agreed to screening after a shared decision process. Among the first 3200 LDCT scans, 45% of participants were female (sex) and 71% were active smokers. The mean PLCO score was 5.2% (median 4.0%). The distribution of Lung-RADS 3 and 4 lesions met the target, with each comprising 7% of cases. Respectively, 94% and 83% of participants came back for their interval LDCT (Lung-RADS 3 and 4A) or annual screening (Lung-RADS 1 or 2). Potentially significant incidental findings were high at 25%, but included severe coronary calcifications (40%) and no chart research was performed to exclude those that were already known. Lung cancer detection rate in the first screening round was 1.6%, with 85% of cases being stage I or II cancers. Treatment modalities included surgery (±chemotherapy/immunotherapy) in 89%, and SBRT alone in 5%. Concerns regarding impact on resource utilization primarily centered around CT access in some centers, where wait times for screening LDCT increased overtime to a level requiring special interventions. To date, we had over 18000 referrals, with over 9000 of them deemed eligible for screening. Additional details of the three-year experience are available in the poster.

Conclusions: Structured LDCT lung cancer screening program in a public healthcare system is able to reach targeted early indicators according to previous randomized trials. Access to CT scans was a concern in our jurisdiction and needs to be specifically addressed.

Keywords: lung cancer, screening, public healthcare

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EP.04A.05 Lung Cancer Screening Outcomes in Aotearoa New Zealand

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Introduction: Lung cancer is the leading cause of cancer deaths for Māori and non-Māori. Māori LC mortality rates are over three times those of non-Māori. Lung cancer screening (LCS) using low dose CT (LDCT) reduces LC mortality by 20-26%. GP clinics were recruited to a clinical trial of invitation to LCS. Participating practices were censored from the invitation trial if they had not completed contacting their list of potentially eligible patients after 8 months and the eligible patient participants from these practices were then contacted and offered LCS. Secondary outcomes in this trial included results of participation at all parts of the screening pathway, nodule findings and incidental findings. These results are presented here.

Methods: GP clinics were recruited to a clinical trial of invitation to LCS. Potentially eligible participants (Maori, 55-74 years, not 'never smokers' in the PMS) in each practice were contacted and invited to participate in the trial. Consented participants underwent PLCOm2012 risk assessment (RA). Those with a risk assessment of ≥2% were offered shared decision making. If they chose to proceed with CT scan an appointment was arranged. Appropriate follow up was arranged according to the results of the CT scan. Information on incidental fundings was collected.

Results: Risk assessment was undertaken on 1013 people. The risk threshold of >= 2% was reached in 546 (54%) of people. After shared decision making 540 (92%) underwent a low dose CT scan. A further 115 received a CT scan under this pathway. Of the 504 completed CT scans: 63% have had no significant nodules (PC1); 24% required a 12 month follow up scan (PC2); 10% had 3 month follow up scan (PC3) and 2% were referred for immediate follow up. Incidental findings were observed in all scans. However, the findings were not usually associated with a beneficial intervention in 29%. Incidental findings that might need: non-urgent primary care intervention e.g. CVDRA, COPD management were seen in 47%; non-urgent secondary care referral in 21% of scans and urgent secondary care referral in 1% of scans.

Conclusions: Participation of Māori who were eligible for LCS was very high (92). This is much higher than Māori participation in current national cancer screening programmes. 47% of scans required subsequent follow up. All scans had incidental findings but most were not associated with a beneficial intervention or suggested conditions that, in this population, should already be managed in primary care e.g. COPD and cardiovascular disease risk assessment and management.

Keywords: Lung cancer screening, Indigenous, Equity

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EP.04A.06 A Comprehensive Lung Cancer Screening Program: Ten Years in Review

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Introduction: Lung cancer remains the leading cause of cancer death worldwide. Lung cancer screening(LCS) provides opportunities for early detection, improved survival and tobacco cessation. The National Lung Screening Trial paved the way for accepted guidelines for LCS with updates after completion of the NELSON trial. Outcomes following implementation of LCS programs are not widely known. This investigation provides outcomes and lessons learned in the first decade of the LCS program at a large tertiary care cancer center. Disclosure of outcomes provides information to enhance success of subsequent programs.

Methods: The screening programs' REDCAP database was queried for the results. Demographics, CAT scan data, lung cancer diagnoses, adherence rates and tobacco cessation rates were computed.

Results: The screening center enrolled 2420 patients between 9/30/14 and 3/1/24 (130 patients were enrolled for tobacco cessation only with 2290 in LCS.

65%/35% Male/Female

49% Current Smokers

CT LungRAD distribution shown on Table 1

Adherence rates were 84% for first follow up CT scan

83(3.7%) lung cancer diagnoses

Cancer Cell Types: 52/83(63%) Adenocarcinoma 17/83(20%) Squamous Cell 5/83(6%) Small Cell 9/83(11%) Other

The distribution of stages in LCS compared to CDC are shown in Table 2.Self-reported quit rates were 29.5% within the first two years of screening.

Five year survival rates for patients diagnosed stage 1A/1B is 100%(n=26)

Conclusions: Lung Cancer Screening provides opportunity for early detection and increased survival rates. The distribution of stages among patients with lung cancer disclosed by CDC for the general population compared with those diagnosed in the screening program are shown in Table 2.LCS patient population had higher rates of early stages.In addition, LCS provides opportunities to engage in tobacco cessation counseling with increased quit rates compared to general population. Further investigation is warranted.

Keywords: screening, early detection, tobacco cessation

Table 1 CT FINDINGS ON FIRST CAT SCAN

LUNG CANCER RATES AMONG PATIENTS ENROLLED IN LUNG CANCER SCREENING PROGRAM

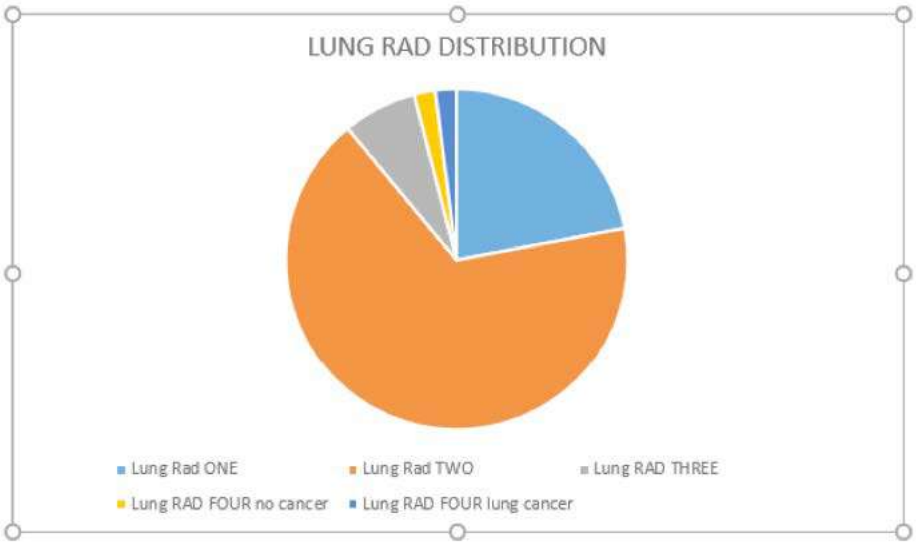
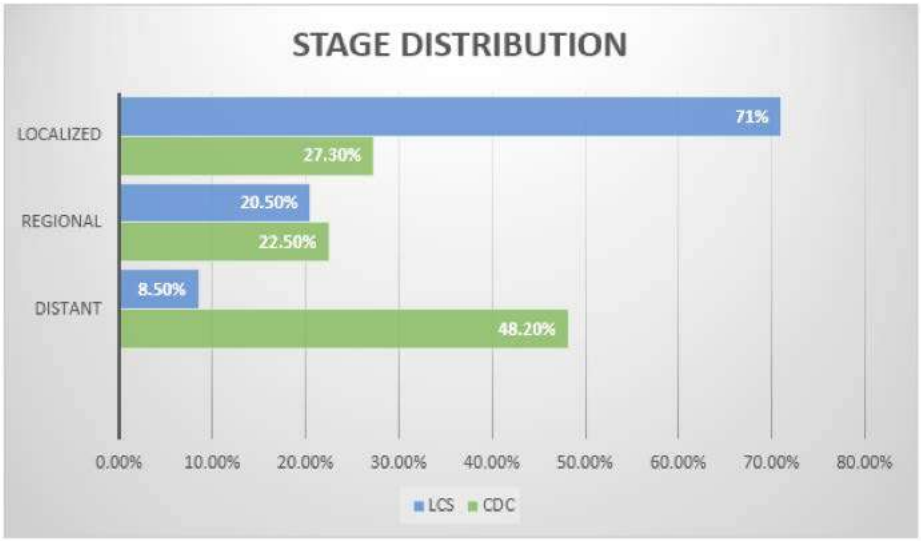


Table 2 STAGE AND HISTOLOGICAL TYPE CDC reports vs LCS program at SB reports



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EP.04A.07 A Framework and Toolkit to Support the Implementation of LDCT Screening with a Focus on Inclusion of Underserved Communities

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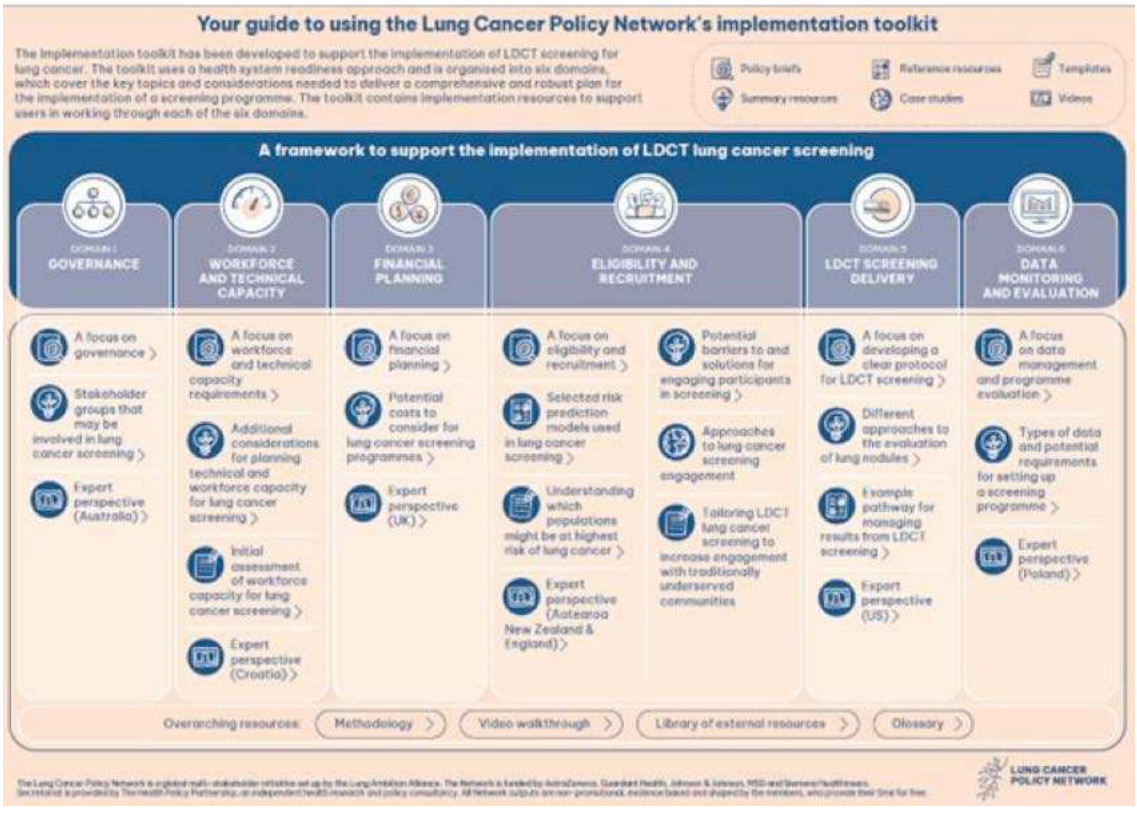
Introduction: The Lung Cancer Policy Network, a global multi-stakeholder initiative of experts in lung cancer, has developed a framework and toolkit to aid the implementation of LDCT screening. The implementation framework spans six domains, consisting of key questions and metrics, aiming to support the implementation of high-quality screening for lung cancer globally. The implementation toolkit assists users in applying the implementation framework to a health system. Individuals at risk for lung cancer often suffer structural discrimination in health systems and public health programmes. To reduce health disparities and inequities, and improve screening uptake, strategies must leverage methods that address barriers to participation. Additional resources focused on increasing engagement with underserved communities have been developed to enhance the toolkit's usability, accessibility, and effectiveness. This expansion complements the Network's efforts to make improving the survival of lung cancer a global policy priority.

Methods: The toolkit was initially informed by a review of existing peer-reviewed and grey literature, interviews with nine experts across four continents, and insights from Lung Cancer Policy Network members. The expansion of the toolkit focuses on Domain 4 of the implementation framework: eligibility and recruitment. This was informed by Network member insights and literature research, including a focus on England and Aotearoa New Zealand.

Results: The first iteration of the implementation framework and online toolkit was published in March 2023. To date, the framework has been downloaded over 800 times and nearly 1,500 people have accessed the toolkit. The expansion to focus on underserved communities was launched in April 2024. To support the usability of the toolkit, the toolkit expansion includes a overview document showcasing the available resources, logically categorised by domain. Additional resources have also been developed to support the engagement and recruitment of traditionally underserved communities for lung cancer screening. This includes: • A template to identify traditionally underserved communities, understand their needs and design an inclusive lung cancer screening programme. • Two case studies of alternative approaches to increasing screening participation of traditionally underserved communities in different national contexts (England and Aotearoa New Zealand).

Conclusions: To our knowledge, this is the first framework to support the implementation of LDCT screening programmes globally. Application of the framework may inform implementation policies - facilitating high-quality, equitable and cost-effective screening. The toolkit development and expansion will support those designing and delivering LDCT lung cancer screening programmes by ensuring effective and equitable implementation to help address lung cancer inequalities.

Keywords: lung cancer screening implementation, global lung cancer screening framework, lung cancer screening policy



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EP.04A.08 Leveraging the Quebec Lung Cancer Screening Program to Create a Collaborative Biobanking Project for Research Purposes

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Introduction: In 2021, the Quebec ministry of health launched the Lung Cancer Screening Demonstration Project. In collaboration with several institutions, the Institut universitaire de cardiologie et de pneumologie de Québec-Laval University (IUCPQ-ULaval) was mandated to implement the program across the province of Quebec, Canada. With the support of the project's coordination center and the Quebec Respiratory Health Research Network (QRHN) Biobank network, we initiated a multicenter project for biobanking of clinical data, low-dose CT (LDCT) chest images and biological samples for research purposes. The objective of this initiative was to build a cohort of biological samples and data from a population at high risk of developing lung cancer and make these samples and data available to the scientific community for research projects on respiratory and non-respiratory diseases.

Methods: The collaboration with the QRHN Biobank provided valuable support, leveraging its established structures, procedures, and management framework across various locations in the province of Quebec. This partnership facilitated the implementation of the screening program in six hospitals, all of which agreed to participate in the project. Notably, nurses from the Lung Cancer Screening coordination center played a pivotal role by engaging eligible patients and inviting them to take part in the biobank.

Results: As of April 2024, 3,374 patients have signed the consent form, and 2,947 of them have also accepted to provide a blood sample. At the beginning of 2024, 718 patients have completed their 2-year follow-up with at least three LDCT scans. To date more than 6,271 LDCT scans have been completed and 22% of these exams show suspicious nodules with a Lung-RADS Score ≥ 3. 2,568 imaging studies are stored in the Biobank and the collection of data is in progress. After the last follow-up expected in 2026, more than 10,000 LDCT imaging studies will be banked for the entire cohort. Data and imaging studies are stored in centralized database and servers. Blood samples are stored and managed by IUCPQ-ULaval and McGill University Health Centre (MUHC) sites of the QRHN Biobank (2,752 and 195 blood samples respectively). Management frameworks for storage of data, images and biological samples were approved by local research ethic boards. A Data/Material Access Committee oversees the use of the Biobank.

Conclusions: This collaborative initiative aims to create a unique cohort of imaging, clinical data and biological samples in the context of a lung cancer screening program for research projects. Upon completion of the patient recruitment, scheduled for summer 2024, the data and samples will be available upon request. With the emergence of artificial intelligence-based applications in health research, and the advancement of blood-based biomarker development, this project holds the potential to uncover novel predictive and diagnostic biomarkers.

Keywords: Lung Cancer Screening, LDCT, Biobank

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EP.04A.09 The Impetus, Formation and Initial Strategic Aims of the UCLCC Screening and Prevention Task Force

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Introduction: California has the second highest number of lung cancer cases and deaths in the US, but the lowest lung cancer screening (LCS) rate at 0.7% of eligible patients. The University of California (UC) system is unique among academic health systems in its reach across the most populous state with >8 million outpatient visits annually. In October 2021, clinical leaders from the 5 NCI-designated UC comprehensive cancer centers (UC-San Francisco, UC-Davis, UC-Los Angeles, UC-Irvine, UC-San Diego) developed a strategic plan, forming the UC Lung Cancer Consortium (UCLCC), and within its framework, a Lung Cancer Screening and Prevention Task Force (LSPTF) to improve screening rates within the UC system and the state. This work describes the formation, initial strategic aims, and accomplishments of the UCLCC LSPTF since inception.

Methods: Screening champions were identified at each UC campus by nomination of their peers, with two co-chairs elected for LSPTF oversight. To improve screening accessibility and prevalence, the LSPTF identified 3 strategic priorities: 1) to improve eligible patient identification, 2) to develop a digital resource to directly engage with eligible patients with smoking histories, and 3) to improve access for underserved communities. Participation in the LSPTF was opened to all interested UC health system employees, as well as members of the UCLCC's four other task forces in diagnostics, novel therapeutics, population health and policy, and tumor biology.

Results: The UCLCC LSPTF has facilitated coordination of lung cancer screening efforts and collaborative learning across UC campuses. To date, the UCLCC LSPTF includes 28 members. To address aim 1, a "standard work" approach to comprehensive LCS was agreed upon by the 5 sites, including stressing the importance of tobacco cessation strategies. Patient eligibility, primary care empanelment, and screening data were captured within the UC data warehouse as a prospective digital dashboard, allowing accurate and transparent tracking of LCS metrics across UC health systems. To address aims 2 and 3, a web-based shared decision-making LCS resource, ucscreenca.org, was created through a rapidly customizable modular platform, allowing UCLCC to reach individuals outside of the UC system. This resource was made publicly available November 2023 and includes screening eligibility assessment, personalized lung cancer screening navigation, and a screening center locator that is UC-agnostic. To support lung cancer awareness month, education and outreach events for patients and providers at each UC campus were coordinated through the UCLCC LSPTF in November 2023.

Conclusions: Through UCLCC LSPTF, the UC health system has developed statewide comprehensive screening metrics and a shared decision-making digital platform that has reached thousands of users. Formation of the UCLCC LSPTF has also inspired regional collaborations across the state between UC and community partners. Next steps in the UCLCC's 5-year plan include improving accurate capture of tobacco use data in the electronic medical record and assessment of the effect of lung cancer screening utilization dashboards on screening uptake and adherence in the UC system.

Keywords: lung cancer screening, task force, regional collaboration

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EP.04A.10 Creating Safe Connections: Usability Testing of an Intervention Co-designed to Increase Equitable Access to Lung Cancer Screening

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Introduction: Patients living with structural marginalization and at high risk of developing lung cancer (due to the social patterning of smoking addiction) report that clinical encounters which are stigmatizing and discriminatory are a major barrier to participation in lung cancer screening. Healthcare providers report a lack of skills and competencies to understand the underlying determinants of lung cancer risk and need training to deliver patient-centered care that is equity-promoting. To address this gap, we co-designed an educational intervention (an e-learning module) to increase equity at the point-of-access to lung cancer screening based on the Trauma and Violence Core Competency Framework, called Creating Safe Connections. Here we describe how we conducted usability testing of the intervention using a patient-centric and patient-partnered approach to maximise learning effectiveness prior to full scale implementation.

Methods: This is an interdisciplinary, patient-partnered, pragmatic, usability testing study. Team members included policymakers, healthcare providers, researchers and patient partners with lived/living experiences intersecting across elements of race, gender, disability, Indigeneity, immigration, poverty and homelessness. The objective of usability testing was to understand barriers and optimise learning effectiveness of the e-learning module. Participants were purposively recruited through snowball sampling from a pool of primary care providers, regional cancer strategic leads, educationists and patients. Data was collected from nine participants using a 5-points Likert scale survey and open-ended questionnaire to record: (i) the design of the interaction (questions related to the device used and navigation of content), and (ii) design of the instruction (presentation of content and learning impact).

Results: Data collection, analysis and modification of the e-learning intervention occurred in tandem and in line with user-centric design principles. 67% of participants accessed the intervention on a smartphone, and 33% used a laptop/desktop. All participants completed the entire module and 83% downloaded the accompanying notebook which contained reflective prompts and resources. 33% reported navigational challenges between segments of the module. 100% found the videos, case studies and learning prompts useful with all participants commenting on the exceptional quality and learning from the embedded videos. Overall, participants found the content useful for practice (67% strongly agree), the right mix of interactive versus non-interactive components (67% strongly agree and 33% agree), and would recommend it colleagues (100%), including institutional staff and healthcare leaders. Using an iterative approach learning effectiveness was enhanced by correcting navigational difficulties, linking to jurisdictionally relevant resources, adding more specific examples and language to the section on de-escalation of unsafe clinical encounters.

Conclusions: We describe an interdisciplinary and patient-centric approach to the usability testing of an intervention co-designed to increase equity in access to lung cancer screening. Through a systematic, iterative method we increased effectiveness of the learning module in preparation for national-level implementation. The e-learning module is now Continued Medical Education (CME) accredited and is freely available to any learner through the University of British Columbia, Canada learning platform.

Keywords: Lung cancer screening, health equity, patient-centric

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EP.04A.11 Patients Reported Outcomes in Short- And Long-Term Lung Cancer Survivors Who Were Diagnosed via Chest Low-Dose CT Screening

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Introduction: Low-dose computed tomography (LDCT) screening reduces mortality from lung cancer. Knowledge is limited regarding the effect of screening on long-term health and psychosocial-related quality of life (QoL). We investigated short and long-term QoL outcomes, comparing LDCT-screening detected to usual-care diagnosed lung cancer patients and to controls who screened negative for lung cancer.

Methods: In our 20-year prospective lung cancer cohort, we analyzed 4122 patients who answered Patient Reported Outcomes (PRO) questionnaires within three years of lung cancer diagnosis (short-term responders) and 1291 patients who answered five years after (long-term responders). From the cohort with PRO data, we identified and compared LDCT-screening detected (CT-screened, n[short]=350, n[long]=105) to the usual-care diagnosed (Usual, n[short]=2406, n[long]=654) lung cancer patients, and each patient group to Controls (n=480). QoL and social factors were scored on a 0 (worst)-10 (best) scale. A difference of 1.0 unit or more in median score was considered clinically meaningful.

Results: (all Ps<0.05) Among short-term responders, compared to the Usual, CT-screened patients were older (66 vs. 64), more females (54.6% vs. 47.9%), more stage I-II disease (72.2% vs. 37.3%) and treated by surgery only (56.0% vs. 25.3%); had a lower proportion of "Moderately-Markedly" reduced appetite (13.9% vs. 20.7%), lower proportion of "quite a lot" of difficulty in daily work or "could not do work" (22.1% vs. 30.9%), and better normal activity (8.6 vs. 7.4) and overall QoL (8.0 vs. 7.0). Among long-term responders, the two groups had similar differences in disease stage and treatment modality as in the short-term. Importantly, both groups in short- and long-term responders reported significant dyspnea (5.5-6.0) and fatigue (5.0 for all four groups). Compared to the Controls, short-term responders in CT-screened patients had similar mean age (66 vs. 67), more females (54.6% vs. 41.7%), longer quit-cigarette-smoking years (16.3 vs. 10.6) and higher proportion with a family history of lung cancer (16.0% vs. 0.6%). Although reporting the same overall QoL as Controls (8.0), in specific QoL and PRO domains, lung cancer patients had higher frequency of "Moderately-Markedly reduced" appetite (13.9 vs. 5.0%), lower social activity (7.0 vs. 8.0); were worse in fatigue (5.0 vs. 7.0), dyspnea (6.0 vs. 7.0), dry cough (8.0 vs. 9.0), physical well-being (7.0 vs. 8.0), mental well-being (8.0 vs. 9.0), emotional well-being (8.0 vs. 9.0); and had higher proportion of "quite a lot" of difficulty in daily work or "could not do work" (22.1% vs. 8.6%), and "often-very often" felt tired after work (43.1% vs. 27.9%). Similar results were observed in long-term responders except for the same social activity score (8.0) between patients and controls. All participants reported strong family/friends support (9.0-10.0), similar spiritual well-being (8.0-9.0), and financial (8.0-9.0) and legal concerns (9.0).

Conclusions: In short-term responders, both CT-screening-diagnosed lung cancer patients and non-cancer controls had better overall QoL and selected symptoms and social factors than the usual-care-diagnosed patients. Remarkably, dyspnea and fatigue were persistent symptom burden for lung cancer patients regardless of how they were diagnosed and how long since initial diagnosis, calling for targeted interventions.

Keywords: Lung Cancer Survivors, CT Screening, Patients Reported Outcomes

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EP.04A.12 Exploring Rural Appalachian Community Perceptions and Practices on Health and Lung Cancer to Inform Screening Interventions

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Introduction: The Rural Appalachian Lung Cancer Screening Initiative is led by the Association of Cancer Care Centers (ACCC), the Appalachian Community Cancer Alliance, and patient advocacy partners. This multi-year initiative, recognized by the President's Cancer Moonshot, seeks to improve lung cancer screening rates by supporting health systems in the rural Appalachian region of the United States to develop and implement interventions through partnerships and technical assistance. Focusing on areas in Kentucky, West Virginia, and Virginia with significant barriers to screening, the initiative supports health systems in Pike County, Kentucky, and Buchanan County, Virginia.

Methods: Seven virtual interviews were conducted with individuals who live and work in the region. Interviews were conducted between September and October 2023 and gathered insights into community needs, strengths, and attitudes toward health, lung cancer, and lung cancer screening (LCS). Participants included multidisciplinary healthcare staff (n=9), public health professionals (n=4), community-based organization staff (n=2), and 1 politician, recruited through snowball sampling. Interviews were recorded, transcribed, and coded using thematic content analysis.

Results: Participants revealed community strengths like altruism, community closeness, diversity, and pride in their region's culture, history, and resilience. The region's isolation, natural beauty, and collaborative health organizations were noted assets. A holistic vision for a healthy community emerged, emphasizing access to education, diverse activities and support systems, health awareness, and addressing social determinants of health. Other aspects included effective primary prevention, resources, responsive community services, and opportunities for positive social connections. Trust between residents and healthcare providers was identified as an important aspect.Personal and perceived community trusted sources for health information included the Centers for Disease Control and Prevention (CDC), local health departments, media, primary care providers, and word of mouth. Motivators for seeking healthcare included family planning or urgent health issues. Barriers for seeking healthcare included transportation, cost, and fear. Lung cancer was perceived as a common problem, often detected late with significant impacts on patients and families, particularly in mining communities. Community barriers, motivators, and perceived solutions to accessing lung cancer screening are summarized in Table 1.

Conclusions: These findings highlight the importance of addressing structural barriers and enhancing awareness of lung cancer screening, particularly in higher-risk communities. Notably, the influence of media, family, and trusted community members offers a strategic avenue for health systems and public health professionals to leverage when tailoring interventions to reach and engage the community effectively.

Keywords: Appalachia, screening, lung cancer

Table 1.

Barriers	• Actual/perceived cost • Avoidance; doesn't want to receive bad news, other health needs or caregiving are higher priorities • Lack of knowledge, education, or awareness • No referral pathway • Primary care providers unaware or unaccepting of LCS • Smoking stigma and guilt; self-blame • Taking time off work • Transportation; long drive times
Motivators	• No cost to patient • Getting screened is beneficial to the family/more time with family if caught early • Ease and speed of scan • Recommendation by a healthcare provider • Seeing positive outcomes or experiences from others who have had screening or have lung cancer
Solutions	• Conduct more community outreach/marketing efforts • Provide free screening or increase awareness of screening coverage • Increase accessibility and convenience; offer more convenient locations • Combine with other screening activities/efforts • Provide transportation assistance • Leverage family members and social network to encourage screening • Create testimonials from similar people/trusted sources with messaging

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EP.04A.13 Necessity for Early Detection and Screening Initiatives: Evidence from Indonesia

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Introduction: Late-stage diagnosis of respiratory diseases significantly hampers the effectiveness of treatment and patient prognosis. This study evaluates the prevalence of late-stage disease presentations at Rumah Sakit Persahabatan, Indonesia's national respiratory center, emphasizing the critical need for early detection and screening programs in the country.

Methods: A comprehensive retrospective review of patient records from 2018 to 2022 at Rumah Sakit Persahabatan was conducted. The analysis focused on assessing the frequency of complications at presentation, identifying the most common complications, and determining the proportion of early-stage disease diagnoses.

Results: An overwhelming 89.2% of patients were admitted with complications, indicative of advanced disease stages at the time of diagnosis. The primary complications identified were pleural effusion (33.4%), superior vena cava syndrome (SVCS) (21.9%), and cerebral metastasis (8.9%). Alarmingly, the data showed that only 0.1% of the diagnosed cases were in the early stages of the disease, underscoring a significant delay in detection and diagnosis.

Conclusions: The prevalence of late-stage presentations and the low detection rate of early-stage diseases reveal a substantial deficiency in the current diagnostic processes. This deficiency not only affects patient outcomes adversely but also places a heavier burden on healthcare resources. The establishment of structured screening and early detection programs is imperative to bridge this gap, facilitating timely intervention and potentially improving survival rates.

Keywords: Early detection, Respiratory disease, Screening programs

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EP.04A.14 Community Outreach for Lung Cancer Awareness: Utilizing the 'Cancer Challenge' to Educate the Public

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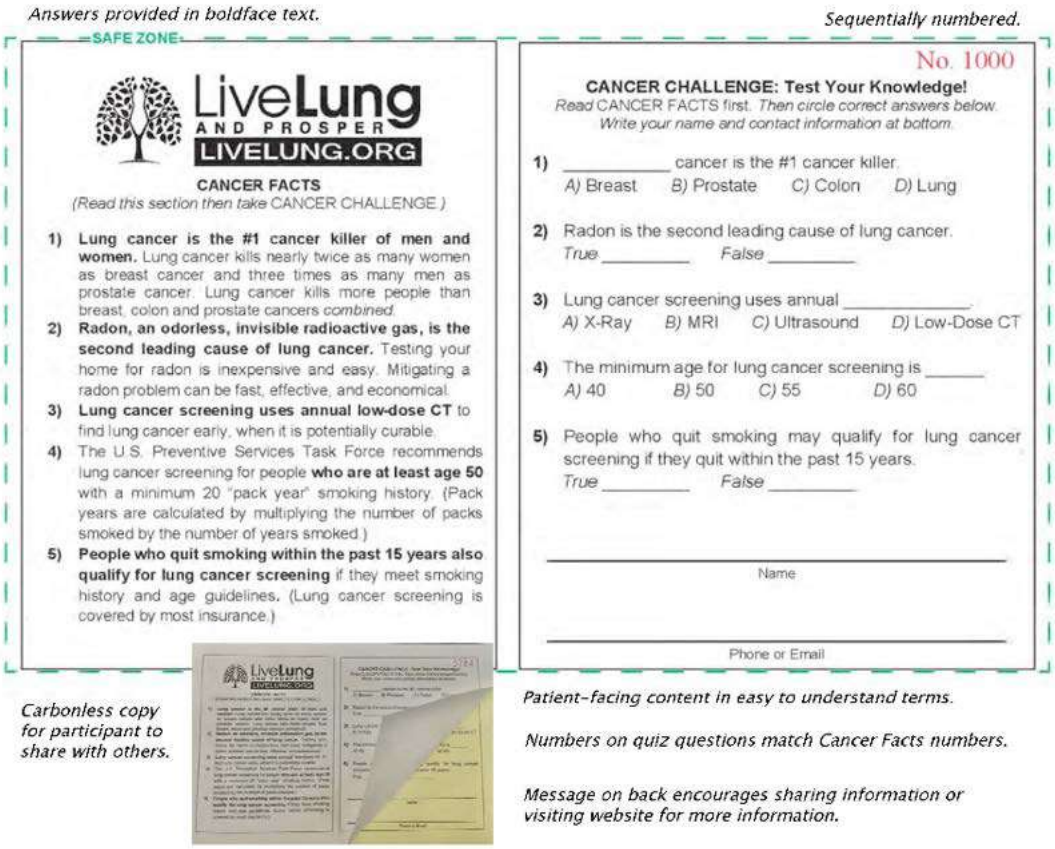
Introduction: Lung cancer remains a leading cause of mortality worldwide, yet awareness of screening options remains alarmingly low. Our nonprofit organization has pioneered a community outreach initiative leveraging the Cancer Challenge tool to address this critical gap.

Methods: Through engagement at festivals and community gatherings, such as First Night Out and Hot Air Balloon Festivals, we have reached more than 2,000 individuals, providing vital information on lung cancer screening and the dangers of radon exposure. Central to our approach is the Cancer Challenge, a simple yet effective educational tool comprising sequentially-numbered quizzes designed to inform participants about screening guidelines. By offering incentives and utilizing an open-book format, we ensure active participation and facilitate learning among attendees. Moreover, our commitment to education extends beyond the event itself by providing duplicate copies of the quizzes on carbonless paper, allowing participants to share knowledge with others.

Results: Our outreach efforts have demonstrated significant impact, with more than 300 participants engaged at the Hot Air Balloon Festival alone and similar success at other events. Importantly, participants are educated about lung cancer screening guidelines and encouraged to correct misconceptions. Furthermore, our initiative has sparked interest in collaboration with primary care physicians to increase screening referrals. Moreover, our initiative stands at the intersection of community engagement and healthcare advocacy, epitomizing a synergistic approach to public health outreach. By harnessing the power of community events and leveraging educational tools, such as the Cancer Challenge, we have not only disseminated crucial information about lung cancer screening but also fostered a culture of proactive health awareness within local communities. The enthusiastic response from participants underscores the potential for grassroots efforts to effect meaningful change in healthcare. As we continue to refine and expand our outreach initiatives, we remain committed to forging collaborative partnerships with stakeholders across the healthcare landscape, paving the way for a more integrated approach to early detection.

Conclusions: Through our innovative approach, we have shown the efficacy of community outreach in raising awareness of lung cancer screening. By expanding our initiatives and fostering partnerships with healthcare professionals, we aim to increase screening, ultimately saving lives and reducing the burden of lung cancer. This community outreach initiative represents a promising strategy for disseminating vital information about early detection and risk reduction of lung cancer to the broader population. Further research is warranted to assess the long-term impact of such interventions and explore avenues for scalability and sustainability.

Keywords: Lung Cancer Screening Tool, Educational Community Screening Outreach, LiveLung Cancer Challenge



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EP.04A.15 Recruitment Strategies in a Lung Cancer Screening Program for Asian Women with No Smoking History

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Introduction: The Female Asian Nonsmoker Screening Study (FANSS) is a pilot study for Asian women with no smoking history to provide low-dose CT (LDCT) Chest scans for lung cancer (LC) screening annually for 3 years. Acknowledging potential challenges to recruit from a non-smoking population that is not typically targeted for LC screening and minority populations who have historically low enrollment rates to clinical trials, several factors including language barriers, participant availability and low awareness of LC in non-smoking populations were considered to support FANSS enrollment. Here we describe various recruitment strategies implemented to aid in study accrual.

Methods: Multimodal recruitment strategies were used. A dedicated phone line answered by receptionists able to speak English, several Chinese dialects and access to phone interpreters was established. Research staff are bilingual or utilized phone interpretation services in all participant interactions. Community outreach included informational flyers available in both English and Chinese that were sent to physicians serving primarily Asian communities and posted in pharmacies and storefronts in NYC Chinatown. A website was developed for interested individuals to submit their contact information. Our institutional EMR, Epic, incorporated DataCore in 3/2023 to aid in identifying potential study participants based on eligibility. A pool of participants with active MyChart accounts was created to search individual medical records with criteria “Asian,” “female,” “OK to contact for Research recruitment,” “age 40-74,” and excluded anyone with a smoking history and the term “Cancer” within the past 5 years. Participants from this pool were sent an IRB-approved recruitment message through MyChart from 3/2023-6/2023. Interested participants who responded directly through MyChart were contacted to verify and determine eligibility. All eligible participants who agreed to participate were consented either in-person or virtually by electronic consent to allow for scheduling flexibility.

Results: From 3/5/21 to 1/27/24, 1518 women inquired about FANSS through our website, dedicated phone line or MyChart messages. After determination of eligibility, 760 participants had an informed consent discussion either virtually or in-person. From 3/5/21 to 2/28/23, 356 participants expressed interest in the study, of which 247 participants underwent the consent process. From 3/1/23 to 1/27/24, 637 participants expressed interest excluding through MyChart, of which 423 participants underwent the consent process. Following the implementation of directed MyChart messaging during that same time period, 525 participants responded through the EMR, however 102 participants were not eligible due to inaccuracy in their charts (i.e. ethnicity or smoking history). Of those eligible, 90 participants were recruited to the study. MyChart recruitment led to an additional 21% (90/423) increase in study enrollment.

Conclusions: To increase recruitment to a LC screening program in participants without a smoking history, specific considerations tailored to engage minority populations are needed. Culturally appropriate outreach and program infrastructure including electronic consents were implemented. Incorporation of directed messaging through the EMR in the FANSS study also is a successful tool to further enhance recruitment to identify potential participants which may also be applied to improve uptake in both lung cancer screening for smoking populations and in recruitment to other clinical trials.

Keywords: lung cancer screening, recruitment, lung cancer in non-smoking populations

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EP.04A.16 Cost-Effectiveness of Adaptive Schedules for Lung Cancer Screening: A Modeling Study

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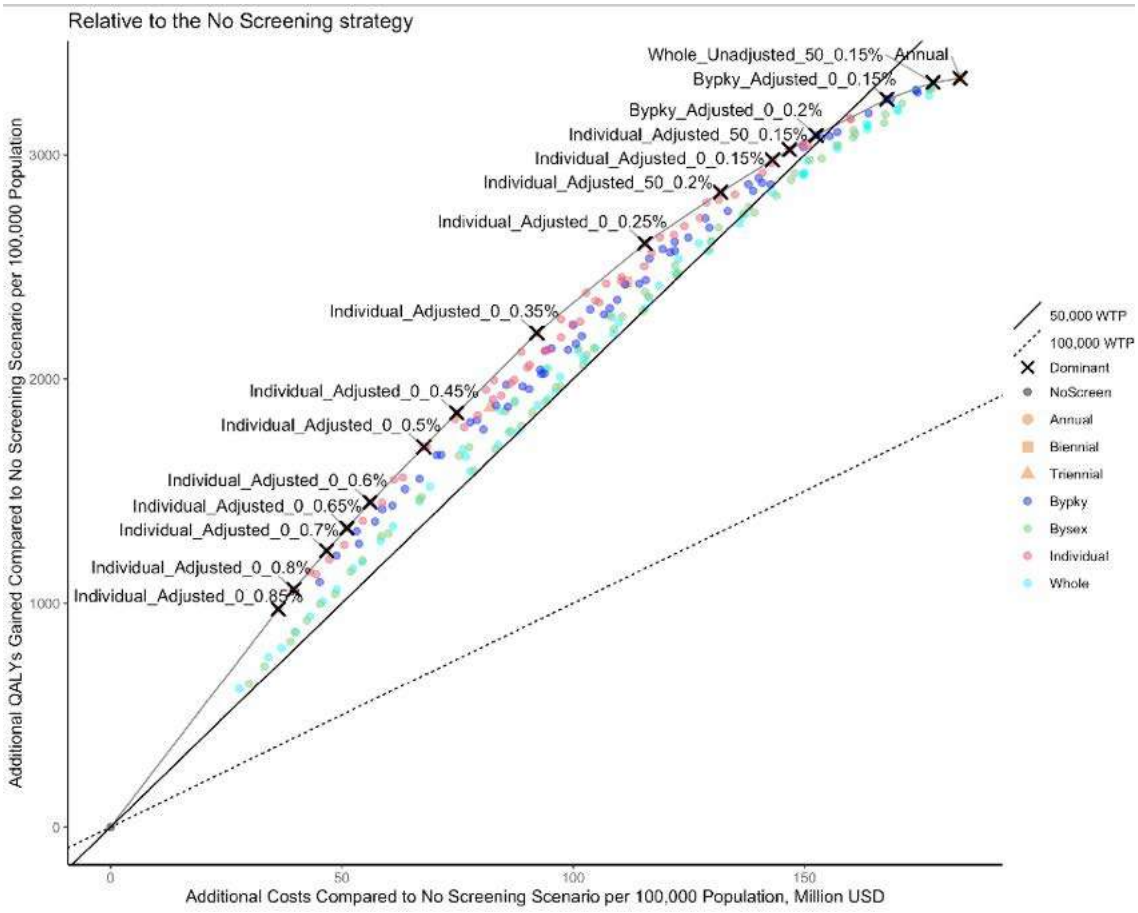
Introduction: Current guidelines recommend annual low-dose computed tomography screening for lung cancer when the person meets the eligibility criteria based on age and smoking history. However, research suggests adaptive schedules, based on individual risk and screening results, offer comparable effectiveness with the potential for improved benefit-harm trade-offs. Given the projected increase in national cancer care costs and the substantial economic burden of lung cancer, it's crucial to assess the economic efficiency of adaptive schedules. Therefore, we conducted a cost-effectiveness analysis comparing adaptive schedules to regular (non-adaptive) screening strategies.

Methods: We extended the Lee and Zelen risk-threshold method to select screening schedules based on average or individualized lung cancer risks and life expectancy for the whole screen-eligible population, specific sub-groups (by sex or by pack year), or for each individual in the study population. We used the validated Two-Stage Clonal Expansion (TSCE) Model for lung cancer risk prediction and varied the annual TSCE risk threshold from 0.15% to 0.85%, with 0.05% increments. We adopted a healthcare sector perspective to assess the long-term cost-effectiveness of 240 adaptive schedules and three regular screening schedules (triennial, biennial, and annual) versus no screening. An established microsimulation model was used to project the costs and effectiveness of different screening schedules over a lifetime for individuals from the 1960 US birth cohort eligible under the 2021 USPSTF guidelines. Lifetime downstream costs (2023 dollars) and effects (life-years gained, quality-adjusted life-years gained [QALYs]) were discounted at 3%. Sensitivity analyses evaluated the impact of varying treatment and screening costs, health utilities, and screening disutilities.

Results: More than 80% of strategies considered in our study had incremental costs per QALY gained lower than $50,000 compared with no screening, with annual screening being the highest (Figure 1). Compared with efficient adaptive schedules, triennial and biennial screening were dominated, whereas annual screening had an Incremental Cost-Effectiveness Ratio (ICER) of $288,000 per QALY. Taking screening disutilities into account, annual screening was dominated. The most cost-effective scenario under the $100,000 willingness-to-pay (WTP) threshold was a schedule selected based on individual risks and adjusted for life expectancy, which had an ICER of ~$97,500/QALY.

Conclusions: Adaptive schedules were cost-effective based on a widely accepted US WTP threshold. Conversely, annual screening was over the WTP threshold and was dominated by adaptive schedules in some scenarios. Hence, in fixed-budget healthcare systems, adaptive schedules could provide better "value for the money" and should be considered.

Keywords: Adaptive screening, Cost effectiveness, Risk-based



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EP.04A.17 Screening for Lung Cancer in Indonesia: Are All the Variables Valid for Determining These Factors?

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Introduction: Lung cancer is a significant health problem in Indonesia that incurs high costs, but the prognosis is very poor due to the challenge of detecting early-stage lung cancer that is operable. To reduce the mortality rate, screening and early detection are essential. The healthcare system in Indonesia follows a referral-based model, so community health centers need tools that are suitable for the facilities. We have utilized a scoring form developed by IASTO (Indonesian Association for the Study of Thoracic Oncology) to assess the risk level of lung cancer. This study aims to screen for lung cancer in Indonesia and evaluate the validity of all variables in determining these factors.

Methods: This was a cross-sectional study conducted at 11 Pulmonology and Respiratory Departments in Indonesia. Clinical characteristics and data were collected from medical records of lung cancer patients at these departments nationwide between January 2023 and December 2023.

Results: A total of 920 subjects who met the criteria were analyzed in this study. Lung cancer was found at a median age of 58 (15 - 93) years old, with the majority of subjects being male (69.3%), diagnosed with adenocarcinoma (60.5%), active smokers (36.6%), ex-smokers (24.2%), and passive smokers (23.3%), and having no family history of cancer (86.8%). Risk factors for lung cancer based on scoring form were categorized as low (9.05%), intermediate (51.8%), and high (39.1%). High-risk patients were predominantly male (54.1%), older (46.3%), smokers (64.4%), and diagnosed with adenocarcinoma lung cancer, showing a different risk profile compared to patients with small cell carcinoma lung cancer, with a high risk of 59.5% and 72.4% for smokers. Patients with a family history of cancer had a risk of 82.1%. Patients without a history of lung cancer and those who were unsure had a moderate risk, at 53.2% and 50.5%, respectively. The majority of patients were exposed to carcinogens in the workplace, at 80.6%. Pollution in the home environment was a high-risk factor for 71.3% of patients. Patients with a history of COPD had a high risk of lung cancer (80%), while those with a history of tuberculosis had a risk of 69.2%.

Conclusions: This scoring assessment can be used as a tool for screening and early detection in Indonesia to follow the referral system from Community Health Centers to Hospitals that have facilities for definitive diagnostic procedures.

Keywords: Screening, Lung cancer, Risk factors

EP.04B SCREENING AND EARLY DETECTION - NODULE IDENTIFICATION AND MANAGEMENT
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EP.04B.01 Evidence Based Communication on Lung Cancer Screening to Political Decision Makers

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Introduction: Lung cancer screening with low-dose computed tomography (LDCT) has been shown to provide a significant reduction on lung cancer mortality. Despite an extensive body of high-quality evidence with a significant number of randomized and non-randomized studies, today very few countries have national screening programs for lung cancer. This creates an implementation and impact gap between screening for lung cancer compared with other cancers. This is despite lower public health relevance of these cancers in terms of mortality and less extensive and compelling evidence for benefits of screening. As cancer screening programmes usually apply to large parts of the population (including health individuals), their financial impact can be greater than other healthcare decisions. In most countries, implementation and/or financing of national screening programmes are political decisions, or at least influenced by political decisions. These decisions are often made by people who are usually not experts in oncology, epidemiology or other relevant disciplines. To enable evidence-informed political decision making and make sure that scientific evidence is translated into political actions, scientific evidence has to be translated in a form that addresses the specific needs of this target group and can be taken up into decision-making. The Lung Cancer Policy Network, a global multidisciplinary alliance of experts in lung cancer, brings evidence-informed consensus policy recommendations to support policymakers to deliver commitments on priority issues in lung cancer, including LDCT screening.

Methods: Political decision processes were analysed for specific regions and decisions, e.g. the European Union's recommendation for cancer screening in the EU member states. Stakeholders in these decision processes were identified. Stakeholders' beliefs, concerns and any misunderstandings about lung cancer screening were identified during discussions. In addition, non-systematic literature searches identified studies that address the issues raised. Based on this, communication concepts for repeating concerns were developed and adjusted to the target group. These concepts were then distributed through various channels (e.g. websites, presentations, direct and indirect communication) to decision markers.

Results: Common concerns were false-positives, costs, exclusion or inclusion of specific target groups for lung screening, resulting unnecessary interventions and radiation dose from computed tomography. Strategies were developed to address these concerns, for example comparisons with other screening programs, cost-comparisons of lung cancer interventions (screening vs. late-stage treatments), positive examples from other, comparable countries or regions where screening is already implemented and results are available.

Conclusions: In order to lead to better political decision making, scientific evidence has to be translated and communicated in a way that addresses the specific background, previous experience, concerns and believes of political decision makers. If this is done, a successful communication of scientific evidence to decision makers can lead to better-informed decisions. The Lung Cancer Policy Network has developed extensive consensus-driven insights and recommendations to support political prioritisation of lung cancer and help improve outcomes from the disease.

Keywords: Lung cancer screening, computed tomography, policy

EP.04B SCREENING AND EARLY DETECTION - NODULE IDENTIFICATION AND MANAGEMENT
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EP.04B.02 Identification of Circulating MicroRNAs Associated with Lung Cancer Diagnosis and Progression

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Introduction: This study aimed to identify circulating microRNAs (miRNAs) associated with lung cancer diagnosis and progression by comparing pre-surgery samples with post-surgery samples at different time points.

Methods: A total of 576 miRNAs were profiled using plasma samples collected from 50 lung cancer patients before surgery and at 3- and 6-month intervals post-surgery. Fold changes in miRNA expression were analyzed, and Pearson correlation coefficients were calculated to assess the consistency of changes over time. Differentially expressed (DE) miRNAs were identified by comparing pre-surgery samples with post-surgery samples. Statistical significance was determined using a p-value threshold of <0.05.

Results: The fold changes in miRNA expression at 6 months post-surgery were generally consistent with those at 3 months post-surgery (Pearson correlation coefficient = 0.76). Several DE miRNAs were identified, with 5 miRNAs significantly upregulated at 3 months post-surgery and 6 miRNAs significantly upregulated and 1 miRNA downregulated at 6 months post-surgery. Notably, miR-339-5p, miR-432-5p, and miR-335-3p showed consistent upregulation at both 3 and 6 months post-surgery, while their expression decreased at later stages based on pre-surgery data. Additionally, miR-629-3p exhibited significant downregulation at 6 months post-surgery, contrasting with its increased expression at later stages. These findings suggest that these miRNAs may play crucial roles in lung cancer progression and could serve as potential biomarkers for lung cancer diagnosis.

Conclusions: The identified miRNAs, particularly miR-339-5p, miR-432-5p, miR-335-3p, and miR-629-3p, show promising associations with lung cancer diagnosis and progression, highlighting their potential as biomarkers for clinical applications in lung cancer management. Further validation studies are warranted to confirm their utility and specificity in clinical settings.

Keywords: circulating microRNAs, lung cancer, diagnosis

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EP.04B.03 The Diagnostic Efficacy of Seven Lung Cancer Autoantibodies in Early Detection of Pulmonary Ground-Glass Nodules

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Introduction: The prognosis for lung cancer patients is significantly correlated with the stage of the disease at diagnosis. Most incidentally discovered pulmonary nodules are benign, but persistent ground-glass nodules (GGNs) carry a potential risk of malignancy. Our study aimed to investigate the diagnostic accuracy of seven autoantibodies in patients with malignant ground-glass nodules smaller than 3cm.

Methods: This study collected data from patients who visited several medical centers, including the PLA General Hospital, and three hospitals in other provinces of China between 2021 and 2023. The inclusion and exclusion criteria were set to clinical findings of pulmonary ground-glass nodule lesions with lung CT imaging data thickness ≤1mm. Based on radiological and histopathological examinations, 512 patients with malignant nodules were identified as the lung cancer group, while 188 patients with benign lung nodules and 130 healthy individuals were selected as the control group. All patients enrolled in the case group had ground-glass nodules less than 3mm. Fasting peripheral blood samples were collected in the morning from all participants. The serum levels of seven antibodies (P53, PGP9.5, SOX2, GAGE7, GBU4-5, MAGEA1, CAGE) were measured using the enzyme-linked immunosorbent assay (ELISA). The study analyzed the diagnostic efficacy of these seven autoantibodies, individually or in combination, for early malignant pulmonary nodules through receiver operating characteristic curve analysis.

Results: The serum levels of the seven autoantibodies in patients were significantly higher than those in the control group ($P < 0.01$). The sensitivity, specificity, and cut-off values for the differential diagnosis of the seven autoantibodies between the case and control groups are provided in Table 1. The combined diagnostic approach of the seven autoantibodies exhibited a sensitivity of 89.43%, specificity of 90.13%, and AUC of 0.9069, surpassing the performance of each autoantibody used individually. Furthermore, we applied XGBOOST for machine learning modeling of the seven autoantibodies, dividing the study population into a validation set and a test set at a 7:3 ratio. The model achieved commendable sensitivity and specificity in the validation set, with MAGEA1, P53, and PGP9.5 having significant feature weight proportions.

Conclusions: Our research assessed the diagnostic performance of seven autoantibodies in early-stage lung ground-glass nodules for benign-malignant distinction. It further established the cut-off values for these autoantibodies in differentiating GGNs, verifying the significance of detecting these autoantibodies in patients with early-stage lung ground-glass nodules. This provides a non-invasive and highly discriminative method for the evaluation of ground-glass nodules in high-risk patients.

Table 1. The sensitivity, specificity, and cut-off values for the differential diagnosis of the seve

Keywords: Ground-Glass Nodules, Seven autoantibodies, Early Detection

	Cut-off	Sensitivity	Specificity	AUC
P53	3.500	83.55	88.50	0.8520
PGP9.5	1.250	84.28	88.50	0.8764
SOX2	1.150	66.84	88.71	0.7785
GAGE7	1.150	78.51	87.89	0.8348
GBU4-5	0.850	61.08	85.01	0.7449
MAGEA1	2.900	83.02	88.91	0.8664
CAGE	2.050	88.92	88.50	0.8874

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EP.04B.04 Defining A Positive CT Screening for Lung Cancer Using Different Nodule Sizes: Implications from a Prospective Cohort Study in China

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Introduction: Low-dose computed tomography (LDCT) effectively lowers lung cancer mortality but raises concerns about false positives. Limited data exist on size thresholds for positive results in Asian countries. Most studies and guidelines do not distinguish between solid and part-solid nodules, despite potential differences in malignancy rates and progression. This study utilizes the National Lung Cancer Screening (NLCS) cohort in China to determine threshold values for defining positive nodules in the baseline screening round, for solid, part-solid, and non-solid nodules, respectively.

Methods: From 2013 to 2018, 4160 participants with at least one positive nodule as defined by NLCS criteria (solid/part-solid noncalcified nodule [NCNs] ≥ 5 mm, non-solid NCNs ≥ 8 mm) were included. We assessed reductions in false positives and diagnosis delays using NLCS criteria and stricter nodule diameter thresholds. Additionally, we simulated a population aged 40-74 years based on the 2019 National Bureau of Statistics of China to estimate potential screening outcomes with various thresholds for the entire Chinese population.

Results: The NLCS baseline round had a 96.1% false positive rate. Compared to NLCS criteria, using an 8mm solid NCN threshold missed 7.35% of lung cancer cases but reduced false positives by 74.26%; a 6mm part-solid NCN threshold led to no delayed diagnoses and a 29.13% false positive reduction; a 10mm non-solid NCN threshold missed 12.00% of cases but cut false positives by 53.36%. Our proposed threshold, compared to Lung-RADS, NCCN, and I-ELCAP, resulted in the lowest rate of missed lung cancer diagnoses (6.02% vs. 20.30%, 19.55%, and 21.05% respectively) and the highest reduction in false positives (65.83% vs. 24.53%, 24.39%, and 41.89% respectively). Using these thresholds would have delayed diagnostic work-up for eight out of 136 cases, mainly adenocarcinomas (75%, 6/8) at stage I. All three missed cases in the non-solid nodules category were adenocarcinomas at Stage I. Implementing these thresholds nationwide in China would identify 4.4 million positive screens, detecting 83.2% (366 thousand) of lung cancer cases and preventing 58.2% (73,290) of lung cancer deaths. Compared to NLCS criteria, the proposed models would reduce false positives by 65.8%.

Conclusions: This study represents an initial step towards the development of evidence-based protocols for managing lung nodules in Asian countries, aiming to implement efficient lung cancer screenings that deliver the right care to the right individuals at the right time. Future studies should evaluate the appropriateness of 8mm, 6mm, and 10mm thresholds in prospective LDCT screening programs.

Keywords: Lung cancer screening, False positives, Nodule threshods

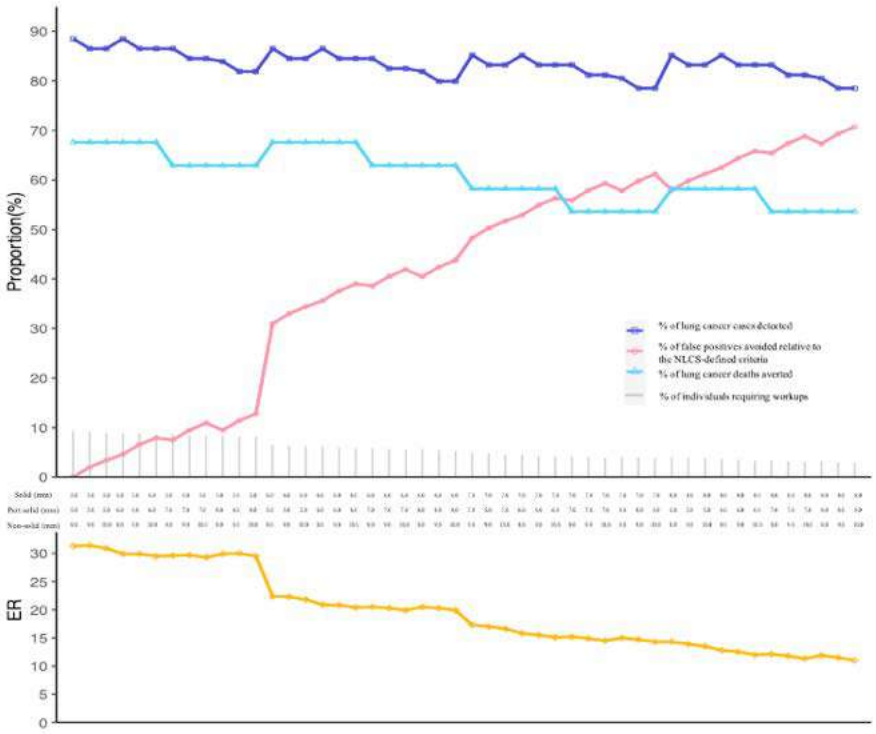

Figure 1 Adapted screening strategies according to different nodule thresholds in the entire Chinese population
ER: Efficiency Ratio (the number of individuals requiring further workup/number of lung cancer cases detected)

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EP.04B.05 Discordance Between Nodule and Lung Cancer Location in Early Lung Cancer Detection Cohorts.

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Introduction: Patients with lung nodules are at increased risk for lung cancer, but it is unclear how frequently lung cancer develops in the identified nodule or a different location. We examined concordance between nodule and lung cancer location in patients diagnosed with lung cancer after lung cancer screening (LCS) or management in lung nodule program (LNP).

Methods: Retrospective analysis of patients diagnosed with lung cancer in a community-based program after LCS with Lung RADS 2-4 at T0 or initial nodule-identifying scan in LNP, with reported nodule location, with nodules <30mm. Discordant cases had anatomic mismatch between nodule and cancer location. We compared demographic, risk factor and clinical characteristics between the discordant and the concordant groups in LCS and LNP cohorts.

Results: Of 1,280 eligible patients, 315(25%) had LCS; 965(75%) were in the LNP. In the LCS cohort, 202(64%) were concordant and 113 (36%) were discordant. In the LNP group, 721 (75%) were concordant and 244 (25%) were discordant. Concordance was significantly more likely in the LNP than LCS cohort (p = 0.0003). There was no significant difference in age, sex, race, ethnicity, insurance, and smoking status between the concordant or discordant LCS cohort, but discordant LNP cohort was more likely to be female, actively smoke, and have multiple nodules (Table). The dominant nodule was significantly smaller in discordant cases, and less likely to be located in the upper lobes. Although adenocarcinoma was the dominant histology in all cohorts, small cell lung cancer was almost twice as common in both discordant cohorts (p = 0.0432 in LCS) and (p = 0.0001 in LNP). The proportion of patients with stage IV was almost double (32% vs. 16%) in the discordant LNP group (p = 0.0005).

Conclusions: The dominant nodule not the source of lung cancer 25% or more of patients with a lung nodule, especially in higher risk patients, such as those eligible for LCS, and those who develop small cell lung cancer and LNP patients who develop stage IV disease. Digital imaging and artificial intelligence algorithms that focus exclusively on nodule characteristics may be limited by this fact.

Table 1. Characteristics of Concordant vs. Discordant Group in LCS and LNP Cohorts

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EP.04B.06 High-Resolution CT with 1024-Matrix for AI-Assisted Diagnosis System in the Evaluation of Pulmonary Nodules

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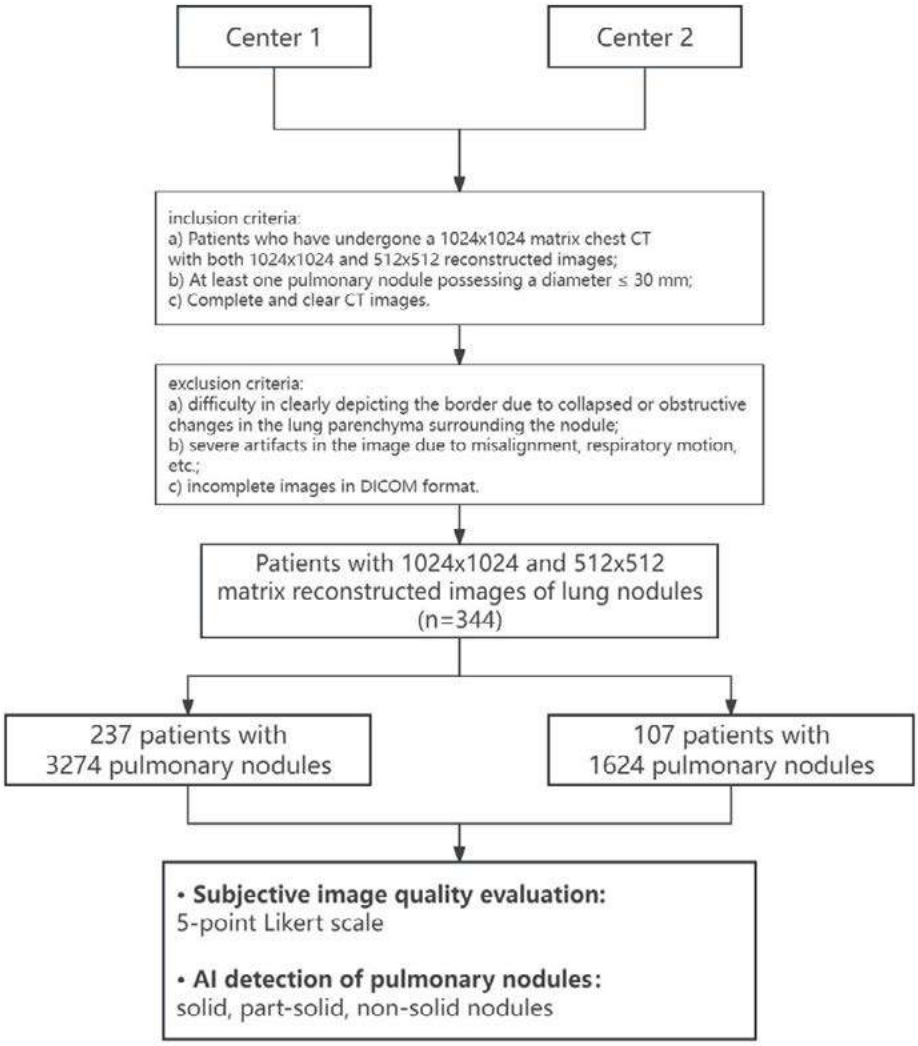
Introduction: Accurate assessment and diagnosis of lung nodules based on computed tomography (CT) images is critical for clinical management. The rapid development of artificial intelligence (AI) has improved the detection and accuracy of lung nodules while reducing the viewing time of radiologists. This study aimed to explore the efficacy of 1024x1024 matrix and 512x512 matrix for an AI-assisted diagnostic system in the evaluation of lung nodules.

Methods: This retrospective study of 344 patients with chest CT from two hospitals between January 2020 to November 2023, during which CT images showing lung nodules of less than 30 mm were reconstructed with 2 different protocols: 512×512 matrix and 1024×1024 matrix. We analyzed both image quality and the detection of lung nodules by AI. Two chest radiologists subjectively rated the image quality using a 5-point Likert. For pulmonary nodule detection, we employed an AI-assisted diagnosis system, which automatically detected pulmonary nodules of different types (solid nodules, part-solid nodules, and nonsolid nodules).

Results: Among 344 patients with 4898 pulmonary nodules, the overall image subjective evaluation score for the 512 matrix was 3.63, and the score for the 1024 matrix was 4.18 ($p < 0.05$). Taking pulmonary nodules as a unit, the detection accuracy rate, precision, and recall of on 512 × 512 matrix and 1024 × 1024 matrix were 91.63% vs 98.32%, 95.68% vs 98.32%, and 95.59% vs 100% respectively. The classification accuracy of solid nodules, part-solid nodules and nonsolid nodules on 512 × 512 matrix and 1024 × 1024 matrix were 89.74% vs. 97.87%, 90.76% vs. 99.04%, and 90.33% vs. 99.36%, respectively.

Conclusions: The use of a 1024 × 1024 matrix improved image quality, increased the detail of the image and provided more accurate results for AI evaluation of lung nodules.

Keywords: AI, Pulmonary Nodules, 1024 matrix



	512x512	1024x1024
Subjective Image Quality Evaluation		
Image Noise	4.21	3.59
Streak Artifacts	3.70	3.32
Pulmonary Nodule Edges	3.43	4.53
Clarity of Small Blood Vessels	3.61	4.03
Homogeneity of Normal Lung Parenchyma	3.36	4.25
Overall Image Quality	3.63	4.18
AI Nodule Detection		
Accuracy	91.63%	98.32%
Precision	95.68%	98.32%
Recall	95.59%	100%

EP.04C SCREENING AND EARLY DETECTION - EXPANDING ACCESS TO EARLY LUNG CANCER DETECTION
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EP.04C.01 The Value of Ultrahigh Frequency Ultrasound in Localizing Small Pulmonary Ground Glass Opacity Intraoperatively: A Prospective Study

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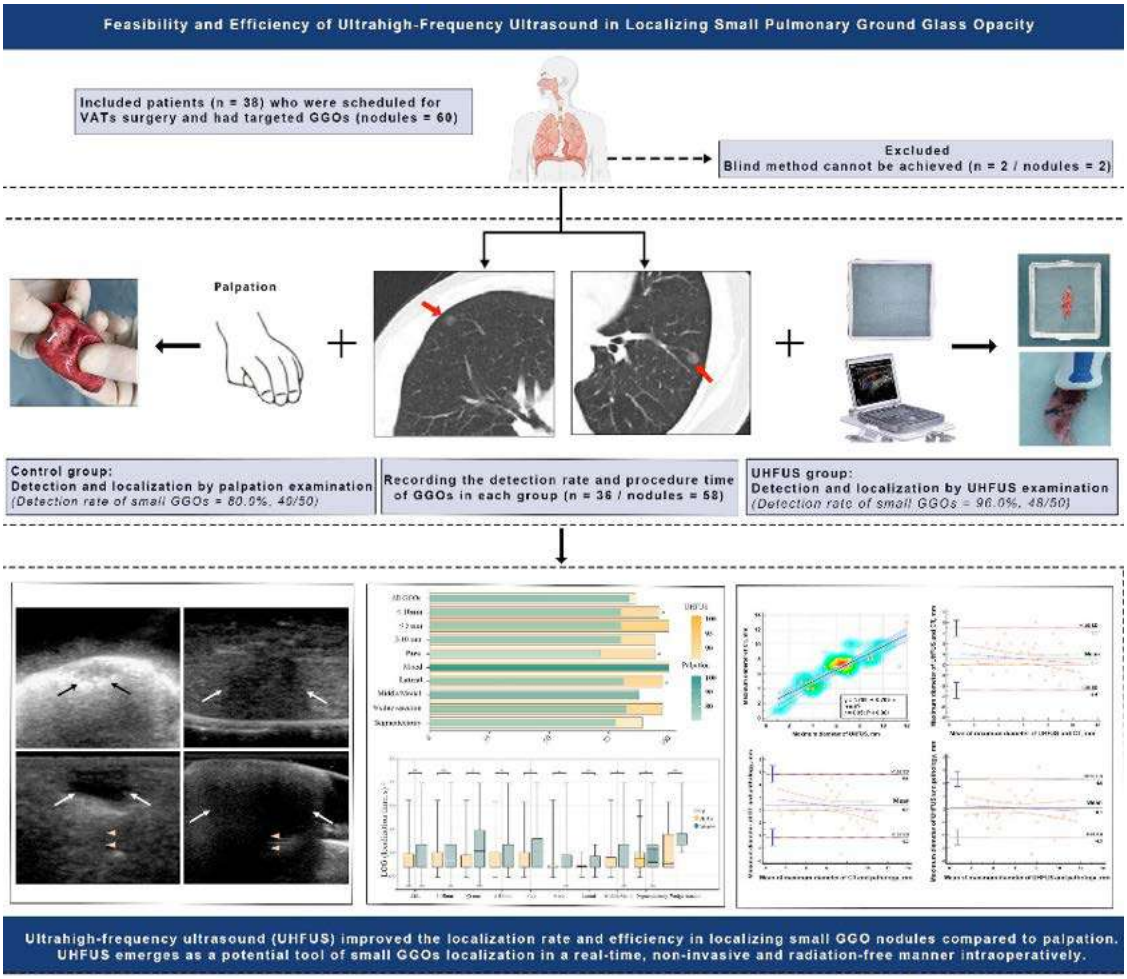
Introduction: Accurate localization of GGO in lung tissue intraoperatively, especially for small GGOs, remains challenging. Ultrahigh-frequency ultrasound (UHFUS), which allows for the visualization of micron-scale structures, is promising in addressing this issue.

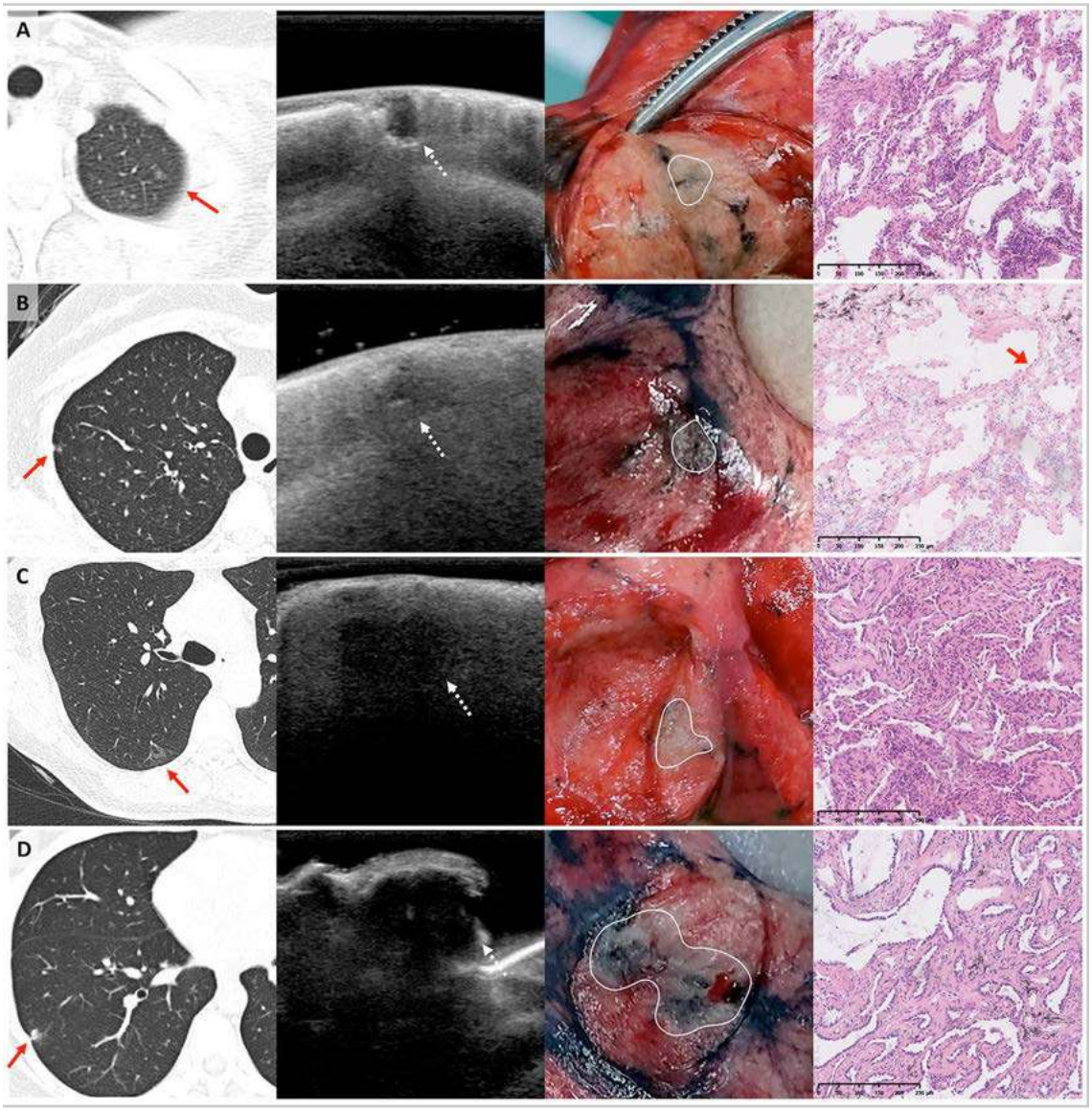
Methods: The prospective observational study (NCT05994898) included patients with GGOs who underwent surgery between June 2023 and March 2024. Each GGO was sequentially detected and localized by palpation and UHFUS (22-38 MHz) in excised lung tissue intraoperatively. The UHFUS features were independently examined by two radiologists. The comparison of localization rate and time consumption were analyzed by the McNemar test and Wilcoxon test.

Results: A total of 36 patients (55 years ± 10; 9 men) with 58 GGOs were included, with 50 small (≤ 1 cm) nodules and 37 pure GGO nodules. For small nodules, UHFUS demonstrated a superior localization rate (48, 96.0% vs. 40, 80.0%, P = 0.02), especially for micro-nodules (≤ 5 mm) (15, 100% vs. 12, 80.0%) and pure GGOs (33, 94.3% vs. 25, 71.4%, P = 0.02), outperforming palpation. The localization time of UHFUS was markedly less than palpation (5 s, IQR: 5–8 s vs. 5 s, IQR: 5–15 s; P = 0.003) in small GGOs, and this difference was more pronounced in pure GGOs (5 s, IQR: 5–10 s vs. 12.5 s, IQR: 5–20 s; P = 0.004). On UHFUS, 83.3% of GGOs appeared as indistinct hypoechoic areas with posterior shadowing. UHFUS found three new GGOs intraoperatively and the agreement in diameter between UHFUS-pathology surpassed that observed with CT-pathology.

Conclusions: This in-human prospective trial demonstrated UHFUS is a real-time, non-invasive, and radiation-free strategy that is promising in localizing GGOs in excised lung tissue intraoperatively with the potential to enhance the efficiency of surgery, and capable of identifying new nodules. Further research exploring this novel localizing method of GGOs in intrathoracic situation is warranted.

Keywords: Ground glass opacity (GGO), Ultrahigh-frequency ultrasound (UHFUS), Intraoperative localization

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EP.04C SCREENING AND EARLY DETECTION - EXPANDING ACCESS TO EARLY LUNG CANCER DETECTION
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EP.04C.02 Estimation of Numbers of Healthcare Providers Eligible for National Lung Cancer Screening in South Korea

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Introduction: Korea's current national lung cancer screening program is confined to specific criteria-meeting tertiary hospitals. However, amidst escalating screening rates and a potentially expanding target population, estimating the number of eligible screening institutions is crucial.

Methods: A survey was conducted from October to November 2023 among primary and secondary healthcare providers participating in the national breast cancer screening program in 2023, excluding oriental medicine hospitals. Of 2,919 surveyed institutions, 479 (16.4%) responded. Eligibility criteria for lung cancer screening participation included having a trained radiologist, possessing a 16-channel or higher computed tomography (CT) scanner, and engagement in the national smoking cessation support program. Data on CT scanner specifications were obtained from Health Insurance Review and Assessment Service, and the number of annual breast cancer screenings per provider and the address of healthcare providers were linked to data from the National Cancer Screening Information System. The probability of eligibility for participation in the national lung cancer screening program was estimated by stratifying characteristics (e.g., area and annual breast cancer screening numbers) of breast cancer screening institutions, extrapolating this to estimate the total number of eligible institutions.

Results: Respondent institutions showed higher rates of annual breast cancer screenings and a greater proportion of CT scanner with 16 or more channels compared to non-respondent (table 1). Among respondents, 24 primary and 33 secondary healthcare providers met the criteria for designation as national lung cancer screening institutions.

Characteristics of breast cancer screening institutes according to response

Conclusions: Expanding national lung cancer screening to primary and secondary healthcare providers could increase lung cancer screening capacity significantly. However, improving accessibility, especially in rural areas, presents challenges. Further evaluation, considering both distribution of screening subjects and institute, is necessary.

Keywords: Mass Screening, Lung Neoplasms, Health Care Surveys

Characteristics of breast cancer screening institutes according to response

	Non-respondent	Respondent	P-value
N	2440	479	
Healthcare provider			<0.001
Primary	2015 (82.6)	328 (68.5)	
Secondary	425 (17.4)	151 (31.5)	
Area			<0.001
Urban	1182 (48.4)	196 (40.9)	
Suburban	1136 (46.6)	246 (51.4)	
Rural	122 (5.0)	37 (7.7)	
16-channel or high CT scanner	452 (18.5)	181 (37.8)	<0.001
Number of annual breast cancer screening			<0.001
<200	1377 (56.4)	217 (45.3)	
200-399	536 (22.0)	102 (21.3)	
400-999	405 (16.6)	112 (23.4)	
≥1000	122 (5.0)	48 (10.0)	

Numbers of institutes eligible for national lung cancer screening program according to requirements

	Current situation	Expanding designation to primary and secondary healthcare providers			Relaxing designation requirements		
Healthcare provider	Tertiary	Primary	Secondary	Total	Primary	Secondary	Total
Urban	166	74	44	118	143	83	226
Suburban	130	50	66	116	98	100	198
Rural	16	0	12	12	0	16	16
Total	312	124	122	246	241	199	440

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EP.04C.03 A Forgotten Group for Lung Cancer Screening: Lung Cancer in Patients with Aortic Aneurysms

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Introduction: Smoking is the main risk factor of both lung cancer and aortic aneurysms with screening for both being based on smoking history. If found early, both lung cancer and aortic aneurysms can be intervened on preventing devastating consequences. However, there is minimal data about the incidence of lung cancer among patients with aortic aneurysms. Our study sought to identify the incidence of primary lung cancer in patients diagnosed with aortic aneurysms.

Methods: TriNetX, a global health research network comprised of 102 centers worldwide and 98 million patients, was queried for adults (age >18) with ICD codes consistent with primary lung cancer and aortic aneurysms from the United States. Demographic information was collected for all patients. Patients with lung cancer and aneurysms were compared to patients with only aneurysms or only lung cancer. These cohorts were propensity score matched for demographic and comorbidity variables. Outcomes were assessed with a multivariate regression and mortality was assessed with Kaplan-Meier Log-Rank Test.

Results: A total of 539,402 patients were diagnosed with thoracic or abdominal aortic aneurysms. Among those, 23,362 (4.3%) were found to also have lung cancer. Of patients with staging data, patients with both lung cancer and aortic aneurysms had a higher rate of Stage I cancer (32% vs 18%, $p<0.001$), and lower rate of Stage IV cancer (24% vs 32%, $p<0.001$), compared to patients with lung cancer alone. Repair of aneurysms occurred in 3.1% of patients with both lung cancer and aortic aneurysms with 2.4% having endovascular repair. Surgical resection of the lung cancer occurred in 6.1% of patients who had both, and 1.7% had both an aortic aneurysm repair and lung cancer surgery. Patients with both lung cancer and aortic aneurysms had higher mortality at five years (62.0% vs 55.7%, $p<0.001$) when compared to patients with only lung cancer.

Conclusions: Patients with aortic aneurysms are at risk of having lung cancer as smoking is the major risk factor of both. While screening guidelines may overlap specifically with a history of smoking, patients with aortic aneurysms represent an at-risk population who should be targeted for lung cancer screening. Practitioners should not hesitate to screen for lung cancer at the same time as aortic aneurysms.

Keywords: Lung Cancer, Aortic Aneurysm, Screening

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EP.04C.04 Extended Inclusion Criteria for Lung Cancer Screening to Tabacco Related Diseases: Comparison of Preliminary Results in Two Prospective Cohorts

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Introduction: Criteria for lung cancer screening (LCS) eligibility are usually based on age, amount of tobacco consumption in pack-years or numbers of cigarettes smoked per day and duration; and active smoking or delay from quitting. These criteria may not be accurate and objectively quantifiable. Therefore, we hypothesized that history of smoking-related disease, which is an objective criteria, could be used as a selection criteria to identify participants at risk of lung cancer (LC) eligible to screening. In the PREVALUNG study (NCT 03976804), we previously reported 3.2% of lung cancer prevalence (14/434) including (10/14) 70% stage I or II LC at a first round of LCS among participants with LCS criteria enlarged to younger age (>45 years old), low tobacco consumption (minimal 1 cigarette per days for 10 years) and history of tobacco related diseases (atheromatous cardiovascular events). Our objective is to report our preliminary LC prevalence after a first LCS round in a new prospective cohort (PREVALUNG ETOILE, NCT 05649046) with inclusion criteria enlarged to other tobacco related diseases (COPD and history of cured tobacco related cancer) and to usual LCS criteria; and to compare these preliminary results to the PREVALUNG results.

Methods: PREVALUNG ETOILE inclusion criteria were age 45-75 years old and history of a tobacco related disease (atheroma, chronic bronchitis and tobacco-related cancer in remission > 5 years) and history of tobacco consumption for 10 years, or NLST (National Lung Screening Trial) and NELSON (Dutch-belgian lung cancer screening trial) trials; or North American recommendation criteria (age 50-80 years-old, pack-years of tobacco consumption, active or smoking cessation <15 years). Exclusion criteria are symptoms of LC, existing follow-up for pulmonary nodule, fibrosis, pulmonary hypertension, severe cardiac or respiratory failure and active pulmonary infectious disease. We measured LC prevalence after a first round of LCS including 5 months of follow-up, positive screening, rate of localized (stage I-II; 8th TNM classification) LC diagnosis and compared these proportions between PREVALUNG and PREVALUNG ETOILE cohorts using Chi-2 or Fisher's exact test when appropriate.

Results: Among 160 participants of PREVALUNG ETOILE, 127/160 (79.4%) had NELSON eligibility criteria and 84/160 (52.5%) had NLST eligibility criteria; 133 underwent a thoracic CT scan, 36 (22.5%) were positive or intermediate and were discussed in a multidisciplinary staff meeting. Five participants were indicated for one step diagnostic and curative minimally invasive thoracic surgery; while 24 were indicated for a follow-up scan at 3 to 6 months. We diagnosed 2 primary non-small cell LC (NSCLC, 1.5%) and 1 type B lymphoma (0.7%), representing 2/133 (1.5%) prevalent LC. Both primary LC were detected at stage I (100%). Two surgical procedures (one mid lobe resection and one left upper-lobe segmentectomy) were performed for hamartochondromas (1.5%). The prevalence of primary LC was not significant between PREVALUNG and PREVALUNG ETOILE participants (14/434 vs. 2/133, P=NS), stage I-II NSCLC were also similar (10/14 vs 2/2, p=NS).

Conclusions: Extended criteria for lung cancer screening to tobacco related diseases may provide relevant, safe and reproducible results.

Keywords: screening, lung, cancer

EP.04C SCREENING AND EARLY DETECTION - EXPANDING ACCESS TO EARLY LUNG CANCER DETECTION
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EP.04C.05 Projected Impact of the Age of Initiation for Lung Cancer Screening on Health Outcomes and Healthcare Resources in Canada

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Introduction: Screening with low-dose computed tomography (LDCT) has been shown to reduce lung cancer mortality, and it is now recommended in Canada for high-risk individuals aged 55-74 years. Some programs are considering starting screening at a younger age due to early and heavy smoking in certain groups. This study aimed to assess the impact of starting lung cancer screening at earlier ages on patient outcomes and healthcare resource use.

Methods: The analysis used OncoSim-Lung, a microsimulation model that simulates smoking and lung cancer histories in Canada. We simulated four scenarios in Canada: (i) no screening; and annual screening for individuals aged up to 74 years who have at least a 1.5% risk of getting lung cancer in the next 6 years at various start ages: (ii) 55 years, (iii) 50 years, and (iv) 45 years. We simulated a two-step intake process. First, individuals aged 45/50/55-74 years with 20+ years of smoking history were referred. Second, their LDCT eligibility was assessed using the Prostate, Lung, Colorectal, and Ovarian (PLCOm2012) risk model. Smoking cessation support was offered at both steps. Sensitivity analysis explored the effects of smoking cessation and a higher risk threshold (2% chance of getting lung cancer in 6 years).

Results: Starting lung cancer screening at 50 or younger requires few additional screening resources because few additional individuals meet the eligibility criteria. The impact is smaller at higher risk thresholds. However, starting earlier could save more lives by encouraging earlier smoking cessation, contingent on quit rates among those who are ineligible for screening but are still referred to smoking cessation intervention.

Conclusions: Starting lung cancer screening earlier for high-risk people could reduce lung cancer disparities without a significant strain on screening resources, but effective smoking cessation support is crucial for maximum benefit.

Keywords: Lung cancer screening, Age eligibility, Smoking cessation

EP.04C SCREENING AND EARLY DETECTION - EXPANDING ACCESS TO EARLY LUNG CANCER DETECTION
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EP.04C.06 Investigation on the Incidence and Risk Factors of Lung Cancer Among Chinese Hospital Employees

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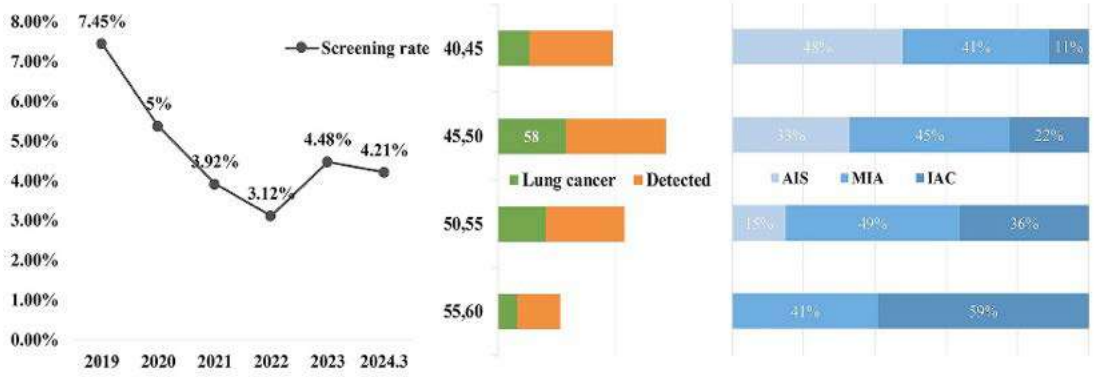
Introduction: With the increasing awareness of health check-ups among the population, there is a rising number of pulmonary nodules being detected and the population is younger. We aim to identify the true detection rate and incidence of pulmonary nodules in the population, as well as to discover the risk factors.

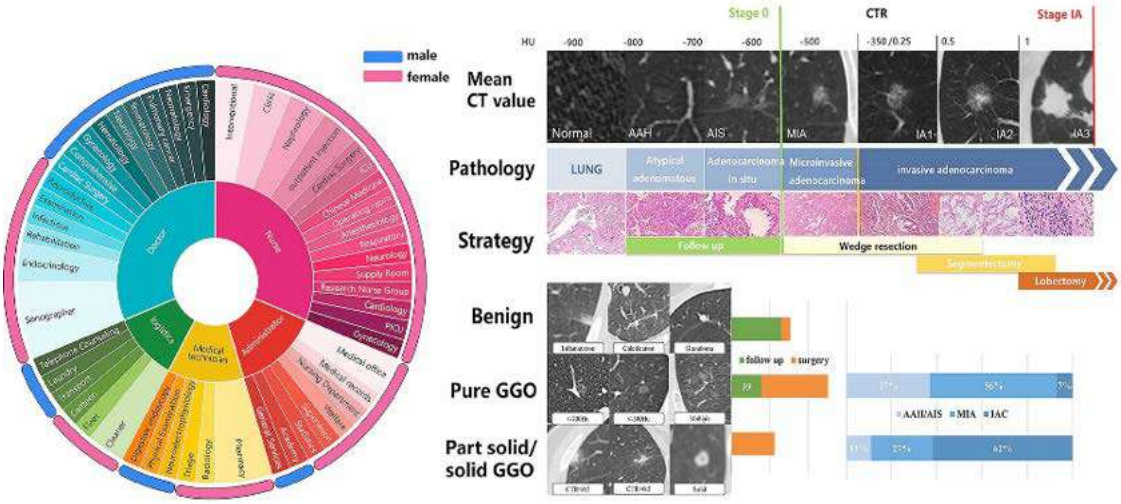
Methods: Hospital employees ≥40 years old who underwent low-dose computed tomography (CT) lung cancer screening from January 2019 to March 2024 were selected to record CT-imaging characteristics, pathology, staging, and questionnaires to investigate past history, smoking history, diet, mental health, etc. PM2.5 and radiation intake in radiation-related occupation received monitoring in hospital.

Results: The detection rate of suspicious pulmonary nodules was 9.84% (259/2633), and the incidence rate of lung cancer (including adenocarcinoma in situ) was 5.43%(143/2633). Morbidity among doctors, nurses, technicians, administers, and logistics was no difference (p = 0.945), but higher in women than in men (7.05% vs 3.73%,p<0.001). The median age of onset was between 45 and 50 years old, with the high-risk age being over 50 years old. The distribution characteristics and exposure factors of employees did not show significant differences from those of the general population(p=0.968), however, the incidence of lung cancer among hospital employees was higher than the general population(9.84% vs 0.041%). The relationship between lung cancer morbidity and PM2.5 was not clear (p = 0.543); and no lung cancer had been found in employees related ionizing radiation.

Conclusions: The high screening rate leads to high incidence of lung cancer, especially after COVID-19. However, with the increase in screening rates, the detection rate of lung cancer has decreased. Newly discovered lung nodules were all from new members who had never participated in lung cancer screening, and no new nodules appeared in the employees without suspicious nodules under following-up. A follow-up strategy for stable ground-glass nodules did not increase the incidence of lung cancer. Currently, small-sample analyses of lung cancer risk factors cannot identify direct causes or determine the exact incidence of lung cancer in the general population. However, increasing the lung CT screening rate helps to detect lung abnormalities earlier and determine whether intervention is needed.

Keywords: Early detection, Incidence rate, Pulmonary nodules





P.04C SCREENING AND EARLY DETECTION - EXPANDING ACCESS TO EARLY LUNG CANCER DETECTION
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EP.04C.07 A Novel NGS Assay Using cfDNA Methylation for Early Detection of Lung Cancer in a Screen-Eligible Population

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Introduction: Early detection of lung cancer reduces mortality, but adoption of lung cancer screening (LCS) is slow. A simple blood test could assist in identifying high risk patients and drive more eligible people to LDCT. Epigenetic changes are important drivers in cancer development. A set of novel methylation-based PCR markers successfully detected stage I NSCLC with 87% sensitivity [Mazzone et al. CHEST23 abstract #164]. We are now investigating the potential to improve performance by using NGS, since unlike PCR that focuses on specific methylation sites, NGS can cover all relevant sites in the genome. We used a novel approach utilizing tumor, normal lung, WBC, plasma samples from each patient in a discovery cohort and ultra deep next generation sequencing (up to 600x) to identify a set of highly informative candidate methylation markers that can be used for the detection of early lung cancer from plasma derived cfDNA. These candidate markers were combined to build a predictive assay. Here we present results from applying this assay to a large cohort of screen eligible patients.

Methods: Eight hundred patients meeting USPSTF LCS criteria for age (50-80y) and pack years (≥20) were prospectively enrolled. Those with a recent history of any cancer were excluded. Cases were pathologically confirmed, treatment naïve, primary invasive lung cancers (n=~200 with approximately 50% stage I). Controls were subjects with LungRADS 1 or 2 findings on their 1st or annual LDCT for LCS (n=~600). Whole blood was collected prior to any cancer treatment and processed into plasma. cfDNA was extracted from plasma, then exposed to methylation restriction specific digestion and then sequenced at a depth of 50x (Lung EpiCheck, Nucleix Inc, San Diego).

Keywords: Lung cancer screening, Biomarkers, Methylation

EP.04C SCREENING AND EARLY DETECTION - EXPANDING ACCESS TO EARLY LUNG CANCER DETECTION
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EP.04C.08 The Potential of Chest X-Ray Artificial Intelligence Detecting Missed Lung Cancer Diagnosis in a Community Based Cancer in Thailand

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Introduction: This study aimed to investigate the benefit of artificial intelligence (AI) chest X-rays in detecting missed lung cancer diagnoses in community-based cancer centres where most of the chest X-ray interpretation is done by general practitioners.

Methods: We retrospectively reviewed the chest X-ray image database of newly diagnosed lung cancer patients from 1 January to 31 December 2022 at Phrapokklao Cancer Center of Excellence. A total of 197 patients were screened, the eligible 77 patients who obtained more than six months before lung cancer (LC) diagnosis. These images were evaluated by CXR Qure.AI software to identify abnormal nodules or perihilar thickening for more than six months before a definite diagnosis of lung cancer, defined as missed lung cancer (MLC) diagnoses. We assessed the median time of MLC diagnosis.

Results: Among the 77 patients analysed, fourteen patients (18.18%) were found to have MLC diagnoses. The mean duration of MLC diagnosis was 32.3 months with a 95% CI from 20.6 to 44.08 months, with a maximum of 101 months and a minimum of 8.2 months. Of 14 MLC patients, six patients (42.9%) were diagnosed with stage IV lung cancer, while three patients (21.1%) were diagnosed with stage III lung cancer.

Conclusions: This study's findings show the potential of AI technology to facilitate the detection of lung cancer from chest X-ray images.

Keywords: missed lung cancer diagnosis, artificial intelligence, chest x-ray

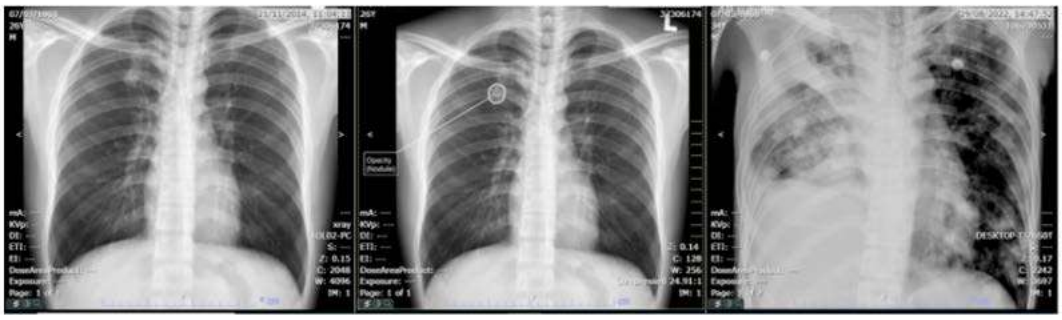

Figure : a case of maximum time MLC diagnosis 101 months.

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EP.04C.09 Liquid Biopsy Assay to Detect Low Levels of ctDNA in Early-Stage Lung Cancer Samples

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Introduction: A fundamental challenge in technologies designed to analyze circulating tumor DNA (ctDNA) is the typically small fraction of cell-free DNA (cfDNA) in a blood sample that comes from tumor cells. This proportion of ctDNA is generally low in early-stage cancers, which are characterized by small, localized tumors, but increases as the cancer progresses and the tumors grow and metastasize. Therefore, the capability to reliably detect minimal quantities of ctDNA is crucial for technologies like liquid biopsies. These technologies are particularly focused on detecting cancers at an early stage, when the tumor size is small and the amount of ctDNA present in the bloodstream is minimal. Early detection is especially relevant in lung cancer, where American Cancer Society studies show that the 5-year survival rates plummet from 65% to 9% as the stage at diagnosis advances. Various approaches are being explored to increase the amounts of ctDNA available for analysis, including simply increasing the amount of blood required from the patient paired with ultra-deep targeted sequencing. A low-pass whole genome sequencing approach, in which global cancer-like patterns can be detected in minimal amounts of cfDNA, can provide a reliable indicator of tumor presence without requiring prohibitive amounts of input material. Here we demonstrate the ability of the Genece Health Lung Cancer Assay to leverage fragment and end-motif analysis of cfDNA to detect low levels of ctDNA from early-stage lung cancer samples, while only requiring minimal input material. With the cfDNA available from a single tube of blood from a patient, the Genece Health Lung Cancer Assay can detect all stages of cancer.

Methods: Plasma collected in Streck cfDNA BCT devices from 19 early-stage lung cancer samples (16 stage I samples & 3 stage II samples) were obtained from Discovery Life Sciences. Two plasma aliquots of each sample were extracted using the Apostle MiniMax High Efficiency cfDNA Isolation kit on the KingFisher instrument. Eluates were pooled, cfDNA was quantified using Agilent Tapestation, and then diluted in water to 2ng, 1ng, 0.5ng & 0.25ng, as possible, based on the measured cfDNA concentration. Additionally, each sample was tested neat (un-diluted). Samples with a low stock concentration were tested at 1.5ng or 1ng & lower depending on the starting concentration. Libraries were prepared and sequenced using low-pass whole genome sequencing. Sequenced reads were analyzed to generate fragment end-motif and size (FEMS) and associated cancer prediction scores using Genece Health's proprietary analysis pipeline and machine-learning algorithm.

Results: All early-stage lung cancer samples were detected neat, and subsequent dilution series of these early-stage samples established that an input of only 1ng cfDNA is required for utilization of the Genece Health Lung Assay.

Conclusions: Signal detection in these early-stage lung cancer samples, even after dilution, indicates that the Genece Health Lung Assay has a sufficiently low limit of detection to ensure highly sensitive performance in early-stage lung cancer samples with only a single tube of blood or less.

Keywords: Early Cancer Detection, Lung Cancer, Liquid Biopsy

EP.04D SCREENING AND EARLY DETECTION - CHALLENGES AND PROGRESS IN EARLY LUNG CANCER DETECTION
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EP.04D.01 Claims-Based Yield Metric for Lung Cancer Screening

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Introduction: Lung cancer is the leading cause of cancer mortality. While lung cancer screening (LCS) has demonstrated high potential reductions in mortality, few people eligible for LCS get screened. HEDIS/Star quality metrics for health plans, including metrics for the portion of eligible people obtaining colorectal, breast, and cervical cancer screenings, have promoted cancer screening, but no such metrics exist for lung cancer. Eligibility for other cancer screenings is largely based on age and sex, but eligibility for LCS is based on smoking history, which is difficult to obtain for all members. Efforts to obtain smoking history from electronic medical records for all plan members may be expensive and difficult to obtain and since the information is self-reported by patients, it is subject to reliability concerns. Therefore, we propose and test a metric based on the portion of incident lung cancers that occurred subsequent to screening.

Methods: The study population was sourced from the 100% Research Identifiable File for 2019-2020, with all Medicare covered claims for about 27 million lives of individuals enrolled in Medicare Advantage (MA) plans and from the Medicare Limited Data Set from 2019-2020, with claims for about 1.8 million lives of individuals enrolled in Medicare Fee-for-Service (FFS) with both Parts A and B. For non-institutionalized individuals between ages 52 and 77 who had coverage for a minimum of 12 months prior to the period, we identified incident lung cancers and the subset that received an LCS in the prior 6 months. The age limitations parallel but shorten LCS criteria of 50-80 to accommodate calendar year considerations.

Results: The yield rate is defined as the portion of incident lung cancers which were identified subsequent to an LCS. We calculated this yield for the entire population by age range and Medicare eligibility status, as well as for the five largest MA carriers. The yield rate was relatively consistent for all cohorts, at ~5%, although there were statistically significant differences among segments by age-sex and between FFS and MA.

Conclusions: A simple claims-based yield metric for LCS is practical and stable across payers. More research needs to be done to determine practical applications, such as minimum population sample sizes, feasible follow-up periods, and stability across time periods. Even with 100% screening of eligible people, not all lung cancers will be detected through screening, so research is needed to determine an ideal yield rate.

		MA Population			FFS Population		
Eligibility	Age	Incident LCs	Preceded by Screen	Yield (95% CI**)	Incident LCs	Preceded by Screen	Yield (95% CI**)
Aged non-dual	Total	22,240	1,160	5.2% (4.9%, 5.5%)	2,425	149	6.1% (5.2%, 7.2%)
Dual	Total	8,050	370	4.6% (4.1%, 5.1%)	547	45	8.2% (6.0%, 11.0%)
ESRD	Total	270	0	0% (0.0%, 1.4%)	33	0	0% (0.0%, 11.2%)
Total	52-54	270	0	0% (0.0%, 1.4%)	26	0	0% (0.0%, 14.2%)
Total	55-59 *	1,120	60	5.4% (4.1%, 6.9%)	300	21	7.0% (4.3%, 10.7%)
Total	60-64 *	2,540	140	5.5% (4.6%, 6.5%)			
Total	65-69	8,160	480	5.9% (5.4%, 6.4%)	804	72	9.0% (7.0%, 11.3%)
Total	70-75	11,460	590	5.1% (4.7%, 5.6%)	1,171	66	5.6% (4.4%, 7.2%)
Total	75-77	7,010	260	3.7% (3.3%, 4.2%)	704	35	5.0% (3.5%, 6.9%)
Total	Total	30,560	1,540	5.0% (4.8%, 5.3%)	3,005	194	6.5% (5.6%, 7.4%)
MA Plan A		7,460	410	5.5% (5.0%, 6.1%)	n/a	n/a	n/a
MA Plan B		5,790	270	4.7% (4.1%, 5.3%)	n/a	n/a	n/a
MA Plan C		2,860	150	5.2% (4.4%, 6.2%)	n/a	n/a	n/a
MA Plan D		1,490	80	5.4% (4.3%, 6.7%)	n/a	n/a	n/a
MA Plan E		750	50	6.7% (4.9%, 8.8%)	n/a	n/a	n/a

* These two bands are combined to meet privacy requirements.
** The 95% confidence interval of the yield rate is based on a Poisson approximation to the binomial distribution.

EP.04D SCREENING AND EARLY DETECTION - CHALLENGES AND PROGRESS IN EARLY LUNG CANCER DETECTION
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EP.04D.02 An Innovative Evidence-Based Laboratory Medicine (EBLM) Test to Help Doctors in the Assessment of Lung Cancer

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Introduction: According to the World Health Organization (WHO), lung cancer is the leading cause of cancer-related deaths, claiming nearly 1.8 million lives each year, and of which primary risk factor remains tobacco smoking. It encompasses two main types: small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC), which represents most cases and comprises adenocarcinoma, squamous cell carcinoma (SCC), and large cell carcinoma. This malignancy is a health concern worldwide, presenting high incidence, mortality, and profound socioeconomic impact due to invasive and costly diagnostic procedures. Thus, we present Venient CDx Lung (Kience Inc., Wilmington, US) a novel non-invasive test that provides confirmatory diagnosis of lung cancer as a doctors' adjunct tool to suspicious image procedures findings, in order to reduce the number of unnecessary tissue biopsies that patients have to undergo.

Methods: The Venient CDx Lung test is a novel diagnostic algorithm designed to exclusively leverage serum and urine biomarkers. This innovative tool combines several independent public algorithms to provide comprehensive diagnostic insights, thus enabling the confirmation of lung cancer diagnosis. To evaluate the estimated accuracy of our new test, we conducted an extensive literature review to identify studies assessing the diagnostic accuracy of constituent algorithms, calculations, and combinations of analytes included within it, on the basis of a previous work by Dr. Rafael Molina et al. in 2016. In this study significant improvements in the diagnosis and classification of lung cancer were reported by combining the tumor markers CEA, CA 15.3, CYFRA 21-1, ProGRP, NSE, and SCC. We developed an upgraded version of this panel and created a refined algorithm that relies on the core set of our three machine learning algorithms: MBDAA, EBLMA and AIRA. We added the tumor marker CA-62 and a set of analytes into the test, to enable it not only confirm the presence of lung cancer but also to determine its type and subtype (SCLC or NSCLC, and within these, adenocarcinoma, SCC or neuroendocrine lung tumor). Additionally, liver and renal function indicators are integrated to enhance specificity. Thus, meeting the 1994 Barcelona criteria, proposed by the SEQC.

Results: With this refined algorithm we obtained a final sample size (n) of 4,296 individuals. With this sample size, we achieved a sensitivity of 0.93 and a specificity of 0.96. Subsequently, we conducted an approximation of the area under the receiver operating characteristic (AUROC) curve, as well as estimations for the positive predictive value (PPV) and the negative predictive value (NPV) based on these results, yielding values of 0.92, 0.95, and 0.93, respectively.

Conclusions: This data suggests that the innovative non-invasive blood and urine-based biomarker algorithm, Venient CDx Lung, holds promise in providing timely and accurate diagnosis of lung cancer, particularly among individuals aged 40 and above. Given the current epidemiological state of this malignancy, our findings underscore the significance of early detection. These results advocate for further exploration, prompting our intention to conduct a clinical study involving 10,000 participants to validate and enhance our findings and inform clinical practice.

Keywords: lung cancer confirmatory diagnostic, suspicious image findings, non-invasive

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EP.04D.03 Shifting Stages: Implications of a Global Pandemic on Cancer Care and A Multipronged Approach to Early Diagnosis for Non-Small Cell Lung Cancer

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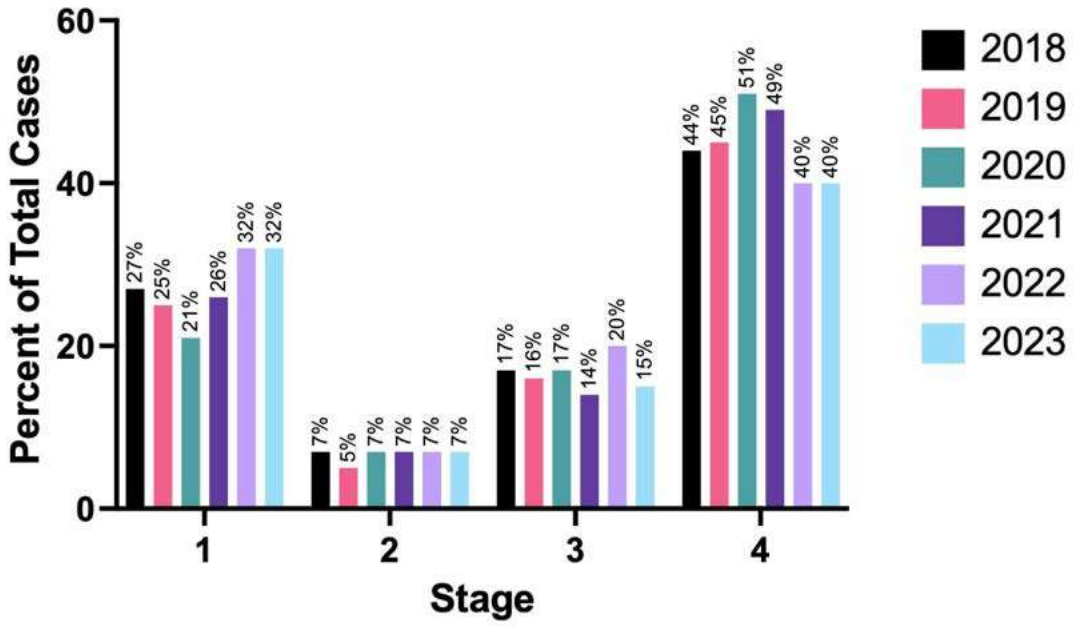
Introduction: Our institution has historically noted lower rates of patients diagnosed with early-stage lung cancer compared to peer institutions, which worsened during the COVID pandemic. In 2021, we established a dedicated early-stage thoracic oncology team, including thoracic surgeons and interventional pulmonologists. Strategic interventions aimed at expanding lung cancer screening, incidental lung nodule management, and patient navigation were implemented. We sought to determine whether these interventions affected the stage distribution for patients diagnosed with NSCLC.

Methods: We reviewed institutional data (1/1/18-12/14/23), identifying patients diagnosed with NSCLC to determine demographics and stage at diagnosis (8th edition AJCC classification). We compared two cohorts: pre-implementation between January 2018 and December 2020 and post-implementation from January 2021 to December 2023. Additionally, we analyzed changes in diagnosis patterns during the height of the COVID-19 pandemic in 2020. Chi-squared analyses were performed. Statistical significance was set at $p<0.05$.

Results: A total of 2,183 patients with a NSCLC diagnosis were identified. Many of these patients came through the newly established lung nodule clinic which manages screen-detected and incidental nodules. Referrals to the lung nodule clinic have steadily increased with over 300 referrals since inception in 2022. Concurrently, there was expansion of lung cancer screening, with an increase in completed tests from 764 in 2018 to 2099 in 2023. Among patients diagnosed with lung cancer, approximately half were women (N=1,124, 51.5%), 38.8% were Black (N=847), 32.3% were Hispanic (N=705), and 62.8% were insured by Medicare (N=1,370). Patients diagnosed as Stage I comprised just 26.7% in 2018, which decreased to only 21.1% in 2020. Since implementation of the early-stage initiatives, the proportion of stage I cases has risen steadily to 31.5% in 2023. Conversely, the proportion of patients diagnosed with stage IV NSCLC began at 41% in 2018, peaked at 51.2% during the COVID pandemic, and has decreased to 39.6% in 2023.

Conclusions: The COVID-19 pandemic prompted a shift in diagnosis patterns, emphasizing the imperative of contingency planning to uphold best practices in cancer care. Following implementation of a team focused on early diagnosis, a stage shift in lung cancer was identified with higher rates of patients diagnosed with stage I NSCLC. We attribute this to increased efforts in screening, incidental nodule management, and renewed focus on timelines of care. These efforts underscore the importance of multidisciplinary efforts to enhance early detection strategies. Further research is warranted to explore factors influencing trends and guide interventions in lung cancer diagnosis and management.

Keywords: early-stage NSCLC, lung cancer screening, multidisciplinary care



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EP.04D.04 COVID-19 and Vaccines: A Decade of Insight from China Onpulmonary Nodules Detection and Progression

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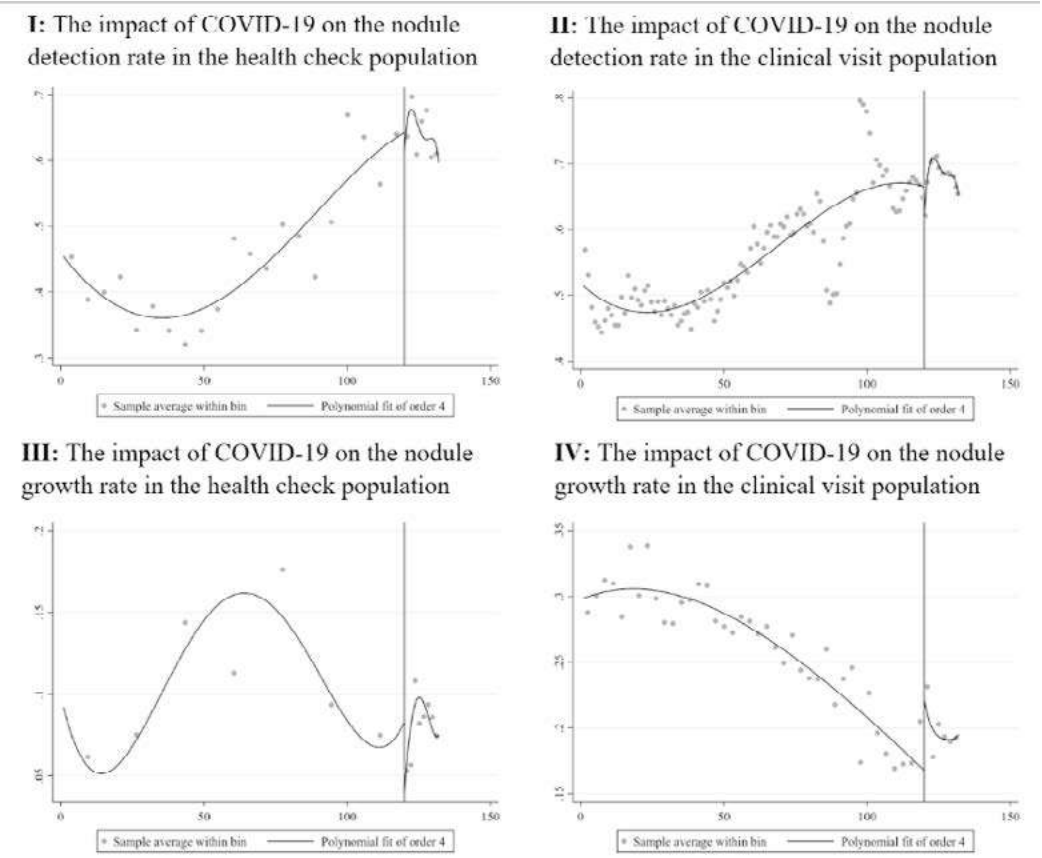
Introduction: The onset of the novel coronavirus (COVID-19) pandemic and the subsequent widespread deployment of vaccines to combat its spread have necessitated an in-depth investigation into their effects on various health aspects, including pulmonary conditions. Pulmonary nodules, which are often incidentally detected on low dose computed tomography (LDCT) scans, serve as potential early markers for lung cancer and other diseases. This study focuses on assessing the impact of COVID-19 infection and the administration of vaccines on the detection and progression rates of these nodules.

Methods: A comprehensive review of 691,412 LDCT scans from January 2013 to December 2023 was conducted. Seasonal adjustments were applied via the X-13ARIMA-SEATS algorithm to control for temporal variations. The study utilized a Regression Discontinuity Design (RDD) to evaluate shifts in nodule metrics adjacent to the December 2022 outbreak and subsequent vaccine distribution milestones. To explore pulmonary nodule detection variation, we classified LDCT scans into four groups based on nodule type: ground-glass only, solid only, both types, and nodules with unspecified characteristics.

Results: Chronologically, surrounding the December 2022 COVID-19 outbreak in China and adjacent to the tri-phasic vaccine dissemination, analysis revealed no significant breakpoints in nodule detection or proliferation rates within the clinical visit population (detection rate: p< 0.952,p<0.311,p<0.342,p<0.693; proliferation rate: p<0.513,p<0.464,p<0.793,p<0.467). Similarly, the health check population evidenced no marked discontinuities in detection or proliferation rates post-December 2022 (detection rate: p-value 0.97; proliferation rate: p-value 0.613). Examining nodule morphology from 2013 to 2023, ground-glass opacities showed a gradual uptrend in both detection and proliferation rates, whereas solid nodules' detection rate notably increased over the decade, inversely correlating with nodules of indeterminate characteristics.

Conclusions: The study concludes that COVID-19 infection and vaccination do not significantly impact the detection rate and progression of pulmonary nodules in LDCT scans. This suggests that the pathophysiological effects of COVID-19 and the immune response elicited by vaccination do not extend to altering the characteristics of pulmonary nodules detectable by LDCT. These findings provide valuable insights for clinicians and patients concerning lung health management during the pandemic. Despite the lack of association found in this study, the importance of vaccination against COVID-19 remains paramount in controlling the spread of the virus and protecting overall public health. Future research should aim to explore the long-term effects of COVID-19 infection and vaccination on pulmonary health and other organ systems to guide comprehensive disease management strategies.

Keywords: COVID-19, Pulmonary Nodules, Low-dose computed tomography



EP.04D SCREENING AND EARLY DETECTION - CHALLENGES AND PROGRESS IN EARLY LUNG CANCER DETECTION
SATURDAY, SEPTEMBER 7, 2024 - 11:58 - 11:59

EP.04D.05 Coronary Atherosclerosis as an Incidental Finding within the Lung Cancer Screening

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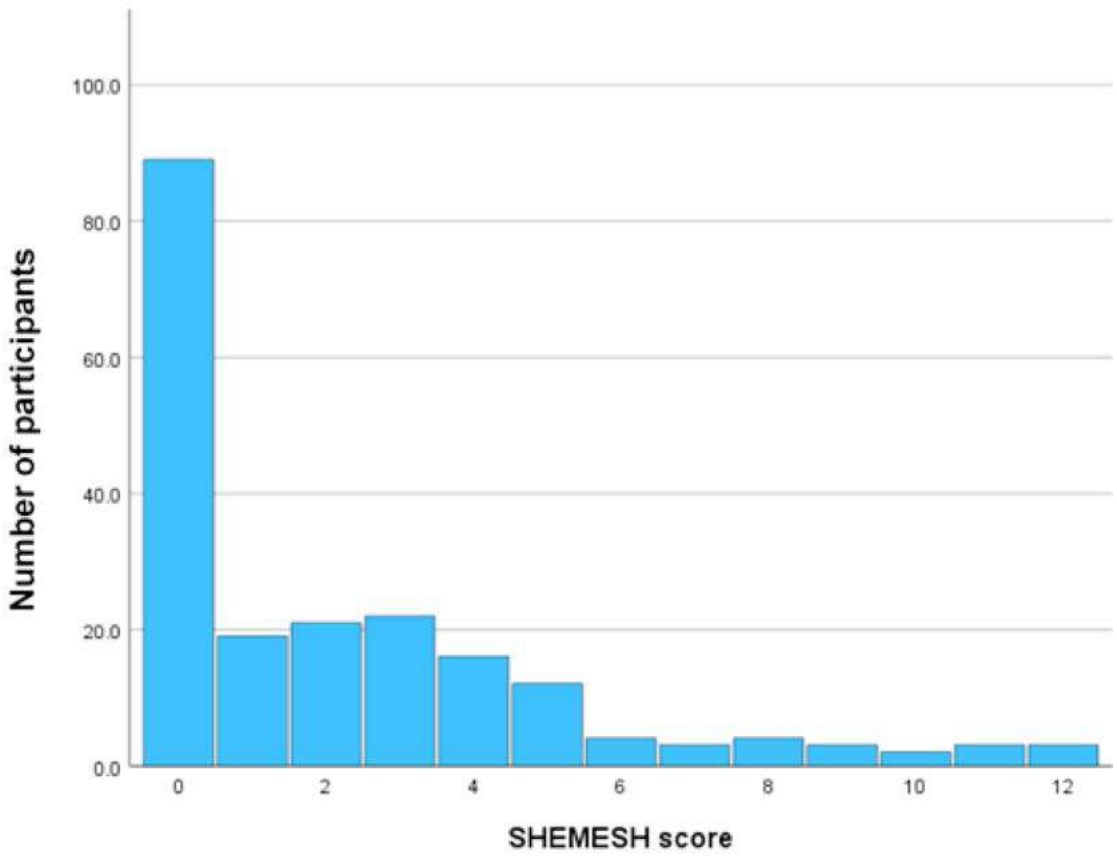
Introduction: Smoking has been associated with a high number of severe health risks such as cancer, chronic obstructive pulmonary disease, stroke and coronary heart disease. Smoking remains the foremost risk factor for lung cancer ranking as the first deadliest tumor. One option, which has been under investigation to mitigate lung-cancer related deaths, is early detection. Since 2019, a study evaluating the feasibility and efficacy of low-dose CT lung cancer screening (LCS) program in Switzerland is ongoing. Concurrently a retrospective analysis was conducted to evaluate the presence of coronary calcification (CAC), as an incidental finding, since smoking has been established as a major risk factor thereof as well.

Methods: Among the 215 participants in the LCS project, atherosclerosis was detected in the coronary artery of 121 individuals. To assess the severity of this condition, the SHEMESH score was utilized, which categorizes CAC in the four coronary arteries as follows: absent (0), mild (1) when less than one-third of the vessels exhibit calcification, moderate (2) when one-third to two-thirds of the artery is affected, and severe (3) when more than two-thirds of the artery is calcified. Two radiologists, gave to every participant a CAC score ranging from 0 to 12. Additionally, the results of the SHEMESH score were compared with age and pack year in a generalized linear mixed model.

Results: CAC was present in 56.1% of the participants. Among them, 31.1% (n = 67) had scores ranging from 1 to 3, 16.2% (n = 35) scored between 4 and 6, and 8.8% (n = 19) had scores between 7 and 12. Figure 1 displays the number of participants per each SHEMESH score. Age (p = 0.032, correlation coefficient = 0.098) and pack years (p = 0.011, correlation coefficient = 0.037) were found as significant predictors both demonstrating statistical significance.

Conclusions: We observed a high prevalence of atherosclerosis among LCS participants. There exists a high association between SHEMESH score and subjects' age and a lower correlation between SHEMESH score and pack years. This observation suggests that although cigarette smoke contributes to the risk of atherosclerosis, the disease may not strictly depend on the number of pack year. Furthermore, the possibility of CAC as an incidental finding as well as its consequences should be considered when setting up a Lung Cancer Screening program.

Keywords: Lung Cancer Screening, Incidental Findings, Coronarsclerosis



EP.04D SCREENING AND EARLY DETECTION - CHALLENGES AND PROGRESS IN EARLY LUNG CANCER DETECTION
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EP.04D.06 Observation of Peripheral Airways Using Ultra-Thin Fiberscope

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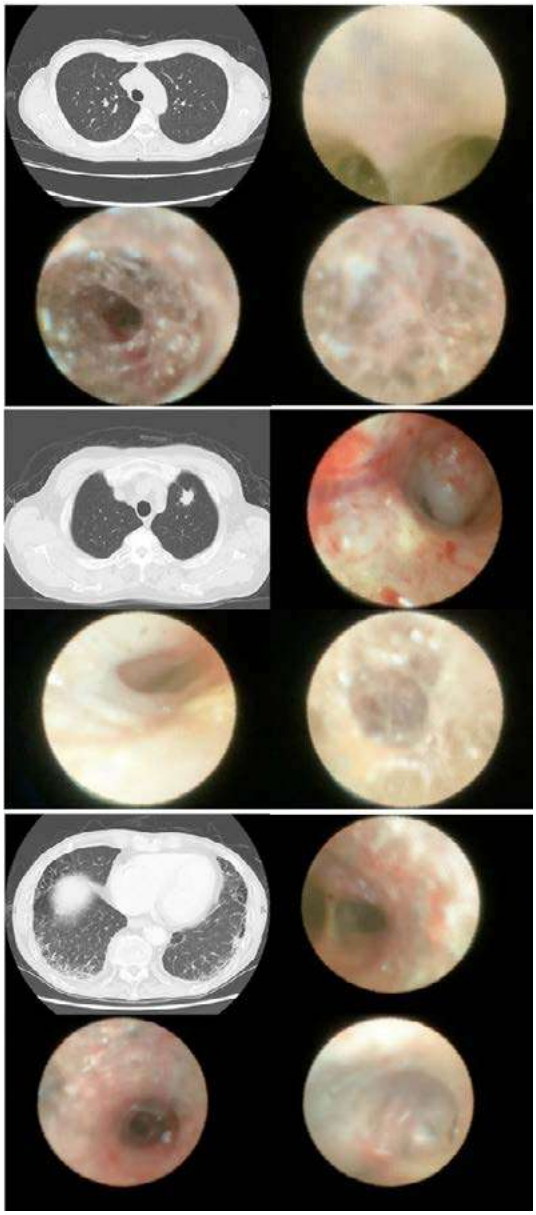
Introduction: The diagnosis of peripheral airway lesions generally relies on computed tomography scanning. Endoscopic observation of such lesions is rarely performed. Although new technologies have been introduced to improve the diagnostic performance of bronchoscopy for peripheral lesions, the yield of bronchoscopic biopsy for such lesions is comparatively low.

Methods: We have developed a 0.97 mm diameter ultra-thin optical fiberscope that can access the peripheral lung fields of human lungs. We used this fiberscope to successfully observe peripheral airway lesions in resected human lungs under negative pressure.

Results: In normal, non-smoker's lungs, the fiberscope was able to visualize individual alveoli beyond the respiratory bronchioles. In a case with a peripheral lung cancer, alveolar structures were destroyed and replaced with red tumors. In a lung specimen with interstitial pneumonia, extensive neovascularization was appreciated, with destruction of alveoli and thickening of the interstitium.

Conclusions: There have been no prior reports regarding the use of a fiberscope to observe human lung lesions at the alveolar level. Since this fiberscope can perform simultaneous observation and laser treatment, access to such peripheral lesions with this device also represents a novel opportunity for treatment.

Keywords: ultra-thin fiberscope, alveolus, bronchoscopy



EP.04E SCREENING AND EARLY DETECTION - STRATEGIES TO IMPROVE EARLY DETECTION
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EP.04E.01 Use of Routine Brain Imaging Surveillance after Definitive Treatment for Early-Stage Non-Small Cell Lung Cancer

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Introduction: Prevalence of brain metastasis in early-stage non-small cell lung cancer (NSCLC) is low, and unnecessary imaging has potential to cause undue burden to patients and health system without survival benefit. Routine brain imaging for staging in early NSCLC occurs in 12-25% of patients in the US, yet estimates for its use in post-treatment surveillance is unreported. We sought to look at use of brain imaging after treatment of NSCLC, utilizing the Veterans Health Administration database to capture patterns and indications of imaging.

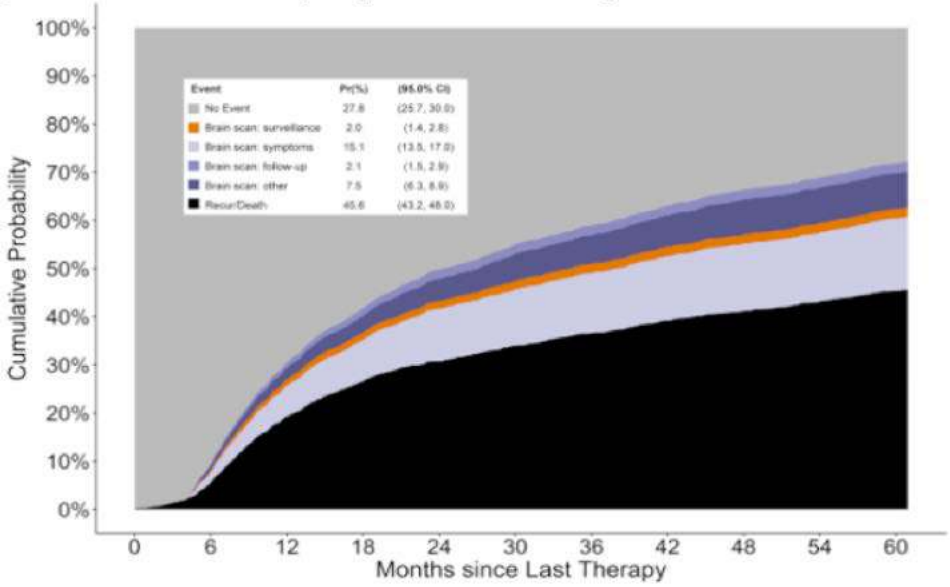
Methods: The primary outcome was receipt of brain imaging stratified by modality and indication (symptoms, surveillance, or follow-up for abnormal imaging). We included Veterans diagnosed with Stage I-III NSCLC between 2008-2016 who underwent definitive treatment and survived minimum 120 days corresponding to the first period of surveillance. We examined rates of imaging (CT or MRI) starting 120 days up to 5 years using claims data. A subset of patients underwent additional chart abstraction to obtain data regarding competing outcomes of second primary cancer, recurrence, or death. Multivariable analysis was used to examine predictors of asymptomatic brain imaging.

Results: Of the 20,532 patients; 43% (n=8,825) received brain imaging after treatment, the majority of which 61% (n=5,419) were CT scans and 39% (n=3,406) MRI. In the subset of 1,620 patients, 27% (n=432) received any brain imaging; however, 46% (n=738) of patients had documented recurrence or death making them ineligible for surveillance. After excluding these competing outcomes, 49% (n=432/882) received brain imaging, of which 7% (n=32) were completed for surveillance. Of these scans, a majority were CT (n=19, 59%) rather than MRI (n=13, 41%) and completed in the first year post treatment. Most surveillance brain imaging was done for Stage I patients (44% vs Stage II 28%, Stage III 25%). There were no predictors of receipt of surveillance on multivariable analysis and no difference in rates of detection on imaging done in the absence or presence of symptoms (4% vs 3.5%).

Conclusions: While only a small proportion patient received brain imaging surveillance, we found that most underwent CT rather than MRI and were done predominantly in Stage I patients with no measurable benefit of metastatic detection. Although a small proportion, inappropriate use of imaging surveillance adds to the burden of care for cancer patients and brings tremendous cost to the healthcare system. Continued work on dissemination of surveillance appropriateness criteria can decrease overutilization of resources without affecting patient care quality.

Keywords: surveillance, lung cancer, brain imaging

Figure 1. Aalen-Johansen competing events model showing cumulative incidence of first events.



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EP.04E.02 Quantification of Cerebrospinal Fluid Tumor DNA in Lung Cancer Patients with Suspected Leptomeningeal Carcinomatosis

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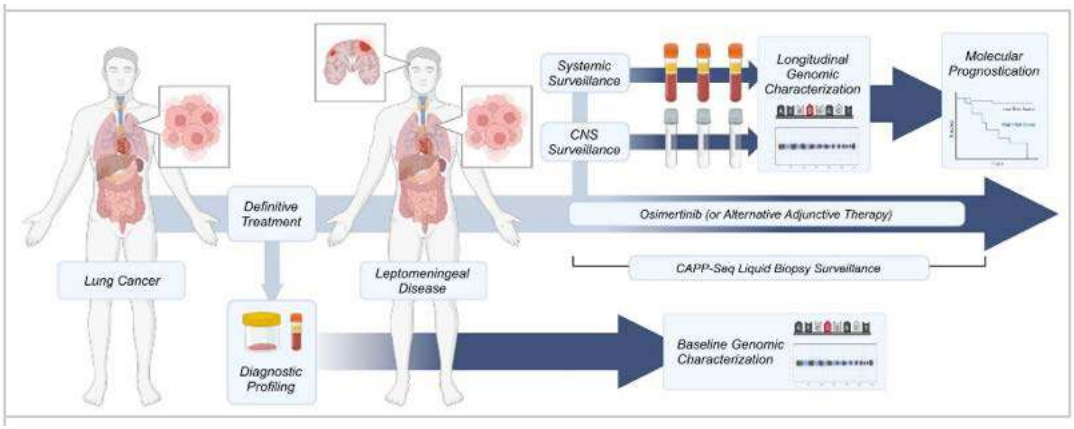
Introduction: The diagnosis and response assessment in leptomeningeal disease (LMD) relies upon cerebrospinal fluid (CSF) cytology, the clinical standard, as well as physical examination and magnetic resonance imaging (MRI) of the brain and spine. CSF cytology is highly specific for LMD but has a reported sensitivity of only 50-60%. Then, we aimed to develop a CSF-tDNA assay using CAPP-Seq, a targeted NGS-based method originally developed for the analysis of plasma ctDNA, for the diagnosis and monitoring of the central nervous system (CNS) metastasis in patients with lung cancer.

Methods: We applied CAPP-Seq using a lung cancer-specific sequencing panel to 81 CSF, blood, and tissue samples from 24 patients with advanced lung cancer who underwent lumbar puncture (LP) for suspected LMD. A subset of the cohort (N = 12) participated in a prospective osimertinib treatment trial for refractory LMD in which serial LPs were performed before and 3 weeks after initiating treatment.

Results: CSF-tDNA variant allele fractions (VAFs) were significantly higher than plasma circulating tumor DNA (ctDNA) VAFs (median CSF-tDNA, 32.7%; median plasma ctDNA, 1.8%; P <0.0001). Concentrations of tumor DNA in CSF and plasma were positively correlated (Spearman's ρ, 0.45; P = 0.03). For LMD diagnosis, cytology was 81.8% sensitive and CSF-tDNA was 91.7% sensitive. CSF-tDNA positivity was also strongly prognostic for overall survival (HR = 7.1; P = 0.02). Among patients with progression disease on targeted therapy, resistance mutations, such as EGFR T790M, were common in peripheral blood but were rare in time-matched CSF, indicating differences in resistance mechanisms based on anatomic compartment. Whereas, MET copy number gain was seen in the CSF-tDNA of 1/5 patients with CNS progression with osimertinib.In the osimertinib treated cohort, patients with CNS progression had increased CSF-tDNA VAFs at follow-up compared to pre-osimertinib CSF. While there was no significant association between pre-osimertinib CSF-tDNA VAFs and CNS progression, on-osimertinib CSF-tDNA VAF was strongly associated with CNS progression (HR = 6.2, P = 0.009).

Conclusions: We provide evidence supporting the utility of CSF-tDNA detection to diagnose LMD in lung cancer patients. Assessment of CSF-tDNA has the potential to measure molecular response of LMD to EGFR-TKI treatment at early treatment timepoints with implications for therapeutic decision making. The use of dynamic measurement of plasma ctDNA and CSF-tDNA status and profiling of co-occurring gene alterations provides support for prospectively testing novel strategies for personalized management of this devastating clinical entity

Keywords: CSF-tDNA, CNS metastasis, Osimertinib



EP.04E SCREENING AND EARLY DETECTION - STRATEGIES TO IMPROVE EARLY DETECTION
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EP.04E.03 Enzymomics of Bodily Fluids Captures CD38-Orchestrated Immunometabolic Disorder for Early Detection of Immunotherapy Toxicity

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Introduction: Enzymomics (omics of enzymes) resides in the core of catalytic processes and might exert immunometabolic effect on systemic diseases. As liquid biopsy allows for noninvasive monitoring of the systemic status, we asked whether liquid-based detection could capture the enzymomic disorder in immune-related adverse events (irAEs), a systemic autoimmune state secondary to immune checkpoint inhibition (ICI) treatment.

Methods: We generated pseudo-bulk profiles of enzyme-encoded genes from single-cell data of bronchoalveolar lavage fluids (BALFs) collected at baseline from 16 ICI-treated patients with non-small cell lung cancer (NSCLC). Differential analyses and gene set variation analyses of ICI-pneumonitis vs control BALFs were conducted at pseudo-bulk and single-cell resolutions. The discriminated capacity of the enzymomic biomarker for irAEs was tested in two external cohorts with different biopsy time points, one comprising 60 patients with pre-ICI blood biopsy and the other comprising 22 patients with post-ICI single-cell profiling of CD3+ T cells.

Results: Pseudo-bulk enzymomic profiles of BALFs revealed metabolic disorders in ICI-pneumonitis vs control, converging to an NAD-consuming enzyme CD38. The risk of ICI-pneumonitis was strikingly increased in patients with higher proportion of CD38+ immune cell in baseline BALFs compared with those with lower proportion. At the single-cell resolution, CD38 was upregulated in ICI-pneumonitis BALFs compared with control, particularly in T cells; mechanistically, CD38+ T cells exhibits a senescent-associated secretory phenotype (Figure 1). In external cohorts, pre-ICI blood-based CD38 expression could also predict higher risk of irAEs rather than durable clinical response derived from ICI; and the T cell-specific CD38 expression sticked to increase in ICI-colitis samples compared with those without ICI-colitis and non-ICI samples (Figure 2).

Conclusions: Liquid biopsy detecting CD38 on immune cells, especially T cells, within bodily fluids, including BALFs and blood, might enable early identification of patients at high risk of irAEs

Keywords: bodily fluids, enzymomics, immune-related adverse events

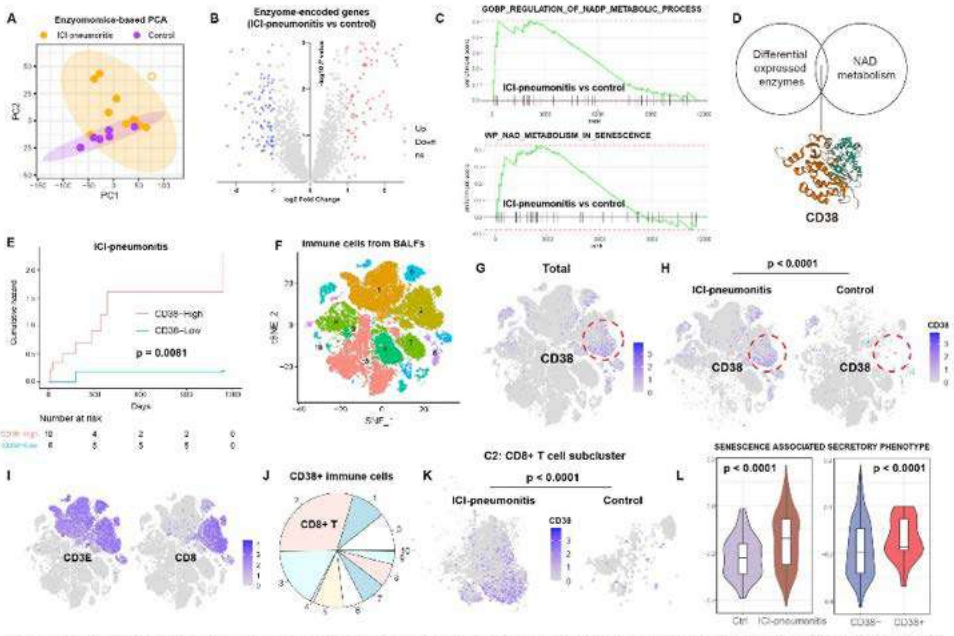

Fig 1. Liquid biopsy of BALFs captures the predictive value of CD38 for ICI-pneumonitis. (A-B) Pseudo-bulk enzymomic profiles of BALFs of ICI-pneumonitis vs control. (C) NAD metabolic signaling enrichment of ICI-pneumonitis vs control. (D) Integration of differential expressed enzymes and NAD metabolism signaling. (E) The risk of ICI-pneumonitis per CD38+ immune cell proportion in baseline BALFs. (F) tSNE plot of immune cell from BALFs. (G-H) CD38 expression of ICI-pneumonitis vs control in total immune cells. (I-J) CD38 expression distribution among subclusters. (K) CD38 expression of ICI-pneumonitis vs control in CD8+ T cells. (L) CD38+ T cells exhibits a senescent-associated secretory phenotype.

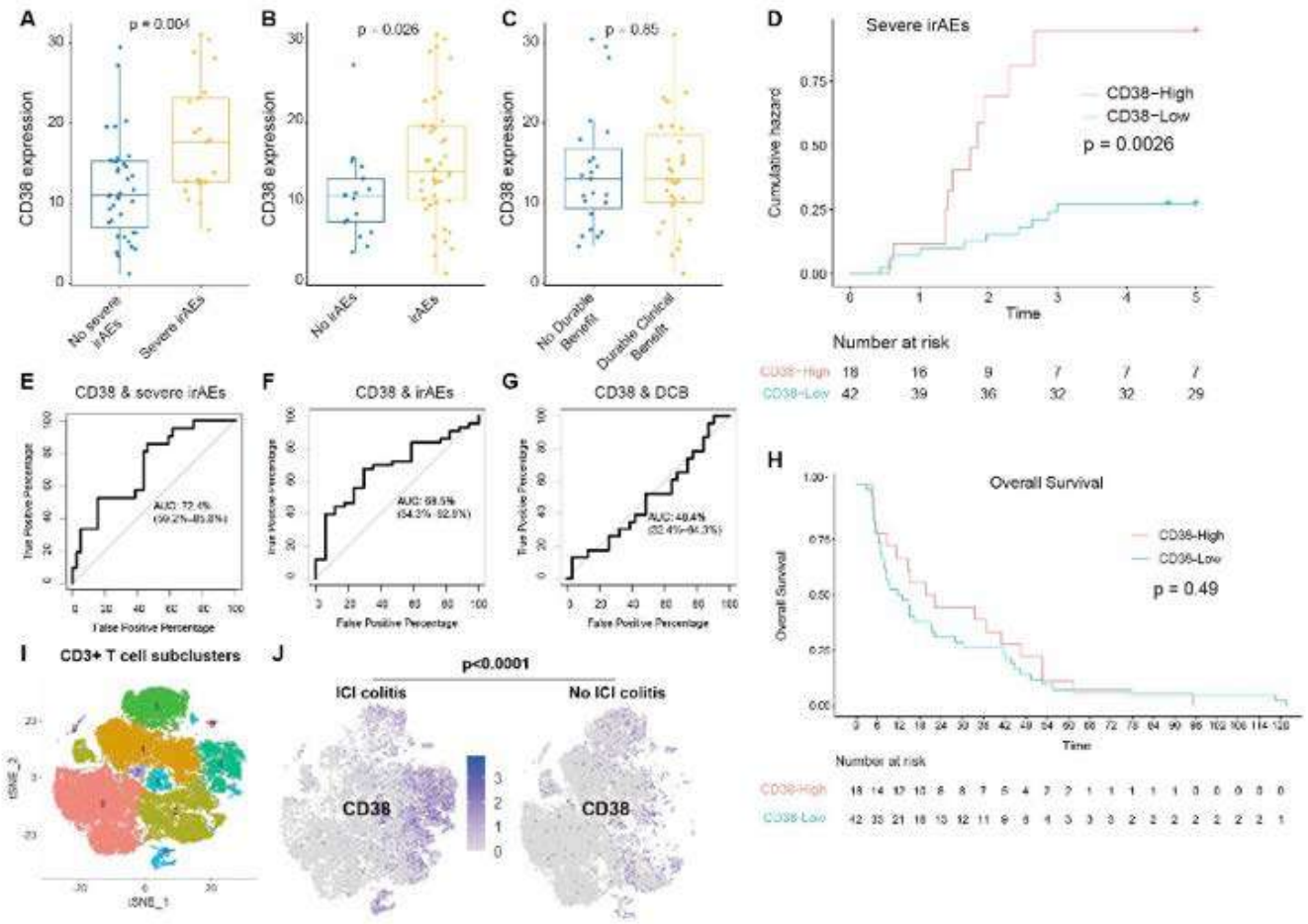

Fig 2. External validation of the discriminated capacity of CD38 for irAEs. CD38 expression per (A) severe irAE status, (B) irAE status, (C) response status. (D) Cumulative hazard curves of irAEs per CD38 expression status. Area under curves of CD38 in predicting (E) severe irAEs, (F) irAEs, and (G) durable clinical benefit. (H) Survival curves of overall survival per CD38 expression status. (I) t-SNE plot of CD3+ T cell subclusters in ICI-colitis and control samples. (J) CD38 expression in ICI-colitis vs control samples.

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EP.04E.04 Machine Learning Classifier for Predicting the Radiation Pneumonia Grade in Non Small Cell Lung Cancer

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Introduction: Radiotherapy is one of the main treatments for lung cancer. Increasing the radiation dose can improve the local control rate and overall survival rate of the tumor, but at the same time it will increase the occurrence of radiation induced lung injury (RILI). Radiation pneumonia (RP) is the main dose-limiting RILT for lung cancer patients. RP not only affects the quality of life and prognosis of patients, but also increases the rate of readmission, which may even lead to death in severe cases. Therefore, early prediction of the incidence and grading of RP can provide decision-making basis for clinical precise treatment, optimize radiotherapy prescription and reduce the incidence of symptomatic RP. We aim to explore a machine learning classifier for early non-invasive prediction of RP grade in non-small cell lung cancer (NSCLC) patients.

Methods: We retrospectively collected 112 patients and they have been pathologically diagnosed as NSCLC. The CT images within 4 weeks before radiotherapy were collected, and the follow-up data of RP were collected within one year after radiotherapy. The RP was classified as 0~5 grades according to the RP grading standard established by Radiation Therapy Oncology Group (RTOG), and we defined the 0~2 levels as low-RP (n=69), and 3~5 levels as high-RP (n=43). All patients were randomly assigned to training group and testing group according to 7:3. The CT images were imported into 3D-slicer software to segment the regions of interest and extract 851 radiomics features. The radiomics features included first-order features, shape features, glcm, gldm, glrlm, glszm, ngtdm and wavelet transformed features. The intraclass correlation coeficient test, minimum redundancy maximum correlation, least absolute shrinkage and selection operator algorithms were used to select radiomics features. The machine learning classifiers including Logistic Regression, Naive Bayes, SVM, KNN, Random Forest, XGBoost, Gradient Boosting, AdaBoost were used to construct prediction model. ROC analysis was used to analyze the predictive efficacy of the model. The DCA curve was used to analyze the clinical value.

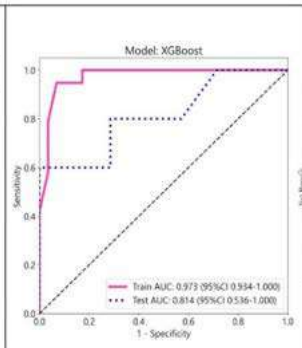
Results: In present study, the XGboost classifier showed the optimal predictive efficacy, the AUCs in the training and testing groups were 0.973 (95% CI [0.801 0.980]) and 0.814 (95% CI [0.800, 0.950]), respectively.

Conclusions: The radiomics features of CT may serve as the potential imaging biomarkers for prediction of RP grade, and the XGboost classifier may have the optimal predictive efficacy.

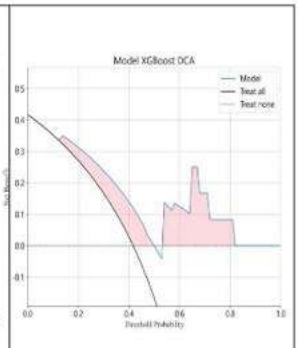
Keywords: Machine Learning, Radiation Pneumonia, Non Small Cell Lung Cancer

Table 1. The AUCs of machine learning classifiers

Task	Machine Learning Classifier	AUC
label-train	Logistic Regression	0.650
label-test	Logistic Regression	0.714
label-train	NaiveBayes	0.633
label-test	NaiveBayes	0.857
label-train	SVM	0.292
label-test	SVM	0.143
label-train	KNN	0.822
label-test	KNN	0.657
label-train	RandomForest	1.000
label-test	RandomForest	0.614
label-train	XGBoost	0.973
label-test	XGBoost	0.814
label-train	GradientBoosting	0.965
label-test	GradientBoosting	0.757
label-train	AdaBoost	0.931
label-test	AdaBoost	0.743



ROC curve of XGBoost



DCA curve of XGBoost

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EP.04E.05 Prevalence and Characterization of MET Overexpression in Chinese NSCLC Patients: A Retrospective Real-World Analysis

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Introduction: Mesenchymal epithelial transition (MET) expression is discerned in 17-35% of non-small cell lung cancer (NSCLC) patients. The current knowledge of its impact on the treatment efficacy of MET-tyrosine kinase inhibitors (TKIs) remains constrained, despite MET being a promising therapeutic target. This study attempt to elucidate the characterization of MET overexpression within a hospital in China. This exploration holds potential significance for forthcoming investigations focusing on targeted MET therapy.

Methods: This retrospective real-world study analyzed non-small cell lung cancer (NSCLC) specimens from 1223 patients who underwent surgical resection or biopsy between June 2020 and August 2023 at the First Affiliated Hospital of Wenzhou Medical University, Wenzhou, China. Specimens deemed suitable for MET immunohistochemistry (IHC) were included in the analysis. MET overexpression was assessed utilizing the anti-MET clone SP44 IHC assay from Roche Tissue Diagnostics, with a positive classification assigned if more than 50% of cells at 3+ intensity. Clinical data were retrieved from electronic health records. Associations among covariates were examined using the Spearman test, with significance set at p values < 0.05. Statistical calculations were conducted using R 4.3.1 software.

Results: Eighty seven patients were included. The detection rate of patients with MET positive (3+intensity) is 7%. MET overexpression patients was found more frequently in male (70.1%), adenocarcinoma (81.6%), IV stage (69.0%), concomitant hypertensin (39.1%). Regimens used were chemotherapy (2.3%), chemotherapy plus immune checkpoint inhibitors (11.5%). target therapy (40.2%). We also found that MET overexpression correlated with red blood cells decreased (correlation coefficient -0.3139, p=0.0036), and hemoglobin decreased (correlation coefficient-0.3805, p=0.0002). Due to the limited follow-up period, the Progression-Free Survival (PFS) in patients with MET overexpression was not reached.

Conclusions: We have successfully demonstrated a higher occurrence of MET overexpression in males, adenocarcinomas, and at stage IV in NSCLC patients. Additionally, our findings suggest a potential association between anemia and MET overexpression, which suggested that MET overexpression may cause anemia. Considering the increasing development and prevalence of MET overexpression, it emerges as a promising avenue for future research, potentially serving as a target for the characterization and treatment of NSCLC.

Keywords: MET overexpression, adenocarcinomas

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EP.04E.06 The Prediction of Spread Through Air Spaces with Preoperative 18F-FDG PET/CT in Clinical Stage I Lung Cancer

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Introduction: Spread through air spaces (STAS) is associated with local recurrence, especially in limited resections such as segmentectomy or wedge resection. It is evaluated through histopathological examination postoperatively. Having information about STAS preoperatively can be influential in determining the type of resection.

The aim of this retrospective study was to investigate the utilization of preoperative F-18 fluorodeoxyglucose positron emission tomography/computed tomography (18F FDG-PET/CT) in predicting STAS in clinical stage I lung cancer.

Methods: The study included 205 patients (mean age: 62.61±8.5; 132 male, 73 female) with clinical Stage I lung cancer who underwent surgery between 2016 and 2024, had PET/CT imaging available at our institution, and did not receive neoadjuvant treatment. Maximum standardized uptake value (SUVmax), metabolic tumor volume (MTV), and total lesion glycolysis (TLG) values were calculated from preoperative PET/CT images. Patients were grouped as STAS absent (STAS 0) and present (STAS 1). Differences between PET/CT parameters of STAS 0 and STAS 1 groups were compared using the Mann-Whitney U Test. Cut-off values to predict STAS status for PET/CT parameters were calculated with ROC analysis.

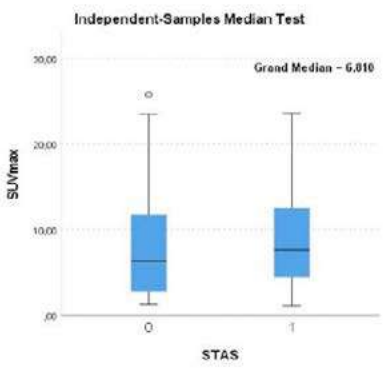
Results: Of the tumors, 168 (82.4%) were FDG avid, while the rest were not visible in preoperative imaging. Surgical procedures included lobectomy, wedge resection, segmentectomy, and pneumonectomy in 131, 45, 16, and 13 patients, respectively. Based on postsurgical histopathological examination, 126 lesions (61.5%) were negative for STAS, and 79 (38.5%) lesions were positive for STAS. The STAS positivity rate for FDG avid lesions was calculated as 69/168 (41%), and for non-FDG avid ones as 9/36 (25%) (p=0.07).

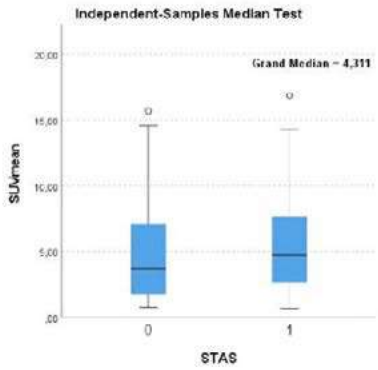
Significant differences were detected in SUVmax (8.2 [range 2.56-12.40] vs. 6.3 [range 0.62-9.78], p = 0.036) and SUVmean (4.9 [range 2.46-8.20] vs. 3.7 [range 0.51-7.60], p=0.018) according to the presence of STAS. However, this difference was not observed in MTV (4.67 [range 0.65-23.76] vs. 4.95 [0.63-20.07], p = 0.95) and TLG (8.73 [range 0.93-48.76] vs. 6.73 [0.70-53.66], p = 0.17).

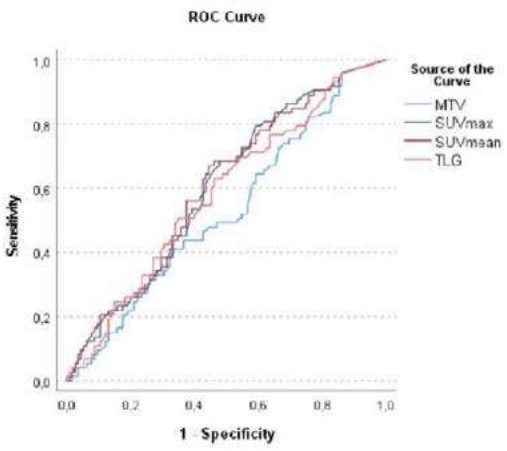
In the ROC analysis, SUVmax and SUVmean showed the best diagnostic performance among PET parameters to predict STAS. SUVmax had an AUC value of 0.60 (95% CI 0.62-0.68) with a sensitivity of 79% and specificity of 41% at a cut-off of 3.47.

Conclusions: Preoperative 18F FDG-PET/CT findings might play a role in predicting STAS status. SUVmax and SUVmean appear to be more valuable indices than MTV and TLG in predicting the presence of STAS in clinical stage I lung cancer and for deciding the type of surgical resection.

Keywords: spread through air spaces, lung cancer, local recurrence







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EP.04E.07 Lung Cancer Patient Reported Experiences with Biomarker Testing

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Introduction: Research was undertaken to better understand awareness and experiences with biomarker testing among patients living with Non-Small Cell Lung Cancer (NSCLC). Additionally, research sort to understand potential health inequities in terms of access to biomarker testing.

Methods: In August 2023, an email invitation to an online survey was sent to US members of MyLungCancerTeam. In total, 82 members living with Non-Small Cell Lung Cancer completed the survey. All respondents were 21 or older and have been diagnosed with lung cancer.

Results: The majority of respondents had stage 3 or 4 lung cancer (53%) and 35% had been diagnosed within the last year. More than half (55%) have discussed biomarker testing with their doctor and 46% have had a biomarker test. Based on biomarker test results, 39% were put on an immunotherapy drug and 32% were put on a targeted therapy. For a small number (11%), results suggested they were not good candidates for immunotherapy. Five percent were able to apply for or enter a clinical trial based on results. The top reason for not getting a biomarker test is lack of familiarity with the test (38%). Other reasons for not getting tested included cancer being in remission (20%), the oncologist had already developed a treatment plan (18%) or did not feel the test was needed (8%). In total, 49% are or had been on an immunotherapy drug. The percent who were extremely satisfied with their treatment regimen was much higher if immunotherapy was part of that regimen (53% versus 29%). Results also identified health inequities regarding who underwent a biomarker test. For example, those who received the test were more likely to have at least an associate college degree (74% vs. 42%), earn $50K or more (56% vs. 40%), have private insurance (26% vs. 14%), live in a non-rural area (80% vs. 59%) and live in a non-Southern census region (70% vs. 61%).

Conclusions: Given the challenges in diagnosing lung cancer at an early stage, getting patients onto the most effective treatment regimen as early as possible is critical. Biomarker testing can help oncologists develop more targeted approaches to treating their patients. As such, eliminating disparities in regard to access to biomarker testing is paramount in ensuring health equity and the best possible outcomes regardless of who the patient is or where the patient lives.

Keywords: Biomarker, Health equity

EP.04E SCREENING AND EARLY DETECTION - STRATEGIES TO IMPROVE EARLY DETECTION
SATURDAY, SEPTEMBER 7, 2024 - 11:58 - 11:59

EP.04E.08 Rapid in House Next Generation Sequencing and Impact on Treatment Decisions and Initiation in Advanced NSCLC

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Introduction: Next-generation sequencing (NGS) in non-small cell lung cancer (NSCLC) has improved the detection of actionable genetic alterations and, subsequently, an increasing number of treatment options. Despite many Canadian laboratories offering NGS testing, there are many regions experiencing an average turnaround time for results of >2 weeks. The William Osler Health System (WOHS) has implemented rapid in-house NGS for patients with NSCLC and other cancers. This study examined turnaround times of in-house NGS to assess whether access to rapid NGS improved time to treatment decisions and access to targeted treatments in patients with advanced disease.

Methods: A retrospective chart review was done for patients diagnosed with NSCLC who underwent NGS from January 1, 2019, to December 31, 2022. Patient demographics, stage of cancer, NGS results, date of medical oncology consultation, treatments provided, and date of targeted therapy initiation were collected. Turnaround time (TAT) for in-house NGS results was defined as the procedure date to when the results were available in the electronic medical record for a physician to review. Two sample t-tests were performed using an alpha value of 0.05 to compare TAT means.

Results: During the inclusion period, 988 NSCLC patients had genomic sequencing performed at WOHS; 495 patients were diagnosed and treated at WOHS, and 493 were from external hospitals. Key demographics of patients diagnosed and treated at WOHS are summarized in Table 1. The mean TAT for all samples (N=988) was 14 days. TAT for WOHS patients shows a statistically shorter TAT (M=11 days) compared to non-WOHS patients (M=17 days) ($p<0.001$).

Table 1. Key WOHS patient demographic and baseline clinical characteristics.

When NGS results were available at the first medical oncology visit, treatment decisions were more likely to be made ($p<0.001$), a shorter wait time between medical oncology consultation and treatment decision ($p<0.001$) was observed and treatment was started faster (M=18 days) than patients without upfront NGS results (M=30 days) ($p>0.001$ not significant likely due to limited sample size). The targeted therapy prescription rate is demonstrated in Table 1. Targeted therapy was not prescribed for patients with targetable mutations where front-line targeted therapy was not available or indicated (e.g., KRAS G12C, ERBB2) or where systemic therapy was not indicated.

Conclusions: This community-based in-house NGS testing model can significantly decrease the TAT for NGS results for advanced NSCLC patients and ultimately improve the time-to-treatment decision and treatment initiation in the advanced setting. The impact this will have on patient outcomes, such as survival, is currently under investigation.

Keywords: In-House Genetic Testing, Next-Generation Sequencing, Non-small Cell Lung Cancer

Characteristics	N=495 (%)
Mean Pack Years (mean)	27
Mean Age, years	70
Sex	
Female	245 (47.1)
Male	233 (49.5)
Unknown	17 (3.4)
Stage	
Unknown	
I	135 (27.3)
II	31 (6.3)
III	92 (18.6)
IV	202 (40.8)
Availability of NGS Result	
At first medical oncology visit	197 (39.8)
After first medical oncology visit	171 (34.5)
Not Seen By WOHS Oncologist	127 (25.6)
Stage IV Patients with Actionable Gene Mutations	
Yes	84 (41.1)
No	118 (58.9)
Stage IV Patients with Targetable Mutations who Received Targeted Therapy	
Yes	52 (61.9)
No	32 (38.1)
PD-L1 levels	
<1%	123 (24.8)
1-49%	178 (35.9)
>50%	80 (16.2)
unknown	114 (23.0)

EP.04F SCREENING AND EARLY DETECTION - CLINICAL TRIALS IN PROGRESS
SATURDAY, SEPTEMBER 7, 2024 - 11:58 - 11:59

EP.04F.01 Challenges in Recruiting for a Randomized Controlled Intervention to Increase Lung Cancer Screening

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Introduction: Lung cancer is the most fatal of all cancers, but of the four US Preventive Services Task Force (USPSTF) recommended cancer screenings, lung cancer screening (LCS) is the least utilized. Nationally, the median LCS rate is 5.0%, lower than that for any other screenable cancer. We are conducting a prospective, randomized clinical trial to test two interventions associated with increasing the completion of low-dose computerized tomography scans for LCS among eligible UC Davis ambulatory patients over usual care. In this preliminary report, we identify the ongoing challenges in recruiting eligible patients during the first 15 weeks of this clinical trial (ClinicalTrials.gov identifier: NCT06351085) involving 309 patients.

Methods: During Aim 1 we conducted key informant interviews with providers, patients who completed LCS, and age-eligible patients who smoked to qualitatively identify patient-centered factors that facilitate and impede participation in LCS. A Patient Advisory Board reviewed these findings and assisted in developing an educational video for patients that addressed perceived barriers and accentuated facilitators to screening. In Aim 2, we adhered to the USPSTF recommendations for LCS including shared decision-making for smoking cessation counseling. Primary care clinics designated a licensed vocational nurse as a Navigator to recruit patients for LCS on their behalf. These findings informed the randomization of two interventions: (a.) Navigator-guided intervention alone and (b.) Navigator-guided intervention plus a LCS awareness video linked to the electronic patient-physician portal to increase LCS compared to a usual care control clinic arm.

Results: The overwhelming proportion of existing electronic health records on patients' smoking histories were not current. Determining actual eligibility of patients ages 50-80 and who are current smokers or former smokers who quit within the past 15 years with > 20 pack-years needed to be done on a patient-by-patient basis. This typically required the Navigator to reach the patient by phone and going through a protocol to assess eligibility by age, smoking status, current cancer diagnosis, as well as recency of LCS if appropriate. Through this protocol, our initial findings indicate that [1] 6.5% (20/309) of patients have a current cancer diagnosis and are presumably in treatment and excluded from further recruitment to LCS; and [2] 80.0% (182/227) of those remaining patients contacted, were not eligible due to not meeting USPSTF recommendations. Sixty-two patients could not be contacted on the first attempt. After all of the other eligibility requirements were assessed, only 8.9% (22/247) of the reachable patients were determined to meet all of the LCS eligibility criteria. To date, among patients whose eligibility was verified, the two levels of Navigator-guided interventions resulted in a LCS rate of 41% (9 scheduled or screened/22 eligible).

Conclusions: These findings are very preliminary and caution should be exercised in extrapolating these results as this only represented the first 15 weeks of our ongoing intervention study. The role of the Navigator to thoroughly assess LCS eligibility beyond dependence of extant electronic patient records of smoking histories and other factors is essential.

Keywords: Lung Cancer Screening, Navigator, Smoking Cessation

EP.05A PULMONOLOGY AND STAGING - ENDOSCOPIC EVALUATION
SATURDAY, SEPTEMBER 7, 2024 - 11:58 - 11:59

EP.05A.01 Efficacy and Safety of Midazolam with Fentanyl for Sedation During EBUS-TBNA: A Randomized, Double-Blind, Phase III Study

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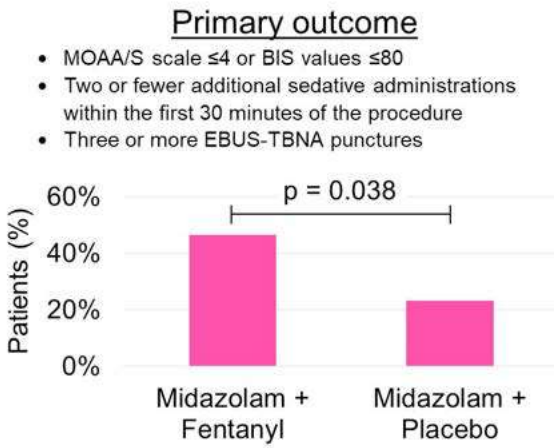
Introduction: Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is the most commonly used technique for histologic sampling of mediastinal or hilar lymph nodes or masses. The CHEST guideline recommends moderate-deep sedation for EBUS-TBNA, and the British Thoracic Society guideline recommends midazolam or propofol in combination with opioids for flexible bronchoscopy. However, with few randomized trials, the optimal sedation regimen for EBUS-TBNA remains unknown. Here we evaluate the efficacy and safety of midazolam with fentanyl for sedation in EBUS-TBNA.

Methods: We conducted a single-center, randomized, and double-blind phase III study between December 2021 and October 2023. We compared the patients who received midazolam with fentanyl (fentanyl group) with the patients who received midazolam with placebo (placebo group) for sedation in EBUS-TBNA. We assessed the depth of the sedation in the procedure with the Modified Observer's Assessment of Alertness and Sedation (MOAA/S) scale and bispectral index (BIS) values. The primary endpoint was the rate of the patients achieving all of the following; 1) MOAA/S scale ≤4 or BIS values ≤80, 2) the number of additional sedative administrations ≤2 within the first 30 minutes of the procedure, 3) ≥3 times of punctures.

Results: We enrolled 84 patients (fentanyl group, 41; placebo group, 43). There were no significant differences in patient characteristics between the fentanyl and placebo groups. The primary endpoint was significantly better in the fentanyl group than in the placebo group (46.3% vs 23.3%; p = 0.038). A significantly lower rate of restlessness or agitation (MOAA/S scale 6) (16.3% vs 38.6%; p = 0.030), lower number of additional sedative administrations [median (range), 2 (1-4) vs 3 (1-4); p = 0.040], and higher rate of ≥3 punctures (87.8% vs 65.1%; p = 0.021) were observed in the fentanyl group than in the placebo group. There was no significant difference in complications such as unexpected deep sedation (MOAA/S scale 0 or 1) and hypopnea between the two groups. The operator visual analogue scale scores, where 0 is good and 100 is bad, for patient's cough [median (range), 30 (3-96) vs 68 (1-100); p = 0.011] and sedation [25 (0-96) vs 51 (0-100); p = 0.011] were significantly better in the fentanyl group.

Conclusions: The addition of fentanyl to midazolam for sedation in EBUS-TBNA not only provided better sedation but also increased the number of punctures without increasing complications. The combination of midazolam and fentanyl should be considered for sedation during EBUS-TBNA.

Keywords: Sedation, Midazolam with fentanyl, EBUS-TBNA



EP.05A PULMONOLOGY AND STAGING - ENDOSCOPIC EVALUATION
SATURDAY, SEPTEMBER 7, 2024 - 11:58 - 11:59

EP.05A.02 Timing of PET-CT has no Significant Impact on Staging EBUS Results in Mediastinal Staging and Diagnosis of Lung Cancer

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Introduction: National Institute for Health and Care Excellence guidance on the diagnosis and management of lung cancer recommends positron emission tomography-computed tomography (PET-CT) scan followed by endobronchial ultrasound (EBUS) sampling in patients with suspected lung cancer who could potentially have treatment with curative intent. Studies have shown that PET CT as a sole test has relatively low sensitivity and specificity for lung cancer in areas with high prevalence of granulomatous diseases. But in combination with EBUS it helps to reduce radiotherapy field and performing PET CT first may help to reduce the need for repeat biopsy in those diagnosed with lung cancer. We compared staging EBUS results and mediastinal staging on PET-CT in patients with suspected lung cancer, depending on whether PET-CT scan performed first or after EBUS.

Methods: Staging EBUS performed in 59 patients referred with suspected lung cancer and hilar or mediastinal lyphadenopathy in a single centre between 2021-2023. Cases divided to EBUS group (EBUS performed prior to PET-CT) and PET-CT group (PET-CT performed prior to EBUS). Results of lymph nodes histology (or visual EBUS assessment, if nodes size were 6 mm or less) compared to fluorodeoxyglucose uptake on PET CT in relevant lymph nodes. Adequate sample with no malignant cells and low uptake, or presence of malignancy with moderate/high uptake considered as findings in agreement in both groups. Chi-squared test performed using MedCalc Software, Ostend, Belgium.

Results: 23 and 36 cases included in EBUS and PET-CT groups, respectively. Benign condition found in 3 (13.0%) vs 2 (5.6%), lung cancer - in 18 (78.3%) vs 32 (88.9%), lymphoma-in 2 (8.7%) vs 2 (5.6%) cases in EBUS and PET-CT groups, p=0.52. Mediastinal staging was in agreement in 16 (69.6%) EBUS vs 29 (80.6%) PET-CT group cases, p=0.34. EBUS downstaged the mediastinum in 1 (4.4%) vs 5 (13.9%), was positive in higher N station node in 2 (8.7%) vs 0 (0%) or confirmed benign condition in 3 (13.0%) vs 2 (5.6%) cases in EBUS and PET-CT groups, respectively, p=0.14. In benign condition - 1 (2.2%) vs 4 (28.6%), in lung cancer - 40 (88.9%) vs 10 (71.4%) and in lymphoma-in 4 (8.9%) vs 0 (0%) cases EBUS and PET-CT findings were in agreement or discordant, respectively, p<0.05. In lung cancer patients PET-CT also revealed EBUS inaccessible or metastatic disease in 4 (22.2%) and 6 (18.8%) in EBUS and PET-CT groups, p=0.44.

Conclusions: Staging EBUS has good diagnostic value and is useful method of mediastinal staging in patients with suspected lung cancer independently from PET-CT timing. EBUS and PET CT results discordance more often found in benign conditions. Performing PET-CT is required to evaluate for the nodes inaccessible by EBUS or for metastatic disease in patients with lung cancer.

Keywords: Lung cancer, EBUS, PET-CT

EP.05A PULMONOLOGY AND STAGING - ENDOSCOPIC EVALUATION
SATURDAY, SEPTEMBER 7, 2024 - 11:58 - 11:59

EP.05A.03 The Accuracy of EBUS, EUS, EBUS Plus EUS, and Mediastinoscopy for Mediastinal Staging in NSCLC - A Systematic Review and Meta-Analysis

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Introduction: Lung Cancer, the leading cause of cancer-related deaths, demands accurate staging to optimize therapy and improve outcomes. This comprehensive systematic review presents the accuracy of EBUS, EUS, EBUS plus EUS, and mediastinoscopy for NSCLC staging.

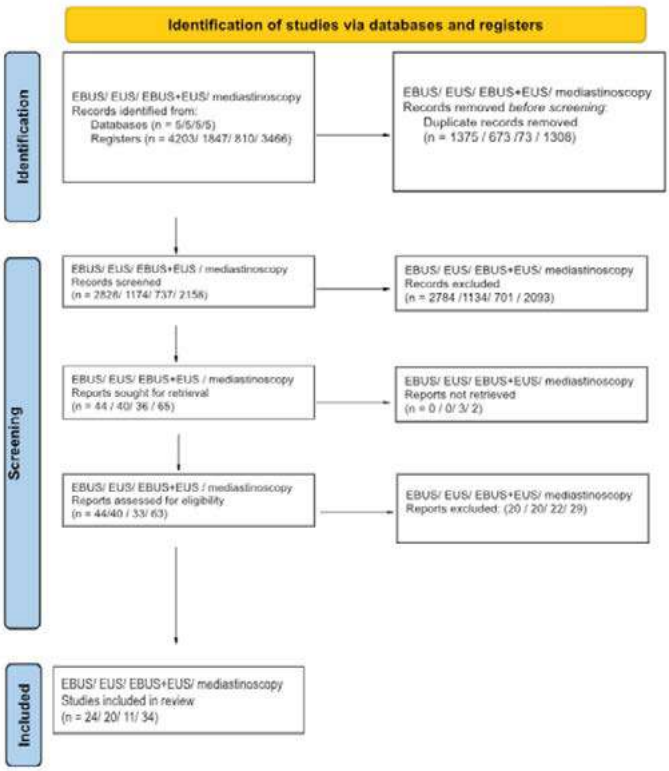
Methods: Our review utilized the GRADE approach to systematically search for evidence on the accuracy of EBUS, EUS, combined EBUS and EUS, and mediastinoscopy for mediastinal staging of NSCLC. The research questions were framed in a PICO format based on the investigators' expertise and available literature. We searched MEDLINE/PubMed, EMBASE, Web of Science, Cochrane Library, and LILACS for each PICO question. Data from the original studies will be presented individually by the study in Tables 2x2 as measures of diagnostic test accuracy (true positives, false positives, true negatives, false negatives). The statistical analysis was performed according to the recommendations of the Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy using the "DTAplots", "mada", and "meta" packages in the R 4.2.1 software. Figure 1 describes the flow charts of study selection in the systematic review of each method.

Results: According to our analyses, EBUS plus EUS has the best diagnostic accuracy with an sROC of 0.99 (CI 95% 0.97-0.99). Also, the pooled sensitivity of EBUS plus EUS is higher than that of each method. The pooled sensitivity of EBUS and EUS is lower than that of both methods used together; however, it is reasonable to perform only one method when one is unavailable. Overall, the sROC of EBUS and EUS is close to that of EBUS plus EUS. In contrast, mediastinoscopy, despite its sROC of 0.99 (CI 95% 0.96-0.99), falls short in terms of pooled sensitivity compared to EBUS plus EUS. Its invasive nature, limited access to all LNs, and potential for significant complications are important drawbacks.

Conclusions: Mediastinoscopy has limitations in accessing some nodal stations, such as paratracheal and subcarinal. EBUS-TBNA plus EUS-FNA is recommended to assess mediastinal LN status accurately. The main EBUS plus EUS advantage is its high sensitivity, NPV, and even higher specificity, which is only comparable to mediastinoscopy. EBUS plus EUS is a minimally invasive technique that usually does not require general anesthesia. This method is generally a safe outpatient procedure. Nevertheless, EBUS plus EUS availability can be limited to tertiary care centers due to the requirement of specialists with dedicated training.

Keywords: mediastinal staging, lung cancer, endoscopic ultrasound

Figure 1. Flow chart of study selection in the systematic review of EBUS, EUS, EBUS plus EUS, and mediastinoscopy



EP.05A PULMONOLOGY AND STAGING - ENDOSCOPIC EVALUATION
SATURDAY, SEPTEMBER 7, 2024 - 11:58 - 11:59

EP.05A.04 Risk Factors for the Development of Pulmonary Infection after Bronchoscopy in Patients with Lung Cancer - A Centre in Greece

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Introduction: Flexible bronchoscopy and its new methods have revolutionized the era of the diagnosis, staging, and restaging of lung cancer. A rare late complication is post-bronchoscopy respiratory infection, which definition differs among studies. The incidence of this type of infection in lung cancer patients ranges from 3% to 6.3% according to published studies. In patients with lung cancer, this type of infection is critical not only due to treatment delays but also because it can lead to treatment cancellation and death.

Methods: We retrospectively studied 182 adult hospitalized patients with undiagnosed lung cancer who underwent bronchoscopy at "ATTIKON" University General Hospital from January 2022 to April 2023 for diagnosis and staging of the disease. The infection and non-infection groups were compared. Two groups were compared for age, sex, body mass index, smoking habit, Charlson Comorbidity Index, comorbidities, recent hospitalization for SARS-CoV-2 in the last month before undergoing diagnostic bronchoscopy, location of the primary cancer, histological type, stage of the disease, chest CT findings, duration of bronchoscopy, type of bronchoscopy procedure, endobronchoscopic finding of the endoscopy, laboratory testing of patients prior to undergoing bronchoscopy, prophylactic administration of antimicrobials before endoscopy.

Results: Pulmonary infection after the diagnostic bronchoscopy occurred in 7 patients (3.9%) and included pneumonia in 5 patients, parapneumonic effusion in 1 patient, and empyema in 1, too. Three of the four patients who developed pneumonia had been hospitalized for COVID-19 infection in the past month. The time from bronchoscopy to symptom onset averaged 5 days with a range (1 - 12 days). A pathogen was isolated in only one patient (14.3%) in sputum culture and blood culture and this pathogen was Acinetobacter baumannii. One died due to the pulmonary infection, and 4 had a delay in starting anticancer treatment of 20 days.

We identified as risk factors for post-bronchoscopy pulmonary infection the personal history of COPD (p=0.046), presence of emphysema in CT thorax (p=0.046), endobronchial lesions which causes stenosis ≥50% of the lumen (p=0.04), disease stage IV of NSCLC (p=0.03) and recent hospitalization for COVID-19 (p=0.04) using multivariate analysis.

Conclusions: We identified as risk factors of this complication the patient's recent hospitalization (in the last month) for COVID-19 infection (OR: 64.88, 95% CI: 8.39 - 501.65, p<0.001), individual history of COPD (OR: 8, 95% CI: 0.94 - 67.86, p=0.03), presence of emphysema on CT scan (OR: 8, 95% CI: 0. 94 - 67.86, p=0.03), the presence of an endobronchial lesion on bronchoscopy causing partial obstruction of ≥ 50% of the bronchus with further inability to advance the bronchoscope (OR: 9.6, 95% CI: 1.58 - 58.41, p<0.01), and stage IV in NSCLC.

There is a need to establish a homogeneous definition of complications and then conduct multicenter studies to identify risk factors.

Keywords: PULMONARY INFECTION AFTER BRONCHOSCOPY, LUNG CANCER PATIENTS, RISK FACTORS

EP.05A PULMONOLOGY AND STAGING - ENDOSCOPIC EVALUATION
SATURDAY, SEPTEMBER 7, 2024 - 11:58 - 11:59

EP.05A.05 Brazilian Single-Center Experience in the Staging of Thoracic Neoplasms Using Endosonographic Methods (EUS/EBUS)

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Introduction: Lung cancer is one of the most frequently diagnosed solid tumors worldwide it is also the leading cancer-specific cause of death. Defining the best treatment strategy depends on accurate staging, which significantly impacts prognosis and patients' outcomes. Evaluating the mediastinum is a fundamental staging step. The non-invasive method EBUS/EUS has been increasingly used. Despite its availability in Brazil, few centers have reported their experience with the method. Even in supplementary healthcare, the cost and learning curve are barriers. At our hospital, we have an important thoracic oncology service, with an increasing number of patients undergoing EBUS/EUS. The aim of this study was to evaluate the performance of EBUS/EUS at this hospital, using sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy, and to compare this with existing data.

Methods: We conducted an observational, retrospective study by analyzing the medical records of patients who underwent mediastinal lymph node evaluation by endoscopic ultrasound (EBUS/EUS), from October 2021 to October 2023 at the Nossa Senhora das Graças Hospital in Curitiba (PR), Brazil. For the analysis of accuracy, sensitivity, specificity, PPV and NPV, only patients who underwent a surgical procedure (and thus had lymph node anatomopathological evaluation) were compared with EBUS/EUS data.

Results: During the period of the study, 160 patients underwent ultrasound evaluation of the mediastinum. The average age was 64 years (31-93), with 88 (55%) patients being male. The average number of lymph node chains examined was 4.78 (0-9) with an average of 2.6 (1-5) nodes biopsied per examination. Finally, 110 (68%) had anatomopathological results of the mediastinal lymph node evaluation (67% N0; 33% N2/N3). Out of the 110, 38 patients were referred for surgery. We found a specificity of 90.6% and a NPV of 93.5%, corresponding to a final accuracy of 86.8%, data that is in line with current literature.

Conclusions: The use of the non-invasive strategy EBUS/EUS, to assess the mediastinum has become a standard practice. Although it has been consolidated in the literature and common in large centers, there are still some challenges for its consolidation in Brazil. However, with our study data, we can demonstrate that the use of this method allows professionals to achieve good results, improving the accuracy staging and, by extension, the outcomes of our patients.

Table 2 – Results	
Sensitivity	66.7%
Specificity	**90.6%**
PPV	57.1%
NPV	**93.5%**
Accuracy	86.8%

*PPV: positive predictive value; NPV: negative predictive value

EP.05A PULMONOLOGY AND STAGING - ENDOSCOPIC EVALUATION
SATURDAY, SEPTEMBER 7, 2024 - 11:58 - 11:59

EP.05A.06 Timing of Thoracentesis in Hospitalized Patients with Malignant Pleural Effusion: A Study of the US National Inpatient Sample

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Introduction: Malignant pleural effusion is often the first presenting symptom in patients with cancer and signifies advanced disease with an associated high mortality. Thoracentesis is the treatment of choice in patients with limited life expectancy for symptomatic management of dyspnea or for patients who are not candidates for more invasive procedures such as drainage with pleural catheter, chemical pleurodesis. The aim of this study is to examine if timing of thoracentesis during hospitalization has an impact on patient outcomes in patients with malignant pleural effusions.

Methods: This is a retrospective cohort study using the 2020 National Institute Sample (NIS). Inclusion criteria were patients with diagnosed malignant pleural effusion, further stratified by diagnosis of primary lung cancer or metastatic lung lesions. Patient cases were matched with control based on demographic factors including age, gender, race, SES, and primary lung cancer or metastatic lung lesions. Primary intervention was thoracentesis and time to procedure during hospitalization. Primary outcomes included mortality and need for endotracheal intubation. Propensity score and nearest neighbor matching was used to assess causative relationship between late thoracocentesis (defined as thoracocentesis beyond day 3 of admission) and all cause mortality, after matching for age, sex, race, and SES. Similar analyses were done for causative association between time to thoracentesis and endotracheal intubation in both the groups.

Results: 30,289 patients were identified with malignant pleural effusion due to primary lung malignancy, of which 7,054 patients underwent thoracentesis during admission. 21,540 patients were identified with malignant pleural effusion due to metastatic lung lesions, of which 5,599 patients got thoracocentesis during admission. Thoracentesis after day 3 of hospitalization had a positive correlation for association with all cause mortality in malignant pleural effusions associated with primary lung lesions (OR:2.13, 95% CI: 1.42-3.20, $p<0.05$) and with metastatic lung lesions (OR: 1.73, 95% CI: 1.15-2.62, $p<0.05$). When done on day 1, 2, or 3 of hospitalization there were no statistically different rates of all cause mortality. While thoracentesis after 3 days of hospitalization was associated with significantly higher rates of endotracheal intubation in patients with primary lung lesions (OR: 1.50, 95% CI: 1.06-2.13, $p<0.005$), there was not a statistically significant difference in rates of intubation in patients with metastatic lung lesions (OR: 1.45, 95% CI: .99-2.11, $p=.052$).

Conclusions: This data demonstrates a correlation with late thoracentesis after day 3 of hospitalization and increased mortality in patients with a malignant pleural effusion. These results suggest thoracentesis should be considered earlier during hospitalizations of patients with malignant pleural effusions with primary lung cancers and metastatic lung lesions.

Keywords: Malignant pleural effusion, Thoracentesis, Lung cancer

EP.05A PULMONOLOGY AND STAGING - ENDOSCOPIC EVALUATION
SATURDAY, SEPTEMBER 7, 2024 - 11:58 - 11:59

EP.05A.07 Feasibility and Safety of Nasal Access for EBUS-TBNA in the Korean Population: A Single Center Experiences

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Introduction: Endobronchial ultrasound (EBUS) is a reliable modality for accurately and safely diagnosing mediastinal lymph nodes and lung lesions. Despite previous studies establishing the feasibility of nasal route insertion, there remains a paucity of data on Asian populations. This study aimed to evaluate the feasibility and safety of EBUS-guided transbronchial needle aspiration (TBNA) using nasal access among the Korean population.

Methods: We conducted a retrospective analysis of patients who underwent an EBUS-TBNA at our institution from Mar 2015 to Mar 2024. Patients with mediastinal lymphadenopathy were included for various indications such as lung cancer staging, diagnosis of TB lymphadenitis, and lymphoma. An EBUS scope with 6.9 mm outer diameter (BF-UC260FW, Olympus, Tokyo) was utilized for all procedures. Initially, EBUS insertion was attempted via the nasal route in all subjects under conscious sedation. In cases where nasal insertion was failed through both nostrils, the oral route was used as an alternative. The primary outcome was to evaluate the success rate of nasal approach as a preferred alternative to oral insertion in the Korean population.

Results: Among the 1029 patients included in the study, the success rate of the nasal approach was 93.8% (95% CI: 92.1-95.2). There were no significant age differences between groups. Females under the age of sixty showed a relatively higher rate of failed nasal approaches. The midazolam level for conscious sedation was similar in both groups, but fewer analgesics were required for the nasal approach. Complications associated with the nasal route were primarily minimal epistaxis.

Conclusions: Nasal insertion has emerged as a preferred alternative for EBUS-TBNA, demonstrating relative safety and feasibility compared to oral route. Ongoing advancements in thinner, more flexible EBUS scope technology promise significant benefits for patients with narrower nasal passages or higher pain sensitivity.

Table 1. Descriptive characteristics between the nasal and oral access group; SD, standard deviation

	Nasal (N=963)	Oral (N=64)	*P* value
Age (years, mean±SD)	68.2±11.2	65.4±12.6	0.054
Sex			0.025
- Male	691 (71.8%)	37 (57.8%)	
- Female	272 (28.2%)	27 (42.2%)	
Procedure time (minutes)	22.3±7.7	24.4±9.4	0.091
Midazolam (mg, mean±SD)	2.5±0.8	2.8±1.1	0.094
Fentanyl (mcg, mean±SD)	53.5±12.0	58.6±14.2	0.007

Table 2. Association factors in nasal approach failures; OR, odds ratio; CI, confidence interval

	Nasal (No.)	Oral (No.)	Ratio	OR (95% CI)	*P* value
			Nasal access failure		
Male	691	37	5.08	1	
Female	272	27	9.03	1.77 (1.05-2.98)	0.032
Age (years)					
< 60	180	23	11.33	2.30 (1.32-4.03)	0.003
60~79	646	34	5.00	1	
≥ 80	137	7	4.86	0.91 (0.39-2.10)	0.818

Keywords: Mediastinal staging, EBUS-TBNA, Feasibility of nasal approach

EP.05A PULMONOLOGY AND STAGING - ENDOSCOPIC EVALUATION
SATURDAY, SEPTEMBER 7, 2024 - 11:58 - 11:59

EP.05A.08 The Accuracy of Bronchoscopy and Transthoracic Needle Biopsy for Diagnosing Lung Cancer - A Systematic Review

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Introduction: The initial work-up of patients with lung cancer (LC), the leading cause of cancer-related deaths worldwide, includes accurate histologic diagnosis and staging, to inform a precise prognosis and to held in the treatment decision. This comprehensive systematic review perused the current clinical data about the accuracy of bronchoscopy and transthoracic needle biopsy (TTNB) for LC.

Methods: Our review was conducted by LC specialists and used the GRADE approach to systematically search for evidence on the accuracy of bronchoscopy and TTNB for LC diagnosis. The research questions were framed in a PICO format. We searched MEDLINE/PubMed, EMBASE, Web of Science, Cochrane Library, and LILACS for each PICO question.

Data from the original studies were presented individually by study in Tables 2x2 as measures of diagnostic test accuracy (true positives, false positives, true negatives, and false negatives). The statistical analysis was performed according to the recommendations of the Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy. It was performed using the "DTAplots", "mada" and "meta" packages in the R 4.2.1 software.

Results: We found a lack of primary studies assessing bronchoscopy's diagnostic accuracy in LC patients, making it impossible to conduct a meta-analysis with the available data. The diagnostic precision of bronchoscopy in detecting premalignant lesions is variable, emphasizing the need for additional non-invasive biopsy methods to improve its accuracy.

We conducted analyses to evaluate the diagnostic performance of TTNB for lung lesions. In our search, 20 studies conducted between 2000 and 2019 were included, with a sample size of 4606 patients. LC prevalence ranged from 59.02% to 95.18% across studies. Nineteen studies performed the CT-guided TTNB, and two performed the CT-FC-guided TTNB. The pooled sensitivity and specificity were 0.90 and 0.96, respectively. The LR+ was 30.6 (CI 95% 15.5-55.0), and the LR- was 0.09 (CI 95% 0.08-0.11). The DOR was 314.00 (CI 95% 143.0-603.0), and the sROC was 0.949 (CI 95% 0.906-0.973). Three distinct scenarios were simulated and characterized by varying pretest probabilities. When the pretest probability was 25%, the post-probability positive (PPP) and post-probability negative (PPN) were 91% and 3%, respectively. In the case of a pretest probability of 50%, the PPP and PPN were 97% and 9%, respectively. Lastly, when the pretest probability was 75%, the PPP and PPN were 99% and 23%, respectively.

Conclusions: Our analysis reinforces that CT-guided TTNB attains high diagnostic accuracy, especially for the diagnosis of peripheral lung nodules. In a 2019 meta-analysis, TTNB showed a pooled sensitivity of 97% and a pooled specificity of 100%. However, the false-negative incidence varies between 5% and 12%, maybe related to lesion sizes, inadequate needle gauge, and operator inexperience, which leads to sampling errors and inappropriate collection for analysis. Although TTNB presents good metrics for lung lesion diagnosis, it does not preclude the necessity of confirming the results by other diagnostic methods, including invasive procedures such as bronchoscopy.

Keywords: CT-guided, bronchoscopy, lung cancer

EP.05A PULMONOLOGY AND STAGING - ENDOSCOPIC EVALUATION
SATURDAY, SEPTEMBER 7, 2024 - 11:58 - 11:59

EP.05A.09 The Accuracy of CT, 18FDG-PET/CT, and Mediastinoscopy for Staging in NSCLC - A Systematic Review and Meta-Analysis

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Introduction: Lung Cancer staging is a crucial step in determining prognosis and optimal therapy. This comprehensive and meticulous systematic review presents the accuracy of the most currently used methods for NSCLC staging: CT (computed tomography), 18FDG-PET/CT (PET/CT), and mediastinoscopy.

Methods: Our review was conducted by lung cancer specialists and used the GRADE approach to systematically search for evidence on the accuracy of CT, PET/CT, and mediastinoscopy for staging in NSCLC. Based on their expertise and available literature, the research questions were framed in a PICO format. We searched MEDLINE/PubMed, EMBASE, Web of Science, Cochrane Library, and LILACS for each PICO question. Data from the original studies were presented individually by the study in Tables 2x2 as measures of diagnostic test accuracy (true positives, false positives, true negatives, and false negatives). The statistical analysis was performed according to the recommendations of the Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy and using the "DTAplots", "mada", and "meta" packages in the R 4.2.1 software.

Results: According to our analyses, CT has limited accuracy for staging (sROC 0.73; CI 95% 0.67-0.75) and is susceptible to flaws (LR- 0.54; CI 95% 0.48-0.62). PET/CT diagnostic accuracy was sROC 0.87 (CI 95% 0.82-0.87). PET/CT is recommended for identifying suspected lymph nodes (LNs) to investigate the tumor extension and discard the presence of distant metastases. PET/CT has high rates of false positive and false negative results regarding mediastinal LN involvement (LR- 0.31; CI 0.95% 0.26 - 0.37), requiring confirmation by invasive methods. Compared with CT and PET/CT, mediastinoscopy has the best diagnostic accuracy method for mediastinal staging, with an sROC of 0.99 (CI 95% 0.96-0.99). The main advantage of mediastinoscopy is the direct visualization of nodes for sampling and dissection. On the other hand, mediastinoscopy is invasive, requires general anesthesia, cannot access all LNs, and can potentially cause significant complications. In addition, mediastinoscopy has a relatively high negative likelihood ratio (LR- 0.20; CI 95% 0.17-0.23), which can be attributed to the failure to dissect all LN stations.

Conclusions: CT scans are considered insufficient for accurately diagnosing and staging NSCLC in suspect LN and oligometastatic cases. PET/CT is useful in the initial evaluation to identify the sites of distant tumor involvement. However, PET/CT is insufficient for accurate mediastinal staging and identification of oligometastatic disease in NSCLC, scenarios in which confirmation by tissue biopsy is recommended. Mediastinoscopy is the preferred method for mediastinal staging in NSCLC, mainly in clinical settings where EBUS/ EUS are unavailable.

Keywords: lung cancer, staging, systematic review

EP.05B PULMONOLOGY AND STAGING - CLINICAL COURSE
SATURDAY, SEPTEMBER 7, 2024 - 11:58 - 11:59

EP.05B.01 Characterization of Patients with Primary Lung Cancer who Attended a Pulmonology Clinic in Bogotá, Colombia

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Introduction: Patients with primary lung cancer have seldom been described in Colombia, as is the opportunity of their access to diagnosis and treatment.

Methods: A cross sectional study was conducted to describe patients with non-lymphoid primary lung malignant neoplasms who attended at least one medical appointment with the thoracic oncology program at Fundación Neumológica Colombiana between January 2019 and August 2023. For those with epithelial neoplasms, often referred as Non-Small Cell Lung Cancer (NSCLC), genomic profiling was included.

Results: Of 163 patients with primary lung cancer identified, 88,3% were NSCLC, which included 67,5% adenocarcinomas and 17,8% squamous cell carcinomas. Another 11% were neuroendocrine neoplasms, which included 5,5% typical carcinoids, 1,2% atypical carcinoids and 3,7% small cell carcinomas. The clinical characteristics of these patients are summarized in table 1. The time elapsed between the clinical suspicion of lung cancer and the pathological confirmation, as well as between the diagnosis and the first oncologic treatment are described in figure 1. Patients with NSCLC were 59% female, 49% had no history of tobacco use, 37,5% had not been significantly exposed to tobacco, wood smoke, asbestos or silica, and 31% were diagnosed in stages 0-II. Information on EGFR status was available for 81 of 144 patients with NSCLC and 42% of these harbored EGFR mutations. Other driver genes were tested in fewer patients; however, altogether 52% of the NSCLC patients evaluated for at least one gene had a driver mutation (EGFR, ALK, RET, MET, ROS1 or BRAF V600).

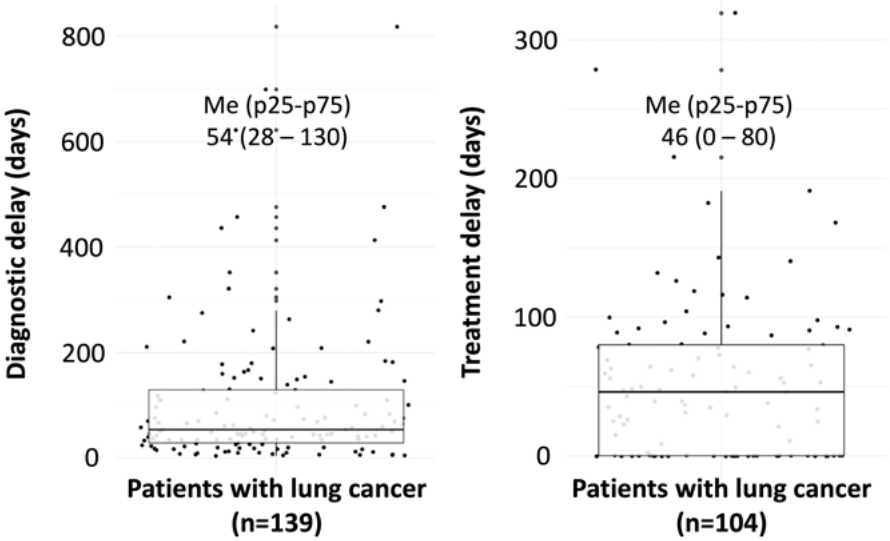
Conclusions: Female sex, absence of a history of tobacco use, the presence of driver mutations and early stages were more frequent among patients with NSCLC at this center than previously reported in Colombia, although selection bias could have overestimated the prevalence of driver mutations. Time to diagnosis and treatment were longer than recommended by international standards.

Clinical characteristics of lung cancer patients by histologic type

Keywords: lung neoplasms, cross sectional study, delayed diagnosis

Clinical characteristics of lung cancer patients by histologic type

	Neuroendocrine carcinomas N=7	NSCLC N=144	Carcinoid tumors N=11
Age (years)	69,4 ± 12,8	67,6 ± 11,1	60,7 ± 16,5
sex (male)	5 (71,4)	59 (41,0)	2 (18,2)
Tobacco use	5 (71,4)	73 (50,7)	4 (36,4)
Tobacco index among smokers/ former smokers (Pack-years)	20 (17,5 - 35,0)	21,5 (10,0 - 38,8)	10 (2,0 - 10,0)
Wood smoke exposure	2 (28,6)	25 (17,4)	1 (9,1)
No exposure risk factor (tobacco, wood smoke, asbestos or silica)	1 (14,3)	54 (37,5)	7 (63,6)
Previous cancer other than non-melanoma skin cancer	1 (14,3)	34 (23,6)	2 (18,2)
1st degree relative with lung cancer	0 (0,0)	1 (0,7)	3 (27,3)
Heart or lung disease	4 (57,1)	62 (43,1)	1 (9,1)
Home oxygen therapy at diagnosis	5 (71,4)	36 (26,9)	1 (9,1)
Stage at diagnosis			
0-I	0 (0,0)	30 (20,8)	5 (45,4)
II	0 (0,0)	15 (10,4)	3 (27,3)
III	2 (28,6)	36 (25,0)	0 (0,0)
IV	5 (71,4)	62 (43,1)	1 (9,1)
unknown	0 (0,0)	1 (0,7)	(18,2)


Diagnostic delay (days)
800
600
400
200
0
Me (p25-p75)
54 (28 – 130)
Patients with lung cancer
(n=139)
Treatment delay (days)
300
200
100
0
Me (p25-p75)
46 (0 – 80)
Patients with lung cancer
(n=104)

EP.05B PULMONOLOGY AND STAGING - CLINICAL COURSE
SATURDAY, SEPTEMBER 7, 2024 - 11:58 - 11:59

EP.05B.02 Mucinous Adenocarcinoma of the Lung in a Brazilian Population: Clinical, Pathological, Molecular Features and Outcomes

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Introduction: Invasive mucinous lung adenocarcinoma (IMA) is a rare subtype of adenocarcinoma with limited data available, especially in specific populations as Brazilian. This study describes the characteristics and outcomes of IMA patients treated at a Brazilian center, focusing on potential differences from other populations.

Methods: Retrospectively was analyzed data from 2,506 patients diagnosed with lung cancer between 2011 and 2023, identifying 106 with IMA. Demographic, clinical, pathological, molecular, and treatment data were collected.

Results: The median age at diagnosis was 65 years, with a female predominance. Most patients had a smoking history. Solitary pulmonary nodules were the most common presentation, unlike the reported multifocal pattern. KRAS mutations were the most frequent genetic alteration (60.6%). Surgery was preferred for resectable disease, while chemotherapy remained the mainstay for unresectable cases. Never-smokers had significantly better overall survival (OS). Solitary tumors were associated with better disease-free survival (DFS), immunotherapy did not improve OS when added to chemotherapy.

Conclusions: This study provides valuable data on IMA in a Brazilian population. While overall findings align with published data, some differences were observed, including potential prognostic factors. Further research is needed to confirm our findings.

Keywords: Mucinous adenocarcinoma, KRAS, Survival

EP.05B PULMONOLOGY AND STAGING - CLINICAL COURSE
SATURDAY, SEPTEMBER 7, 2024 - 11:58 - 11:59

EP.05B.03 Evaluating the Risk of Pneumonitis from G-CSF in Thoracic Cancer Patients with Pre-Existing ILD

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Introduction: In the chemotherapy of thoracic malignancies, granulocyte colony-stimulating factor (G-CSF) agents are sometimes used. There have been reports of pneumonitis associated with the use of G-CSF agents. It is cautioned to use these agents carefully in cases with pre-existing interstitial lung disease (ILD) due to the potential risk. However, the evidence supporting this caution is scant, and whether it actually poses a risk remains unclear.

Methods: We conducted a retrospective analysis of pneumonitis in patients treated with cytotoxic chemotherapy for thoracic malignancies. Data was collected from medical records to examine whether the use of G-CSF agents and the presence of pre-existing ILD findings influenced the development of pneumonitis after the initiation of chemotherapy.

Results: From September 2006 to January 2024, 1,029 patients were treated with chemotherapy for thoracic malignancies at our institution. The breakdown of diseases was as follows: 782 cases (76.0%) were non-small cell lung cancer, 171 cases (16.6%) were small cell lung cancer, and malignant mesothelioma and thymic carcinoma were both 23 cases (2.2%). Pre-existing ILD was found in 159 (15.5%) patients, of whom 79 (7.7%) had honeycomb lung findings. G-CSF agents were used in 437 (42.5%) patients. Pneumonitis following the initiation of chemotherapy was observed in 137 (13.3%) cases. The presence of pre-existing ILD was considered a risk factor for the development of pneumonitis (Odds ratio 1.75 [95% Confidence Interval 1.12-2.72]). However, the effect of G-CSF agent use was not statistically significant (Odds ratio 0.70 [95% Confidence Interval 0.48-1.01]). Furthermore, when assessing the risk of pneumonitis development due to G-CSF administration in cases with pre-existing ILD and those with honeycomb lung findings, no significant risk was identified in either scenario (Odds ratio 0.80 [95%CI 0.36-1.82], 0.57 [95%CI 0.16-1.98]).

Conclusions: The presence of pre-existing ILD in patients receiving G-CSF agents for thoracic malignancies may not influence the risk of developing pneumonitis during chemotherapy.

Keywords: G-CSF, pre-existing ILD, pneumonitis

EP.05B PULMONOLOGY AND STAGING - CLINICAL COURSE
SATURDAY, SEPTEMBER 7, 2024 - 11:58 - 11:59

EP.05B.04 Correlation Between Radiologic Feature and Spread Through Air Space in Lung Solid Adenocarcinoma 30.0 mm or Less in Maximum Diameter

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Introduction: Tumor spread through air space (STAS) has been recognized as an important prognostic indicator for lung cancer patients. However, few studies have focused on radiologic features for predicting STAS for patients with small solid lung adenocarcinomas 30.0 mm or less in maximum diameter.

Methods: A retrospective study of 511 participants in the XXX with first primary clinical stage IA solid adenocarcinoma (ADC) 30.0 mm or less in maximum diameter who received surgical treatment. Patients with STAS-positive or STAS-negative were compared using a Wilcoxon rank-sum test and chi-squared or Fisher exact test. Significant predictors of STAS were identified using multivariable analyses.

Results: Of 511 patients with surgical resected solid ADCs 30.0 mm or less in maximum diameter (42% male, 58% female, median age 70 years [IQR: 64-77]), STAS was present in 63 (12.3%). Multivariable analyses showed that STAS was significantly associated with distance (mm) to the mediastinal pleura (OR=0.97; 95% CI, 0.96-0.99; P<.001), distance to the diaphragmatic pleura (OR=0.99; 95% CI, 0.99-1.00; P=.03), distal post-obstructive changes (OR=0.2; 95% CI, 0.05-0.5; P<.001) and vascular embedding (OR=2.2; 95% CI, 1.1-4.4; P=.02), after adjusting for age, sex and smoking. No significant relationship was found between preoperative CT-guided biopsy and presence of STAS.

Conclusions: Among solid ADCs 30.0 mm or less in maximum diameter, distance to the mediastinal pleura, distance to the diaphragmatic pleura, vascular embedding and distal post-obstructive changes were significant radiologic predictors of STAS. There was no evidence of significant relationship between pre-operative CT-guided biopsy and presence of STAS.

Keywords: Adenocarcinoma, radiologic, spread through air space

EP.05B PULMONOLOGY AND STAGING - CLINICAL COURSE
SATURDAY, SEPTEMBER 7, 2024 - 11:58 - 11:59

EP.05B.05 Integrative Prediction Model for Radiation Pneumonitis: Genetic and Clinical-Pathological Factors Utilizing Machine Learning

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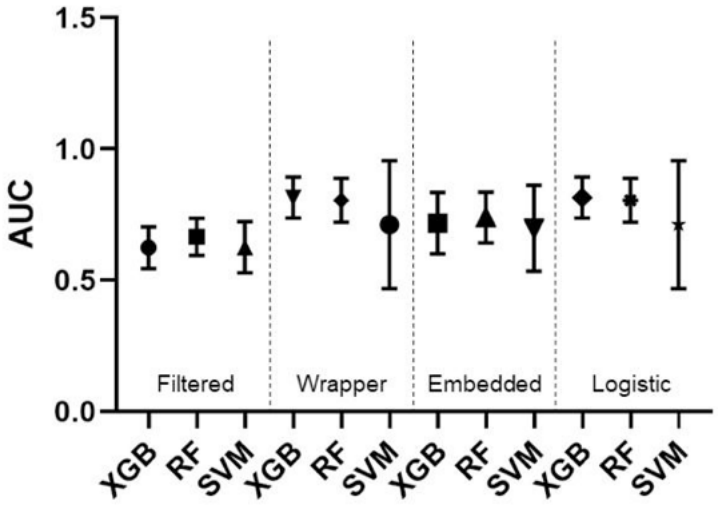
Introduction: Clinical and dosimetric parameters are linked to radiation pneumonitis (RP), while single nucleotide polymorphisms (SNPs) in TGF-β1 pathway genes are also associated with RP. However, research on the predictive value of SNPs for RP remains limited. In this study, we aimed to develop the most optimal model for RP prediction using machine learning (ML) methods. Additionally, we compared RP prediction models using clinical/dosimetric factors alone with those incorporating genomic factors.

Methods: A total of 59 patients with primary lung cancer undergoing thoracic radiotherapy between 2017 and 2019 were prospectively enrolled. We analyzed their pretreatment blood samples along with all clinicopathological/dosimetric variables and performed genotyping for 11 functional SNPs in the TGFβ pathway genes (TGF-β1, BMP2, and BMP4). Using Synthetic Minority Over-sampling Technique (SMOTE) and nested cross-validation (CV), we developed a ML-based prediction model for severe RP (grade ≥2). Feature selection was conducted using four methods (filtered-based, wrapper-based, embedded, and logistic regression), and performance evaluation involved three ML models: Extreme Gradient Boosting (XGBoost), Random Forest (RF), and Support Vector Machine (SVM), utilizing another round of Nested CV for both hyperparameter optimization and performance evaluation.

Results: With a median follow-up of 39.7 months, severe RP occurred in 20.3% of patients. In the logistic regression model, age (>66), smoking history, PTV volume (>300cc), and AG/GG genotype in BMP2 rs1979855 were identified as the most powerful factors for predicting severe RP. Additionally, incorporating SNP data for prediction alongside clinicopathological factors significantly improved the AUC compared to using clinicopathological factors alone (0.822 vs. 0.741, p = 0.029). The wrapper-based method selected the same feature set as the logistic regression method, showing the best performance across all ML models (the area under the curve (AUC): XGBoost 0.815, RF 0.805, SVM 0.712, respectively).[Figure: The predictive performance (AUC: mean ± standard deviation) of the different combinations of feature selection methods and machine learning models, as evaluated through repeated nested cross-validation with SMOTE]

Conclusions: We successfully developed an ML-based prediction model for severe RP, integrating clinicopathological and genetic factors. Age, smoking history, PTV volume, and BMP2 rs1979855 genotype emerged as significant predictors. Notably, incorporating SNP data significantly enhanced predictive performance compared to clinicopathological factors alone.

Keywords: Radiation pneumonitis, Single nucleotide polymorphism, Machine learning



	Filtered			Wrapper			Embedded			Logistic		
	XGB	RF	SVM	XGB	RF	SVM	XGB	RF	SVM	XGB	RF	SVM
AUC (mean)	0.624	0.665	0.625	0.815	0.805	0.712	0.717	0.738	0.698	0.815	0.805	0.712

EP.06A PATHOLOGY AND BIOMARKERS - ARTIFICIAL INTELLIGENCE
SATURDAY, SEPTEMBER 7, 2024 - 11:58 - 11:59

EP.06A.01 Computational Linguistic Analysis for the Isolation of Propitious miRNA Biomarkers in Lung Cancer

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Introduction: In the realm of lung cancer research, microRNAs (miRNAs) are increasingly recognized as small, non-coding RNA entities that play a critical role in the disease's development. Individual studies have provided valuable insights into the mechanisms of miRNAs in lung cancer; however, their limited focus often restricts a comprehensive understanding of the full extent to which miRNAs contribute to the pathogenesis and treatment approaches of lung cancer.

Methods: In an effort to overcome the inherent biases of individual studies in lung cancer research, we employed computational linguistic analysis to elucidate the functions of microRNAs (miRNAs) in lung cancer and their potential as biological indicators. This involved tokenizing abstracts from academic publications and extracting key biomedical terms for thematic modeling. To categorize lung cancer, we utilized five machine learning models: Logistic Regression (LR), Naïve Bayes, Decision Curve Analysis (DCA), Random Forests, and Support Vector Machines (SVM). The significance of specific features was assessed to construct networks illustrating the interactions between miRNAs and lung cancer

Results: In our comprehensive analysis of microRNA (miRNA) studies related to lung cancer, we identified three distinct topics demonstrating specific tendencies among miRNAs in this context. Notably, Random Forests model emerged as a particularly promising tool for lung cancer prognosis, achieving an accuracy rate surpassing 60%. Crucially, miR-21 was identified as a key biomarker for lung cancer prognosis, targeting a broad spectrum of genes and signaling pathways involved in the disease.

Conclusions: Utilizing an integrative approach, we gained comprehensive insights into the relationship between microRNAs (miRNAs) and lung cancer, affirming the potential of miRNAs as biological indicators for this malignancy. This methodology offers a broad perspective on the interaction between miRNAs and lung cancer, underscoring their significance in the disease's context.

Keywords: miRNA, Lung cancer, text mining

EP.06B PATHOLOGY AND BIOMARKERS - BIOMARKER
SATURDAY, SEPTEMBER 7, 2024 - 11:58 - 11:59

EP.06B.01 The Actual Status of Biomarker Testing and Prognosis in Postoperative Recurrent NSCLC: Subgroup Analyses of WJOG15421L (REVEAL)

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Introduction: We previously reported the real-world status of biomarker testing and drug therapy in advanced or recurrent non-small cell lung cancer (NSCLC) (WJOG15421L). Although the problems in biomarker testing became apparent in clinical settings, there is no report to investigate biomarker testing focused on postoperative recurrent cases. Therefore, a subgroup analysis targeting postoperative recurrence cases was conducted in the WJOG15421L trial.

Methods: This retrospective multicenter study enrolled 1500 pts with advanced or recurrent NSCLC diagnosed between 1 July 2020 and 30 June 2021 from 29 centers. Of these, 229 postoperative recurrent pts were included in this subgroup analysis. The primary endpoint was the actual status of biomarker testing.

Results: The median age was 74.0 (range: 40-92) with 46.5% of pts diagnosed as stage I at primary surgery, and 67% was adenocarcinoma. The median time from primary surgery to recurrence (TTR) was 511 days, and 169 pts had distant metastasis. For the confirmation diagnosis of recurrence, approximately 23% underwent re-biopsy. The multiplex gene testing was performed in 100/229 pts (44%), and OncomineDxTT was performed in 78/229 pts (34%). The implementation rate of biomarker testing was as follows: EGFR 84%, ALK 77%, ROS1 68%, BRAF 55%, and MET 52%. The multiplex gene testing was performed more in patients with distant metastasis compared with local recurrence (47% vs 35%). There was no significant difference in the success rates of multiplex gene testing between resected archival specimens and recurrent specimens by re-biopsy. Additionally, although there was no difference in success rates during the time from surgery to sample submission, multivariate analysis revealed that when the interval between surgery and recurrence exceeded 3 years, multiplex gene testing was often not performed. Survival analysis, comparing 1192 pts with advanced stage in the REVEAL study, showed that postoperative recurrence pts had significantly better overall survival in both the overall population (HR=0.60 [95%CI: 0.47-0.76]) and the driver+ subgroup (HR=0.49 [95%CI: 0.28-0.86]), as compared to advanced pts.

Conclusions: Despite an ample quantity of specimens from surgical samples, the submission rate for multiplex gene testing in postoperative recurrence cases was only 44%. It was also revealed that multiplex gene testing was not often performed in pts with the interval until recurrence exceeded 3 years. Postoperative recurrence cases, even among the driver+ population, demonstrated a favorable prognosis compared to advanced cases. The widespread evaluation of driver mutations through multiplex testing is needed.

Keywords: Multi-gene testing, Biomarker, postoperative recurrence

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EP.06B.03 Performance of a Prognostic OTP, CD44, Ki-67 Biomarker Panel for Relapse in Paired Biopsies and Resections of Pulmonary Carcinoids

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Introduction: Previously OTP, CD44 and Ki-67 were identified as prognostic biomarkers for pulmonary carcinoids (PCs). We aimed to examine prognostic biomarker performance in PC biopsies (Bx) compared to paired resection (Rx) specimens. A previous ENETS 2024 abstract with preliminary data has been amended using additional cases.

Methods: Patients with PC (stage I-III, 2003-2012) who underwent curative resection were selected from Dutch pathology archives. 119 paired Bx-Rx cases were collected, of which 89 cases were eligible for biomarker evaluation, including 11 recurrences. WHO 2021 classification revision was applied by a single pathologist. Atypical carcinoid (AC) histology was defined as the presence of 2-10 mitoses/2mm2 and/or necrosis. H-score was used for OTP and CD44 expression, whereas the Ki-67 proliferation index was scored by eyeball estimation with hot-spot scoring. Biopsy cases diagnosed as typical carcinoid (TC) and carcinoid NOS were grouped as one separate entity; non-AC. PCs were subdivided into low risk (OTP≥50; CD44≥30; Ki-67<5%) or high risk for recurrence (all others).

Results: WHO 2021 revision classified n=75/85 PC's from patients without recurrence as non-AC on Bx, whereas the IHC biomarker panel subdivided n=54/55 PC's as low-risk. On Rx, WHO classification revealed n=68/74 PC's from patients without recurrence as TC, while the IHC biomarker panel identified n=56/57 PC's as low-risk (Fig. 1). In Bx, stratification of recurrence-free survival based on WHO diagnosis (i.e non-AC vs. AC (p=0.389)) improved significantly when applying the IHC biomarker panel (i.e. low-risk vs. high-risk (p<0.001)). Spearman's correlation between Bx and Rx for markers OTP, CD44 and Ki-67 were 0.935 (p<0.001), 0.515 (p<0.001) and 0.247 (p=0.020), respectively.

Conclusions: Our data indicate that the OTP, CD44 and Ki-67 biomarker panel improves selection of patients with low-risk PCs and are applicable to Bx specimen, unlike the WHO classification. This may have clinical implications regarding the surgical treatment strategy. Validation with multiple pathologists is ongoing.

Keywords: Pulmonary carcinoid, Recurrence, Biomarkers

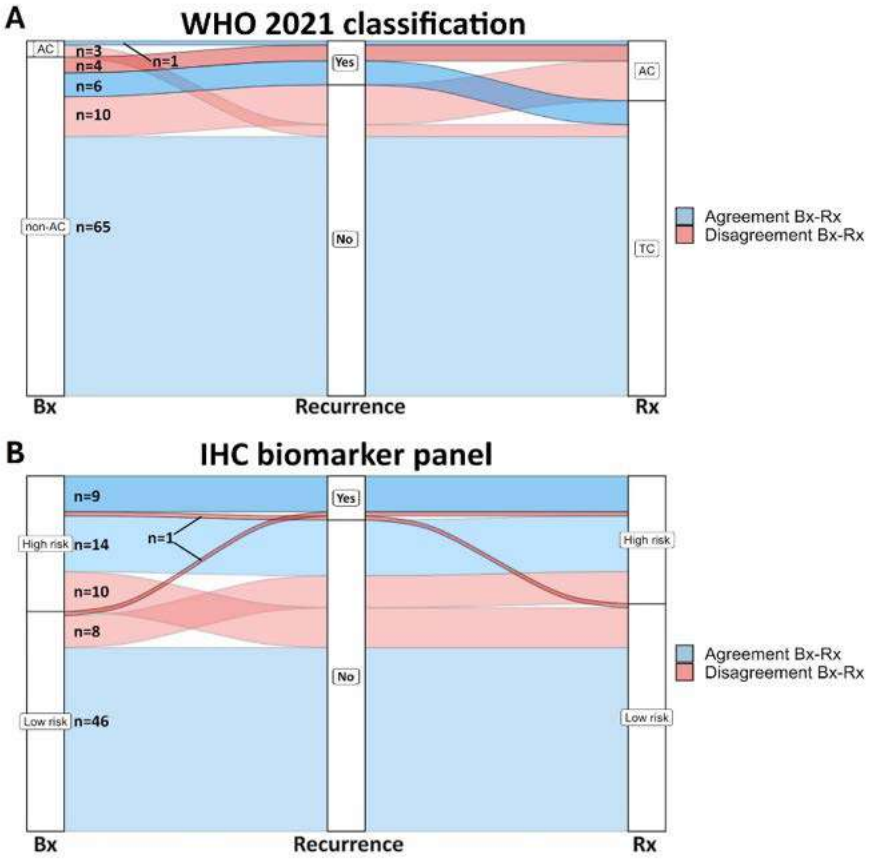

Figure 1A) *WHO 2021 classification diagnosis patient distribution on preoperative biopsy (Bx) vs. resection specimen (Rx).* ***Figure 1B)*** *IHC-based risk stratification patient distribution on Bx vs. Rx.*

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EP.06B.04 Aging Alteration of Biomarkers and Its Prognostic Role in Elderly Lung Cancer Patients Treated with Adjuvant S-1 Chemotherapy

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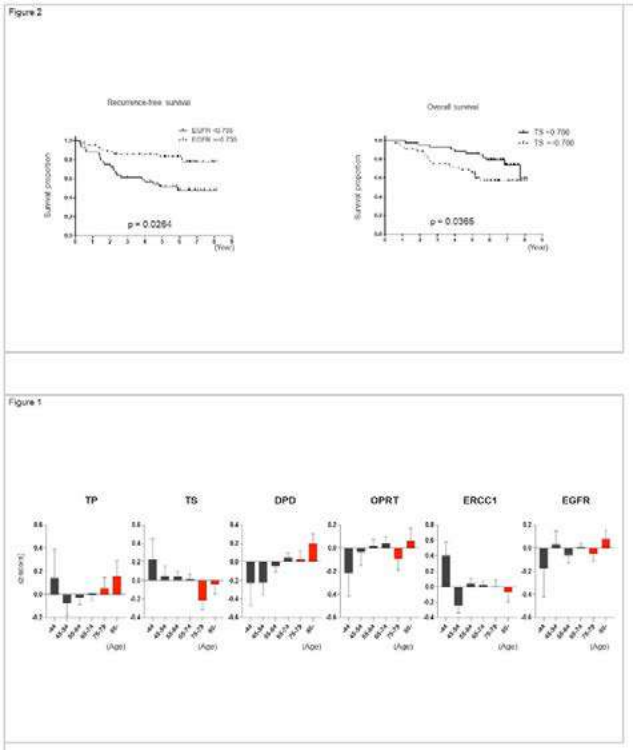
Introduction: Treating elderly patients presents challenges due to age-related declines, but recent recommendations advocate for age not being a sole determinant for adjuvant treatment decisions in non-small cell lung cancer (NSCLC) patients. Aging may alter expression levels of 5-fluorouracil (5-FU) biomarkers.

Methods: Expression changes with aging were explored using The Cancer Genome Atlas (TCGA) database. 5-FU-related biomarker expressions, including thymidylate synthase (TS), dihydropyrimidine dehydrogenase (DPD), orotate phosphoribosyltransferase, epidermal growth factor receptor (EGFR), and excision repair cross-complementation group-1 (ERCC1), were assessed in 89 NSCLCs elderly patients (≥ 75 years old) receiving adjuvant S-1, an oral fluoropyrimidine agent, therapy in a phase 2 trial named as the Setouchi Lung Cancer Group Study 1201 (SLCG1201).

Results: TCGA analysis (n=955) indicated decreased TS expression with aging, particularly in those aged 75 or older (Figure 1). In the SCLG1201 study, EGFR mutation patients (n=27) showed significantly higher DPD (p=0.0066) and EGFR (p<0.0001) expressions and lower TS (p=0.0125) and ERCC1 (p=0.0015) expressions. Low TS and high EGFR expressions correlated with favorable recurrence-free survival (RFS)(p=0.0365) and overall survival (OS)(p=0.0264) in univariate analysis (Figure 2). Multivariable analysis confirmed pathological stage as an independent prognostic factor for both RFS and OS (p=0.0052 and 0.0352, respectively).

Conclusions: Age-related decrease in TS expression supports the potential benefit of 5-FU-based therapy in elderly NSCLC patients. Low TS expression may predict better clinical outcomes in elderly NSCLC patients with adjuvant S-1 therapy, despite pathological stage being an independent prognostic factor. Further research is warranted to validate these clinical implications.

Keywords: lung cancer, biomarker



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EP.06B.05 Ultra-Stat Idylla EGFR Testing for Non-Small Cell Lung Carcinomas: Patient Selection and Impact on Clinical Outcomes

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Introduction: Eligibility for EGFR targeted therapy for non-small cell lung cancer (NSCLC) is dependent on molecular testing results. Our institution recently began offering ultra-stat Idylla EGFR testing upon clinical request for NSCLC, which has the potential for faster turnaround time. However, this testing is limited to a single gene, such that negative or failed Idylla tests require subsequent next-generation panel sequencing. We aimed to (i) assess the demographics of patients selected for ultra-stat testing and how these demographics correlate with EGFR positivity rates, and (ii) assess the impact of ultra-stat testing on clinical outcomes.

Methods: Requests for ultra-stat Idylla EGFR testing between February 2nd, 2022 and February 26th, 2024 were identified from laboratory records, and clinical information on the ultra-stat tested patients was retrospectively compiled through an outcomes database and chart review. Associations were assessed using Fishers exact tests, and survival analysis was performed using Cox proportional hazards models.

Results: Sixty-eight NSCLC patients with ultra-stat Idylla EGFR test results were identified. Ultra-stat testing was most frequently requested by medical oncologists (42/68 cases, 62%) and respirologists (13/68 cases, 19%), with 21/68 patients (31%) admitted to hospital at the time of test request. The median laboratory turnaround time for ultra-stat testing was 1 day (range 0 to 7 days). Seven samples failed ultra-stat testing, and 44 of the remaining 61 (72%) were positive for EGFR mutations, much greater than the 19.7% EGFR positivity rate for panel-based sequencing at our institution between May 2021 and February 2024 (n=3,287). The detection of an EGFR mutation was significantly associated with Asian race (47/64 patients; P=0.0001) and had a near significant association with never smoking (54/68 patients; P=0.058). Thirty-eight (86%) of the EGFR mutation-positive patients were treated with EGFR-targeted therapy, initiated a median of 5 days (range 0 to 28 days) after ultra-stat results were reported. Patients who received targeted therapy after a positive Idylla result had significantly longer overall survival compared to other ultra-stat tested patients (P=0.017; HR 0.30, 95% CI 0.11-0.80; median follow time 161 days). Panel-based sequencing identified other targetable alterations in 9 out of 20 patients (45%) who had a negative or failed ultra-stat test. The median sequencing turnaround time was 10 days (range 7-29 days). Of the 24 ultra-stat tested patients with a failed/negative ultra-stat test, five (21%) died less than 14 days after receipt of the specimen for ultra-stat testing.

Conclusions: Rapid identification of EGFR mutations is possible through ultra-stat Idylla EGFR testing, allowing expedient targeted treatment initiation. The high EGFR-positivity rate among ultra-stat tested patients indicates effective identification of probable EGFR-positive cases by clinicians, with race being the most significant predictor of EGFR mutation. These findings will support the development of decision aids for selection of EGFR testing modality.

Keywords: EGFR, Non-small cell lung carcinoma, Biomarkers

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EP.06B.06 A Meta-Analysis of Advanced Lung Index (ALI) in Advanced Lung Cancer Patients

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Introduction: Systemic inflammation has been identified as an adverse prognostic factor in cancer development and progression. The advanced lung index (ALI) [body mass index (BMI) x albumin (ALB) / neutrophil-lymphocyte ratio (NLR)], has been demonstrated to be a prognostic indicator in several types of solid and hematological malignancies. However, the optimal cutoff values of ALI remain unclear.

Methods: We conducted a meta-analysis to evaluate the prognostic significance of pre-treatment ALI values, utilizing data extracted from 9 articles focused on advanced lung cancer. The primary endpoints were overall survival (OS) and progression-free survival (PFS). Pooled hazard ratios (HR) and corresponding 95% confidence intervals (95% CI) were computed using the random-effects model. In addition, we performed meta-regression analysis to assess the impact of ALI cutoff values across the studies.

Results: High pre-treatment ALI values above the cutoff were significantly linked to longer OS, both based on univariable HRs (HR = 1.94, 95% CI = 1.68-2.23) and multivariable HRs (HR = 1.57, 95% CI = 1.37-1.79) extracted from studies (Figure 1A and 1B). It's important to note that the analysis for PFS could not be conducted due to the limited number of studies reporting relevant HRs. The ALI cutoff values for distinguishing between high and low ALI groups in lung cancer patients ranged from 18 to 47. Our meta-regression analysis revealed that although marginally significant, the multivariable HRs for OS extracted from individual studies varied with ALI cutoff values ranging from 18 to 47 (P = 0.055). Specifically, higher ALI values (>40) were associated with better survival, while lower pretreatment ALI values (<20) were associated with worse survival.

Conclusions: This meta-analysis has affirmed that high pre-treatment ALI values are linked with longer survival in advanced lung cancer patients. However, the binary cutoffs of ALI values have shown variability across studies. Instead, the identification of a three-tier classification for pre-treatment ALI values (e.g., <20, 20-40, >40) is crucial for indicating varying prognoses in advanced lung cancer patients and could potentially be translated into clinical practice.

Keywords: advanced lung index (ALI), advanced lung cancer, prognostic markers

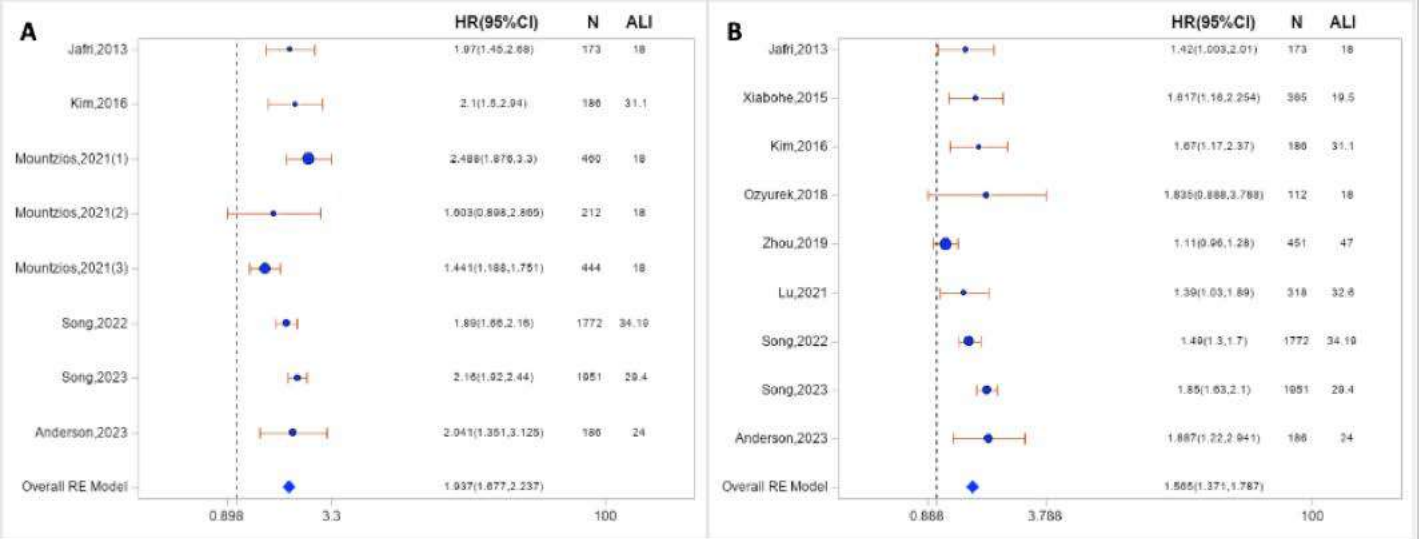

Figure 1 Forest plot illustrating prognostic significance of ALI value on overall survival from lung cancer based on univariable HRs (A) and multivariable HRs (B) reported in individual studies.

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EP.06B.07 CARE: Developing a Clinical Composite Score for mNSCLC and Co-Design Solutions to Bridge the Metropolitan vs Regional Gap

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Introduction: Despite being the fifth most common cancer in Australia, NSCLC-related mortality remains the highest among all cancers with a five-year survival rate of approximately twenty percent.

Moreover, there is an absolute difference of six percent in five-year survival between patients from regional/rural areas, compared to metropolitan counterparts.

In addition to this geographical difference, the biology of wild-type mNSCLC is extremely varied (e.g. PD-L1, metabolic activity on FDG-PET, tumour differentiation) leading to significantly variable responses to treatment.

Developing clinical tools to identify patients upfront with worse tumour biology could aid prognostication and therefore may mitigate the need for over/under treatment.

Poorer clinical outcomes in regional patients compared to city patients also highlight the fact that treatment outcomes are not just dependent on tumour factors, but also dependent on patient- and health-service-related factors (e.g. distance to treating centre, delayed referral/diagnosis, guideline non-concordant treatment, lack of clinical trials etc).

Thus, through funding by the Thoracic Oncology Group of Australasia (TOGA), we aim to develop a Clinical Composite Score (CCS) encapsulating patient, tumour and health service factors that could help identify patients who are at risk of poorer outcomes, leading to reallocation of resources to develop and implement a co-design solution to address these issues at a system level.

Methods: To identify predictors of lung cancer outcomes across clinical, patient and health service factors, a retrospective analysis of hospital records will be conducted.

Measure patient and health service factors, including non-clinical independent variables, e.g. socio-economic index for area, distance from hospital, Aboriginal or Torres Strait Islander heritage, and clinical independent variables e.g. PDL1 score, TTF1 status.

Measure dependent variables e.g. timeliness to care, OS, PFS, adherence to guideline concordant treatment, as well as co-variates e.g. age, sex, smoking status, tumour differentiation, presence of visceral metastases, presence of central nervous system metastases, grade of tumour differentiation, mean SUV on FDG-PET scan.

A total sample of 293 participants will be required to reach a power of 0.95.

Variables which remain significant ($p<0.05$) after multivariate analysis will be used to create a composite score to predict lung cancer outcomes.

To describe clinical and non-clinical variables, means and standard deviations will be reported, t-tests and chi-square will be used to report differences between groups.

To explore the association between independent and dependent variables, univariate and multivariate regression models with significant variables in univariate analysis will be conducted.

Cox regression models will be used for analysis with timeliness to care, PFS and OS. Survival probabilities will be estimated using the Kaplan-Meier method and survival curves compared using the log-rank test.

All regression models will be adjusted for co-variates a priori.

Results: Awaiting results pending data collection.

Conclusions: The project aims are to develop a Clinical Composite Score for mNSCLC, incorporating tumour, patient, and health service factors, to identify patients at-risk of poorer outcome, in addition to co-designing a solution in the regional setting, addressing issues identified through the CCS, to propose system-level change.

A validation study for CCS in a larger, prospective, multi-centre study will also be proposed.

Keywords: Biomarker, mNSCLC, Equity

EP.06B PATHOLOGY AND BIOMARKERS - BIOMARKER
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EP.06B.08 Biomarker-Guided Treatment Selection in NSCLC: A Quality Improvement Initiative to Strengthen Multidisciplinary Care

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Introduction: Biomarker testing plays a central role in guiding treatment selection for advanced non-small cell lung cancer (NSCLC). The increasing number of biomarkers creates a high need for multidisciplinary coordination to ensure timely and comprehensive testing, appropriate interpretation of results, and evidence-based application to treatment decision-making.

Methods: In 2023, 58 health care providers (HCPs) at 4 US community oncology clinics completed surveys on barriers to molecular testing, multidisciplinary care coordination, and treatment selection in NSCLC. HCPs (n=30) then participated in audit/feedback (AF) sessions, featuring a mock tumor board, to review guidelines and clinical evidence and develop clinic-specific action plans to address identified gaps.

Results: HCPs reported ongoing challenges to integrating biomarker testing in routine practice, including prioritizing tests on limited tissue samples, deciding whether to begin treatment prior to receiving results, optimizing tissue collection, and inconclusive or failed tests. Although 76% reported that patients started systemic therapy ≤15 days following diagnosis, 31% reported testing turn-around times of 15-20 days. While most HCPs reported regular EGFR, PD-L1, BRAF, KRAS and ALK testing, testing was <50% for MET, ROS1, HER2, RET, and NTRK. Most HCPs (72%) were less than fully satisfied with the quality of communication between specialties in their practices. Frequency of communication varied: some teams reported that every case was discussed (24%) while others discussed only complex cases (24%) or only when an issue was raised (11%). About half (53%) participated in weekly multidisciplinary tumor boards. After the AF sessions, clinic-level action plans included improving integration of biomarker testing into standard clinical workflows, working as a multidisciplinary team to increase recognition of actionable biomarkers, improving patient monitoring protocols to manage adverse effects of newer therapies, and improving patient education on reasons for testing. On a follow-up survey, most clinical team members (86%-100%) agreed that program participation had led to improved communication and workflows, reduced time between diagnosis and test ordering, and increased use of guideline-concordant testing before treatment initiation.

Conclusions: NSCLC care teams recognize the value of guideline-concordant biomarker testing but continue to face practical challenges including lack of sufficient tissue, poor tissue quality, and long turn-around times. Integration of sustainable changes in clinical workflows and care coordination stemming from this QI initiative improved communication between specialties, leading to more timely and comprehensive testing.

Keywords: Biomarker Testing, Multidisciplinary Care, Quality Improvement

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EP.06B.09 The Role of Cytokines in Predicting the Efficacy of Immunotherapy in Advanced NSCLC Patient

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Introduction: Immunotherapy checkpoint inhibitors (ICIs) have notably increased the 5-year survival rate for advanced non-small cell lung cancer (NSCLC) to up to 31.2%. However,it is important to note that not all patients benefit from this treatment,there's a lack of effective biomarkers for predicting ICIs' efficacy and adverse reactions. Studies suggest cytokines play a crucial role in tumor immune response and suppression,have been considered as potential biomarkers in clinical settings. In this study, our objective was to assess whether the levels of cytokines in the patient's blood sample are associated with tumor response and adverse reaction to ICIs as well as the survival of patients with advanced non-small cell lung cancer.

Methods: A total of 12 plasma cytokines were measured in advanced NSCLC patients(n=100) who underwent combined treatment using ICIs combination therapy every cycle treatment. Tumor assesment was conducted two cycles according to iRECIST standard in solid tumors. Patients are divided into stable disease group and progression disease group to compare the differences in cytokine levels between the two groups and the changes in cytokines before and after treatment.

Results: 20 patients have been enrolled currently, suggesting that the expression of IL10, $TNF\alpha$, and $IFN\gamma$ in the stable disease group (SD) were significantly lower than those in the progressive disease group (PD) ($p<0.05$) ,and the reductions of IL-17A, $TNF\text{-}\alpha$, IL-12P70, and $IFN\text{-}\gamma$ in patients after two or four cycles confers a better prognosis.

Conclusions: Our preliminary study suggests that cytokines can be served as indicators for predicting efficacy in non-small cell lung cancer patients undergoing ICIs with chemotherapy treatment. Subsequent studies with larger sample sizes are currently underway.

Keywords: Immunotherapy, Cytokines, biomarkers

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EP.06B.10 Clinical Feasibility of Multiplex Digital PCR for Major Mutation Detection in NSCLC Patients: The Droplex NSCLC Panel Test

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Introduction: In recent years, the treatment landscape for non-small cell lung cancer (NSCLC) has evolved with the development of immune checkpoint inhibitors and targeted therapies aimed at various genes. Next-Generation Sequencing (NGS) technology is currently the gold standard for detecting variants in multiple genes simultaneously. However, NGS has limitations such as long turnaround time (TAT) and the need for substantial DNA or RNA extraction, along with expertise in performing advanced NGS. Therefore, we aimed to develop a Droplex NSCLC Panel Test Kit based on multiplex digital PCR, which may offer first-line multigene diagnostics due to its simple workflow, short TAT, low sample input amount, high sensitivity, high specificity, and lower costs compared to NGS. To date, a multigene mutation detection system using digital PCR has not been developed, and here, we validated the clinical effectiveness of the Droplex NSCLC Panel Test Kit. The Droplex NSCLC Panel Test Kit is designed to detect over 170 mutations commonly found in the target genes of major targeted therapies, including EGFR, ALK, ROS1, BRAF, MET, RET, KRAS, HER2, NTRK1, NTRK2, and NTRK3.

Methods: We retrospectively collected samples from patients diagnosed with NSCLC and having results of NGS and companion diagnostics. DNA and RNA were extracted from formalin-fixed paraffin-embedded tissue (FFPET). Subsequently, digital PCR was performed using the multiplex Droplex NSCLC Panel Test Kit with 20 ng of DNA and RNA simultaneously extracted from the patient's tissue samples. This was done through equivalence testing of 11 genes in FFPET of NSCLC patients, by comparing previous molecular testing results.

Results: Using FFPET samples from 35 NSCLC patients, a blinded NSCLC panel test was conducted. The results revealed EGFR mutations detected in 13 patients and cMET exon 14 skipping in 4 patients. Additionally, KRAS G12 mutations were found in 11 patients, while ROS1 fusion was detected in 3 patients, and HER2 mutation was found in 1 patient. No mutations were detected in 3 patients. The overall percent agreement for the detection of mutations using the Droplex NSCLC Panel Test and existing results was 91%. The three discordant samples were confirmed to contain mutations not currently covered by the kit's detection capabilities. Among these mismatches, two samples lack corresponding targeted agents at present.

Conclusions: The Droplex NSCLC Panel Test is an accurate and effective tool for detecting clinically relevant NSCLC mutations, as demonstrated by its high level of concordance with existing molecular results. It can serve as a first-line multiplex diagnostics due to its low DNA/RNA input requirement, lower cost, and minimal TAT. Additional studies with larger sample sizes are currently underway.

Keywords: targetable mutations, Multiplex testing, Digital PCR

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EP.06B.11 Construction of a Prognostic Model for Lung Adenocarcinoma Based on Disulfidptosis-related LncRNAs

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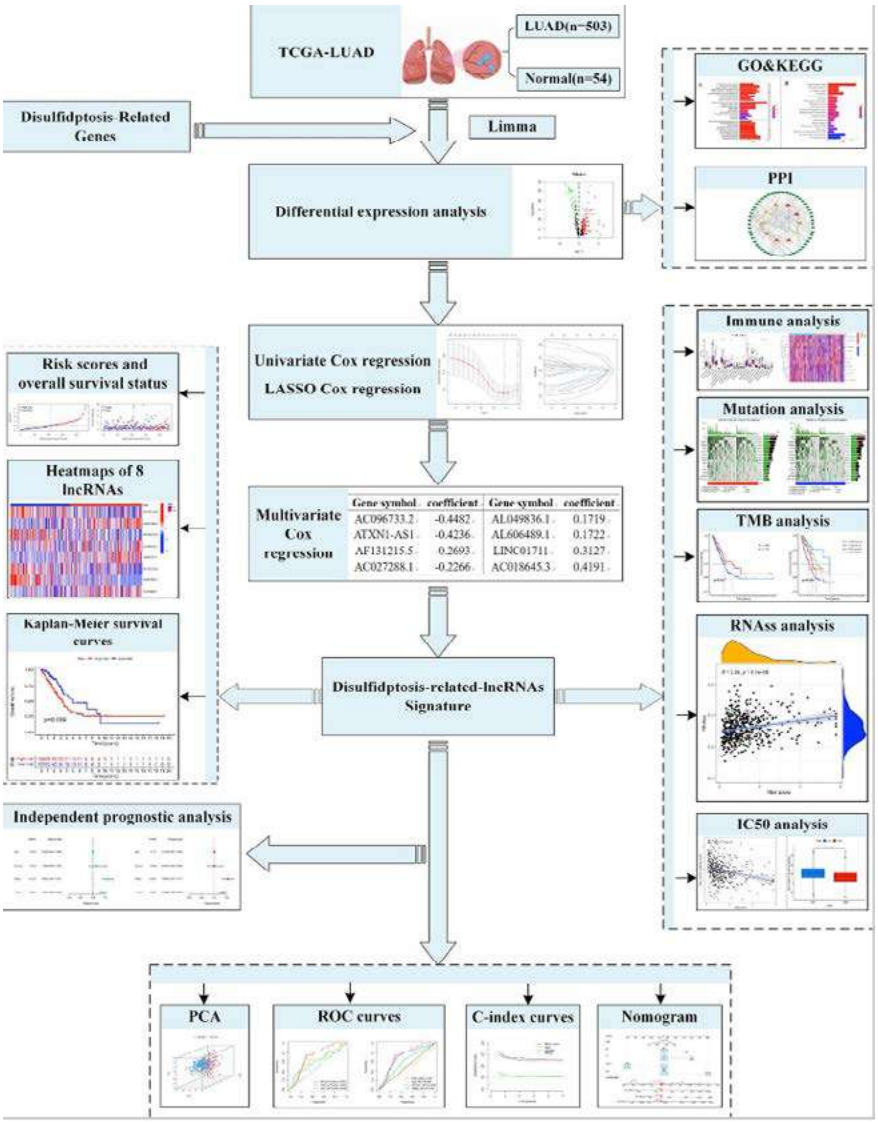
Introduction: Lung adenocarcinoma (LUAD) is the most common pathological type of lung cancer, with high incidence and poor prognosis. Disulfidptosis is a novel form of death induced by disulfide stress caused by excessive intracellular cystine accumulation under glucose starvation conditions. This study aims to investigate the significance of disulfidptosis-associated lncRNAs (DRlncRNAs) in the risk assessment and prognosis prediction of LUAD.

Methods: RNA-Seq data and clinical information of LUAD patients were obtained from The Cancer Genome Atlas (TCGA) database. Genes associated with differential expression of disulfidptosis were screened using Univariate Cox regression analysis. Subsequently, a prognostic model was constructed by LASSO-Cox regression analysis to classify patients into high-risk and low-risk groups. Time-dependent Receiver Operating Characteristic (ROC) curve, C-index curve, and Kaplan-Meier curve were plotted and compared to evaluate the predictive validity of the prognostic model. Functional Gene Set Enrichment Analysis (GSEA) and single-sample Gene Set Enrichment Analysis (ssGSEA) were used to explore the characteristics of enrichment pathways, immune-related functions and treatment response in high-risk and low-risk groups.

Results: A risk prognostic model was constructed consisting of 8 DRlncRNAs (ATXN1-AS1, AC018645.3, AC096733.2, AL049836.1, LINC01711, AF131215.5, AC027288.1, AL606489.1). Univariate and multifactorial COX analyses further revealed the model to be a prognostic factor independent of multiple clinicopathologic parameters.

Conclusions: The 8-lncRNA prognostic model we constructed can be used as a valid biomarker to predict the prognosis of LUAD patients.

Keywords: lung adenocarcinoma, disulfidptosis, Prognosis



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EP.06B.12 A Knowledge-Based Database on 1100 Non-Small Cell Lung Cancer from Italian Clinical Experience: The Biomarkers ATLAS

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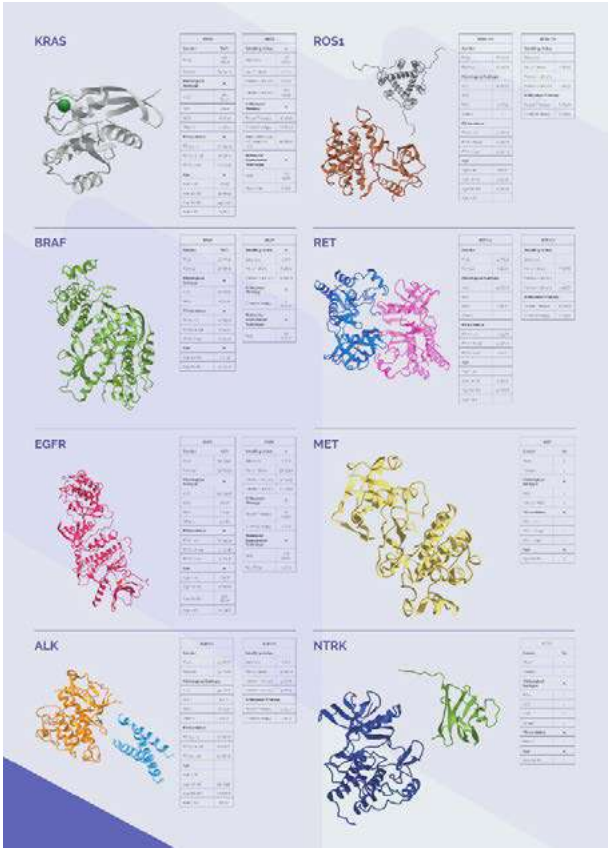
Introduction: Personalized medicine plays a key role in clinical management of Non-Small Cell Lung Cancer (NSCLC) patients. A rapidly increasing number of predictive biomarkers have been yet approved by international societies to optimized therapeutical decisions for NSCLC patients. Several opening challenges drastically impacts on the reliability of molecular profiling in clinical practice including pre-analytical (sample management of scant diagnostic specimen), analytical (technical performance of diagnostic assays/platform) and post-analytical (data interpretation of complex molecular hallmarks) issues. In this heterogeneous scenario, harmonized procedures and comprehensive database integrating technical, molecular, and clinical records are essential to optimize clinical administration of NSCLC patients. Here, an audit of clinical and molecular records from n=1100 NSCLC patients collected among 80 referral Italian institutions (from January 2019 to December 2020) are retrieved from knowledge-based database (Biomarkers ATLAS, https://biomarkersatlas.com/).

Methods: By consulting Biomarkers ATLAS, we systematically collected molecular (technological approaches, KRAS, EGFR, BRAF, ROS1, ALK, RET, NTRK, MET molecular status) and clinical records (sex, age, histological type, smoker status, PD-L1 expression, therapy) from NSCLC patients administrated by two coordinator institutions (University of Turin and University of Naples). These data were structured in free of charge Biomarkers ATLAS repository and harmonized to be easily interpreted

Results: A list of clinical and molecular records were retrieved from n=1100 (n=552 mutated and n=548 wild type) NSCLC patients. Druggable molecular alterations were found n= 152 EGFR (13.8%), n=291 KRAS (26,5%), n=29 BRAF (2.6%) hot spot mutations, n= 46 ALK (4.2%), n=15 RET (1.4%), n=11 ROS1 (1.0%), and n=1 NTRK (0.1%) aberrant transcripts. Moreover n=3 MET exon 14 skipping (0.3%) positive cases were recorded. Molecular data were matched with five clinical variables

Conclusions: Biomarkers ATLAS, https://biomarkersatlas.com/) consists of an innovative, easily managing, and clinically informative diagnostic tool supporting healthcare figures by the integration of clinical and molecular data of real-world practice NSCLC patients

Keywords: knowledge-based database, predictive biomarkers, lung cancer



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EP.06B.13 Prognostic Impact of Serum CA125 Level in Patients with cN0 Non-Small Cell Lung Cancer

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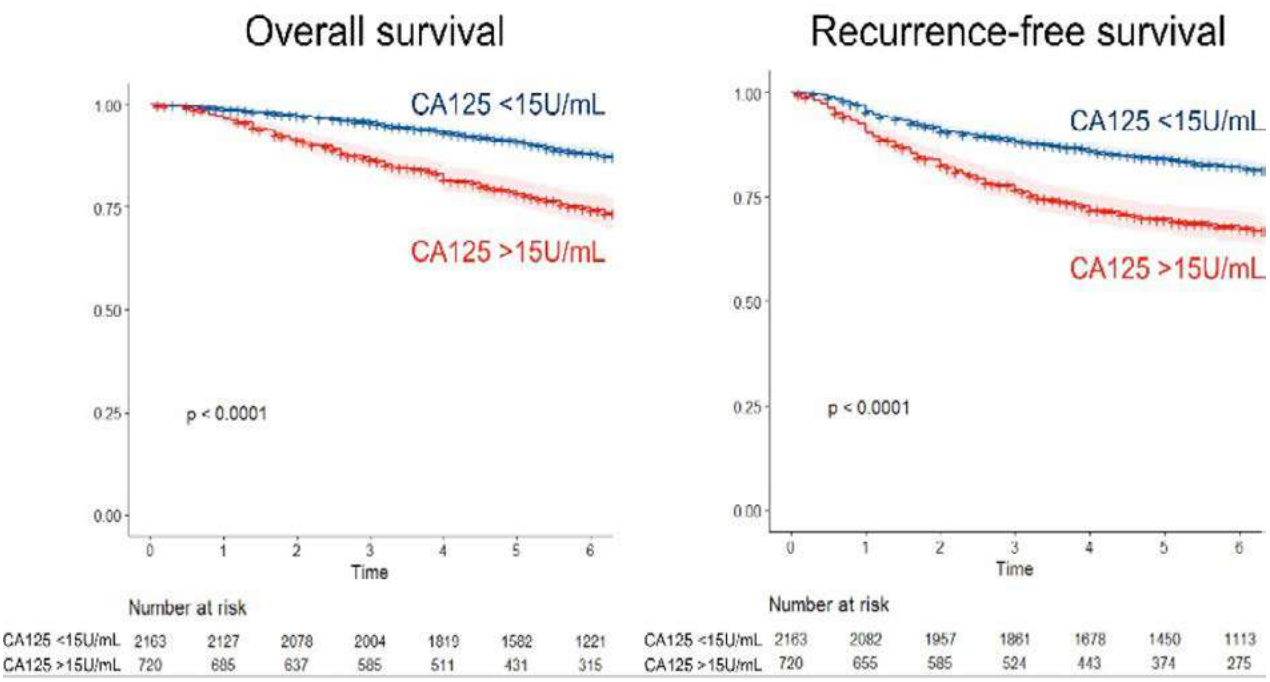
Introduction: This study aimed to investigate the prognostic significance of serum carbohydrate antigen 125 (CA125) level in patients undergoing resection for non-small cell lung cancer (NSCLC).

Methods: Patients who underwent macroscopically complete resection for cN0 NSCLC between 2005 and 2020 were included. The influence of preoperative serum CA125 level on overall survival (OS) and recurrence free survival (RFS) was evaluated by multivariable analyses using Cox proportional hazard models. The cut-off value of CA125 was set at 15 U/mL. The correlation of the elevation of CA125 with clinicopathological factors and recurrence patterns was analyzed. OS and RFS were estimated using the Kaplan-Meier method and compared using the log-rank test between the high CA125 group and the low CA125 group.

Results: After excluding 1158 patients (820 lacked preoperative serum CA125 data, 131 who underwent macroscopically incomplete resection, and 207 with clinical node-positive disease), a total of 2883 patients were included in this study. Among them, 720 (25%) had preoperative serum CA125 >15U/mL. Elevated CA125 was significantly correlated with male sex, smoking index, tumor size, non-adenocarcinoma histology and elevation of preoperative serum carcinoembryonic antigen. High CA125 group had more frequent nodal upstage (13.3% vs. 8.6%, p = 0.001), pleural invasion (23.3% vs. 13.1%, p <0.001), lymphatic invasion (24.7% vs. 18.1%, p <0.001), and venous invasion (36.1% vs. 25.5%, p <0.001). Long term prognosis was significantly poorer in patients with higher CA125 level than in patients with lower CA125 level (5-year OS, 78.3% vs. 91.0%, p <0.001; 5-year RFS, 69.7% vs. 84.0%, p <0.001). There was no significant difference between the two groups in the rate of positive pleural lavage cytology and in the frequency of first recurrence presenting with pleural dissemination or malignant pleural effusion. Preoperative CA125 level was significantly associated with poor OS (hazard ratio = 1.006, p <0.001) and poor RFS (hazard ratio = 1.005, p <0.001) in multivariable analyses.

Conclusions: Serum CA125 level is an independent prognostic factor in patients undergoing resection for cN0 NSCLC.

Keywords: serum CA125 level, cN0 non-small cell lung cancer, complete resection



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EP.06B.14 Differential Expression in Potential Therapeutic Target Protein by Treatment in Small Cell Lung Cancer with and without Transformation

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Introduction: Small cell lung cancer (SCLC) is a disease with a poor prognosis. Besides combination strategy with immune checkpoint inhibitors (ICIs) and cytotoxic agents, antibody-drug conjugates (ADCs) and bispecific T-cell engagers (BiTE) are being developed. These drugs target tumor-associated surface protein. Transition of protein expression affected by treatment has not been fully investigated especially in the era of ICIs. The purpose of this study is to evaluate changes in protein expression in small cell lung cancer tissues before and after treatment.

Methods: This study included patients diagnosed with SCLC by surgery or biopsy and experienced re-biopsy after treatment, and patients initially diagnosed with non-small cell lung cancer and transformation to SCLC was diagnosed by re-biopsy at the National Cancer Center Hospital between 2014 and 2023. Tissues were obtained by surgery, bronchoscopy, or CT-guided biopsy with an interval of at least 100 days.

Results: Five resectable SCLC cases with paired surgical specimens and biopsy specimens at disease progression, and 18 cases with paired biopsy specimens at diagnosis and progression, were included. Of these, pathology specimens could be evaluated in a total of 15 cases: 5 for the former and 10 for the latter group. The median age of all patients was 68 years, 11 (73%) were male, 11 (73%) were smokers, 8 (53%) were in clinical stages I-IIIA, 1 (7%) in stages IIIB-IIIC, and 6 (40%) in stage IV. Among the latter 10 patients, 4 patients experienced SCLC transformation and 3 of them were treated by osimertinib. Progression free survival from first-line therapy was 362 days (264-NA) vs. 314 days (245-NA) and overall survival was 1466 days (567-NA) vs. 901 days (517-NA), respectively for non-transformed and transformed small cell carcinoma cases.

Conclusions: In this study, we plan to investigate clinicopathological features in paired specimens focusing on DLL3, ASCL1, NEUROD1, POU2F3, YAP1, and MDM2.

Keywords: small cell lung cancer, tumor associated surface protain, rebiopsy

Pt No.	Age	Sex	Surgery	Driver mutation	Histology at diagnosis	Histology at rebiopsy	TKI before rebiopsy	ICI before rebiopsy
1	73	M	No	Negative	SCLC	SCLC	No	Yes
2	69	M	No	Negative	SCLC	SCLC	No	No
3	69	M	No	ND	SCLC	SCLC	No	No
4	63	F	No	Negative	SCLC	SCLC	No	No
5	59	M	No	ND	SCLC	SCLC	No	No
6	68	M	No	ND	SCLC	SCLC	No	No
7	76	M	Yes	ND	SCLC	SCLC	No	No
8	68	M	Yes	ND	SCLC	SCLC	No	No
9	67	M	Yes	ND	SCLC	SCLC	No	No
10	47	M	No	EGFR	ADC	SCLC	Osi	Yes
11	69	F	No	EGFR	ADC	SCLC	Osi	No
12	58	M	Yes	EGFR	ADC	SCLC	Osi	No
13	64	F	Yes	EGFR	ADC	SCLC	Osi	No
14	56	F	No	EGFR	ADC	SCLC	other	No
15	70	M	No	Negative	ADC	SCLC	No	No

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EP.06B.15 Targetable Genetic Alterations Associated with Non-Small Cell Lung Cancer Mortality

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Introduction: Non-small cell lung cancer (NSCLC) biomarker testing recommendations have evolved rapidly with targeted therapy development: Biomarker testing was first recommended for advanced non-squamous cancer in 2011 and current guidelines recommend biomarker testing consideration for advanced NSCLC and stages IB-IIIA adenocarcinoma. Patients with targetable genetic alterations who received targeted therapy survive longer, but the prognostic value of targetable genetic alterations is unclear. This study retrospectively evaluates the overall mortality of NSCLC patients associated with the presence of targetable genetic alterations.

Methods: We evaluated patients aged 18-89 diagnosed with NSCLC from 2013-2020 in a large, integrated healthcare system serving a diverse population. We ascertained sociodemographic and cancer characteristics, receipt of valid biomarker testing within 6 months of diagnosis (IHC, FISH, PCR or NGS), test results, and overall mortality from institutional databases. We compared one- and three-year mortality after NSCLC diagnosis between patients with and without alterations in each targetable gene, after adjusting for age, sex, race/ethnicity, neighborhood deprivation index, smoking status, histologic subtype and cancer stage, using Cox regression analysis.

Results: Among 9834 NSCLC patients, 38.8% received biomarker testing, and most testing yielded valid results (77-92%). Among the 3256 patients with valid results, 54.9% were female, 36.2% were 75-89 years, 41.6% were non-White, 69.7% had a smoking history, 74.7% had stage IV cancer and 7.8% had squamous histology. EGFR was the most commonly tested gene. Genetic alteration prevalence was as follows: KRAS mutation or amplification 26.1% (410/1569); EGFR exon 18-21 mutation 25.5% (872/3421); MET mutation or amplification 5.5% (85/1540); ALK rearrangement 3.8% (113/2970); BRAF mutation or amplification 3.1% (78/1479); ERBB2 mutation or amplification 3.1% (45/1464); ROS1 rearrangement 2.1% (52/2511); RET rearrangement 1.1% (16/1459); NTRK rearrangement 0.3% (2/799). The adjusted hazard of death within one year after NSCLC diagnosis was lower for patients with EGFR or ALK alterations, but higher for patients with MET or ROS1 alterations (Table 1). The adjusted hazard of death within three years after NSCLC diagnosis was lower for patients with EGFR or ALK alterations, but higher for patients with ERBB2 alterations. There was no difference in one- or three-year mortality for patients with BRAF, KRAS, or RET alterations.

Conclusions: Biomarker testing and targeted therapy is transforming NSCLC management and outcomes. Although our data likely partially reflect the evolution of targeted therapy from 2013-2020, EGFR and ALK alterations may have a positive prognostic value, irrespective of treatment.

Keywords: Targetable genetic alteration, Non-small cell lung cancer (NSCLC), Mortality

Table 1. Adjusted Overall Mortality by Presence of Genetic Alteration

Genetic Alteration Present[1]	No. Patients with Valid Test	Prevalence of Alteration	1 Year Mortality			3 Year Mortality		
	n	%	aHR[2]	95% CI	p	aHR[2]	95% CI	p
KRAS Mutation or Amplification	n=1569	26.1%	1.15	(0.96-1.37)	0.12	1.10	(0.95-1.27)	0.21
EGFR (Exon 18-21) Mutation	n=3421	25.5%	0.51	(0.44-0.60)	<0.0001	0.70	(0.63-0.78)	<0.0001
MET Mutation or Amplification	n=1540	5.5%	1.50	(1.04-2.16)	0.03	1.31	(0.95-1.79)	0.10
ALK Rearrangement	n=2970	3.8%	0.55	(0.36-0.85)	0.007	0.56	(0.42-0.75)	0.0001
BRAF Mutation or Amplification	n=1479	3.1%	1.11	(0.78-1.58)	0.57	0.96	(0.71-1.28)	0.76
ERBB2 Mutation or Amplification	n=1464	3.1%	1.44	(0.93-2.22)	0.10	1.54	(1.10-2.16)	0.01
ROS1 Rearrangement	n=2511	2.1%	1.54	(1.01-2.34)	0.04	1.14	(0.79-1.63)	0.49
RET Rearrangement	n=1459	1.1%	1.08	(0.48-2.45)	0.85	1.05	(0.56-1.98)	0.88
NTRK[3] Rearrangement	n=799	0.3%	-	-	-	-	-	-

[1]Reference: Absence of genetic alteration
[2]Adjusted for age, sex, race/ethnicity, neighborhood deprivation index, smoking status, histologic subtype, cancer stage
[3]Adjusted analyses were not conducted for NTRK rearrangements due to low prevalence

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EP.06B.16 Latin-American Non-Small Cell Lung Cancer Patient's Tumors Harbor Many Novels Potentially Actionable/driver Mutations.

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Introduction: Therapies that target activating EGFR, ALK, ROS1 and other mutations are first-line treatments in NSCLC patients. Latin-American patients are very poorly represented in clinical trials and in genomic databases, thus little is known about the prevalence of actionable mutations in this population. This study characterizes somatic mutations (SNVs and Indels) found in the DNA of eight NSCLC actionable genes (ALK, BRAF, EGFR, ERRB2, KRAS, MET, RET and ROS1) and describe a novel set of potentially actionable mutations, in 1890 NSCLC patients from Chile, Brazil and Peru.

Methods: DNA from NSCLC tumors, collected at the time of diagnosis in Chile, Brazil and Peru, were sequenced using a NGS panel (Oncomine Focus assay). After a stringiest quality control and variants filtering step, mutations (SNVs and Indels) were annotated using the Variant Effect Predictor, COSMIC, the Oncomine Variant Annotator (OVA), OncoKB, the Cancer Genome Interpreter and CancerVar to categorize somatic mutations.

Results: In the eight actionable genes a total of 1117 somatic DNA mutations were found. 46% (517/1117) of them corresponds to variants already described in COSMIC and/or OVA. 21% (239/1117) variants are present in OncoKB, including, as expected, well characterized and known driver actionable mutations. 44% (491/1117) are novel mutations, at the time databases were interrogated. Among those, 34% (167/491) are predicted passenger mutations by all the algorithms utilized and 66% (327/491) mutations are considered potentially driver mutations by one or more algorithms. Among these, 23% (74/327) are predicted high confidence novel driver variants by all algorithms. ALK (23%) and ROS1 (23%) account for most of these variants, followed by ERBB2 (14%), EGFR (11%), RET (11%), BRAF (8%), MET (7%) and KRAS (3%).

Conclusions: The analysis of many Latin America subjects revealed a significant number of clinically actionable but also novel somatic mutations in cancer genes highlighting the importance of including less-represented populations in clinical trials and molecular studies.

Keywords: NSCLC, Latin America, Precision medicine

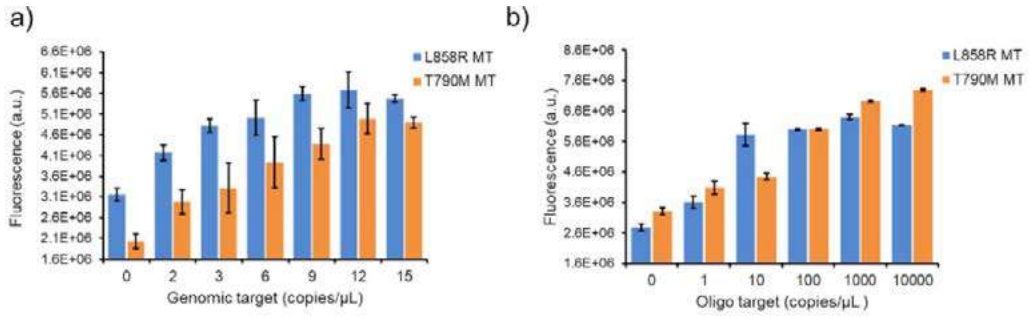

Figure 1. Sensitivity of assay for detection of L858R mutant (MT) and T790M mutant (MT) in plasma samples containing (a) genomic target and (b) oligo target.

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EP.06B.17 Detection of EGFR Mutations T790M and L858R for Therapeutic Guidance of NSCLC

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Introduction: A common occurrence in most non-small cell lung cancer (NSCLC) patients that respond well to epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitor (TKI) therapy is that they eventually develop resistance to it. This resistance to EGFR-TKI therapies has been linked to the emergence of secondary EGFR mutations in exon 19, exon 20 (T790M), or exon 21 (L858R). Therefore, timely detection and characterization of EGFR mutations is critical for the prediction of response to EGFR-TKI, early identification of acquired resistance, and the subsequent implementation of personalized TKI therapy to ensure progression-free patient survival. Mutation monitoring in NSCLC patients is a significant challenge since tumor biopsy and surgery are invasive interventions that cannot be performed frequently and cannot account for tumor heterogeneity. As a result, up to 25% of patients fail to undergo proper EGFR assessment before receiving treatment.

Methods: To address these limitations in the current diagnostics and therapeutic guidance, Giner, Inc. has developed a highly specific assay that analyses circulating tumor DNA (ctDNA) in patient plasma to check for EGFR-based genomic alterations. The strong, established correlation between mutations detected in blood plasma ctDNA and mutations in tumor tissue makes liquid biopsy an ideal non-invasive alternative for the assessment of molecular aberrations and resistance to therapy. However, specific detection of ctDNA is extremely challenging since they exist at trace concentrations and are vastly outnumbered by other cell-free DNAs. Giner, Inc. has developed an integrated detection method for rapid, sensitive, and selective detection of single-base mutations in the EGFR genes T790M and L858R.

Results: Giner's PCR-enhanced ligation assay provides genomic DNA sensitivity down to 2 copies/μL (Figure 1) which corresponds to mutation allele frequency (MAF) levels of 0.01% (data not shown). This addresses the clinical sensitivity requirement and is 10 times more sensitive than the current standard digital droplet PCR (ddPCR) which has a limit of 0.1% for MAF.

Conclusions: Ongoing work aims to adapt the assay for multiplexed ctDNA detection, validate it with patient plasma samples, and integrate it into a prototype, thus achieving a significant milestone toward regulatory evaluation. Fully developed, this technology will facilitate the enactment of personalized therapy, improve treatment outcomes, and offer significant advantages over existing methods such as lower test cost, easier sample preparation, and faster sample-to-result turnaround.

Keywords: NSCLC, EGFR mutation, ctDNA detection

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EP.06B.18 Biomarker Landscape of Antibody-Drug Conjugates and Bispecific Antibodies in Clinical Trials for Lung Cancer

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Introduction: Despite the rapid advances in immunotherapy and targeted therapy, lung cancer remains the leading cause of cancer-related fatalities globally. The emergence of antibody-based therapeutics such as antibody-drug conjugates (ADCs) and bispecific antibodies (BsAbs) has sparked significant interest due to their promise in improving patient outcomes. While these therapies are designed to target tumor-associated antigens, there is a notable absence of biomarker-driven approaches in their development. We aim to explore the frequency and prevalence of biomarker-guided approaches in the ongoing clinical development of antibody-based therapies.

Methods: We surveyed clinical trials listed on clinicaltrials.gov for "non-small cell lung cancer" and "small cell lung cancer," specifically examining interventions involving "antibody-drug conjugates" or "bispecific" therapies. With a cutoff date of February 1st, 2024, the study focused solely on trials that were actively recruiting or not yet recruiting, excluding those that had been completed. For each trial, we gathered data on the phase of the trial, cancer stage, treatment line, drug target, linker-payload profiles (for ADCs), inclusion of, and method for target biomarker testing for patient selection. Utilizing descriptive statistics, we analyzed the collected information.

Results: Of the 95 clinical trials screened, 47 were included based on the specified criteria. Phase 1 trials comprised 34.04% (n=16) of the total, while combined Phase 1 or 2 trials represented 40.04% (n=19). Phase 2 trials accounted for 19.14% (n=9), and Phase 3 trials comprised 6.38% (n=3). The majority of trials targeted advanced stages of cancer, encompassing 95.7% (n=45), and predominantly investigated investigational therapies in second-line settings or beyond (85.1%, n=40). When considering drug categories, BsAbs took precedence, being the focus of 68.1% (n=32) of trials, while ADCs were involved in 31.9% (n=15) of trials. In terms of biomarker inclusion criteria, 44.7% (n=21) of trials incorporated this strategy, indicating a commitment to personalized medicine strategy, while 55.3% (n=26) did not. Among trials with biomarker selection, the majority utilized NGS-based genomic subsets (59.1%), while only 40.9% studied antigen expression through immunohistochemistry. The most common drug targets for BsAbs were EGFR x c-MET (28.1 %, n = 9 of 32) and PD-1 x CTLA-4 (9.4%, n = 3 of 32), whereas for ADCs, they were TROP2 (33.3%, n = 5 of 15) and HER2 (20%, n = 3 of 15). The payloads utilized most frequently among ADCs were monomethyl auristatin E (MMAE) (40%, n = 6), followed by topoisomerase 1 inhibitor payload (26.6%, n = 4).

Conclusions: Our study highlights the utilization of antibody-based therapies in lung cancer treatment, revealing a trend toward incorporating biomarker-guided approaches that are still evolving. Alongside retrospective biomarker exploratory analysis, future trials should prioritize the integration of prospective biomarker strategies for a more comprehensive understanding and implementation of personalized treatment approaches.

Keywords: Biomarker, Lung Cancer, Clinical trial

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EP.06B.19 WNT/ß-Catenin Signalling Pathway in Non-Small Cell Lung Cancer: Study of Immuno-expression GSK-3ß, ß-Catenin, And CD44.

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Introduction: This study aimed to assess the role of the WNT/β-catenin signaling pathway in non-small cell lung cancer (NSCLC) and the association of GSK-3β, β-catenin, and CD44 with the clinicopathological profiles of NSCLC in the Indonesian population. GSK-3 β-β-catenin, and CD44 immuno-expression are expected to be markers for predicting response to platinum-based chemotherapy and have the potential to be target therapies in advanced-stage NSCLC patients.

Methods: This is an observational study. We retrospectively collected data on every patient diagnosed with advanced-stage (stage III-IV) adenocarcinoma (EGFR-wild type) and squamous cell carcinoma (SCC). Patients received platinum-based chemotherapy for three cycles between January 2018 and July 2023 from six hospitals in Indonesia. Patients with complete medical records and sufficient tissue samples were included. Subsequently, we stained the paraffin blocks with three immunohistochemistry antibodies. Positive GSK-β expression was identified in the cytoplasm, β-catenin in the nucleus, and CD44 in the membrane of the tumor cells. Immunohistochemistry staining was evaluated using an H-score by two pathologists who were blinded to the study. We analyzed the staining results along with clinicopathological factors, including RECIST status. RECIST statuses were classified as follows: Complete response, partial response, and stable disease were grouped into good outcomes, while progressive disease was categorized as a poor outcome.

Results: Out of 62 NSCLC patients, 53.2% were under 60 years old, 79% were male patients, 75.8% were at stage IV, 80.6% had an adenocarcinoma subtype, and 40.3% had progressive disease. There was a significant association between GSK-3β and clinicopathological factors. GSK-3β was expressed higher in subjects with male gender (p = 0.033), stage III (p = 0.031), and SCC subtype (p = 0.015). β-catenin and CD44 expression were higher in stage III. GSK-3 β expression was higher in subjects with a poor response, and β-catenin and CD44 expression were lower in subjects with a poor response, but this was not statistically significant.

Conclusions: The WNT/ β-catenin signalling pathway has a specific role in lung cancer. This study provides valuable insights for disease understanding in NSCLC.

Correlation between Clinical and Histopathological Characteristics and Biological Marker Expression

Keywords: GSK-3β, non-small cell lung cancer, WNT/β-Catenin Signalling

	GSK-3β	β-Catenin	CD44
	p-value	p-value	p-value
Age	0.832	0.631	0.667
Sex	0.033	0.802	0.938
Stage	0.031	0.537	0.588
Subtype	0.015	0.387	0.109
Treatment response	0.590	0.304	0.126

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EP.06B.20 Prognostic Impact of Nectin-like Molecule-5 (CD155) Expression in Non-Small Cell Lung Cancer

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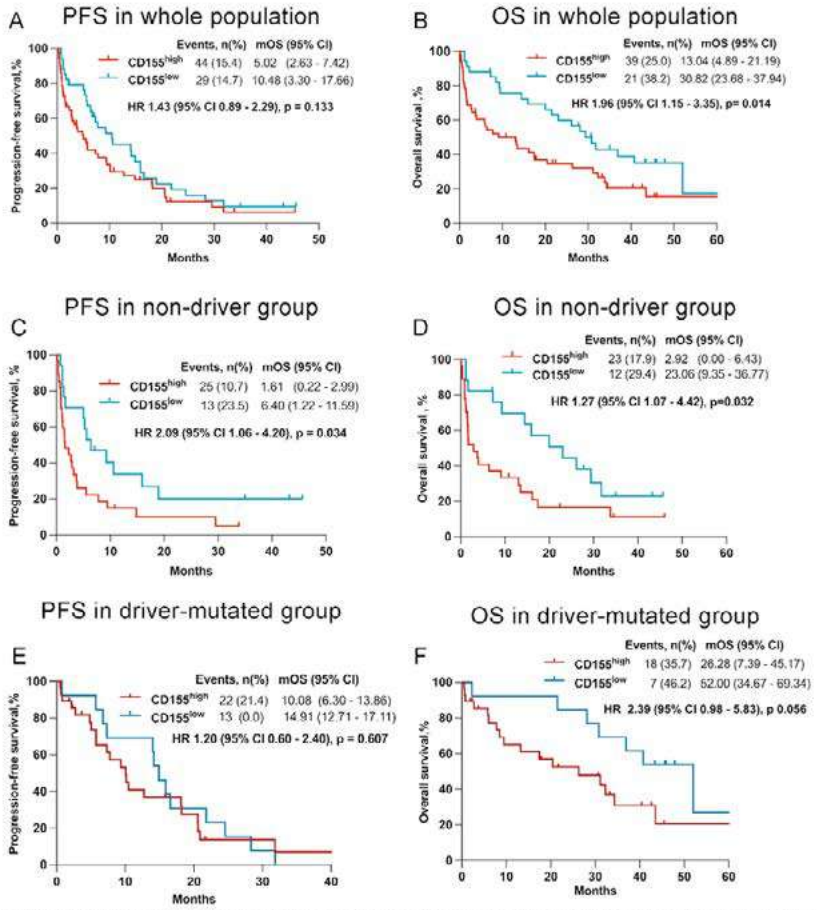
Introduction: CD155, a transmembrane protein which inhibits antitumor immune responses, has been shown to be a predictor of worse clinical outcomes in non-small-cell lung cancer (NSCLC). However, its association with the prognosis, clinical and genomic characteristics of Latin American patients remains unexplored. Thus, this study characterizes CD155 expression in NSCLC.

Methods: Tissue biopsies from 86 consecutive Latin American patients with locally advanced or metastatic NSCLC were assessed for CD155 protein expression, ALK rearrangements and EGFR mutations. Optimal cutoff values for CD155 expression were determined from receiver operating characteristic (ROC) curves according to the 2-year survival of patients with driver and non-driver mutations. Its association with clinicopathological features, median progression-free survival (mPFS), and median overall survival (mOS) was evaluated.

Results: The cutoff for high CD155 expression (CD155high) was 155 in the entire cohort and in patients without driver mutations, and 110 in patients with driver mutations. CD155 was detected in 84 patients (97.7%), more frequently (52.3%) and at higher levels (62.2%) in patients without driver mutations. EGFR L858R mutation was associated with lower CD155 expression than exon 19 deletion. CD155high patients had a significantly shorter mOS (13.0 vs 30.8 months; HR: 1.96 [95% CI, 1.15-3.35]; p=0.014). Among patients without driver mutations, CD155high was related to significantly shorter mPFS (1.61 vs 6.40 months; HR: 2.04 [95% CI, 1.03-4.02]; p = 0.034) and mOS (2.92 vs 23.06 months; HR: 2.17 [95% CI, 1.07-4.42]; p=0.032). In patients with driver mutations, CD155high was only borderline significant for shorter mOS (26.3 vs 52.0 months, HR: 2.39 [95% CI, 0.98-5.83];p=0.056).

Conclusions: CD155high is a predictor of worse survival outcomes in patients with advanced NSCLC, predominantly among those without onco-driver mutations. CD155 could be a potential biomarker and a molecular target in patients with poor responses to current therapies.

Keywords: nectin-like molecule-5, immune checkpoints, Non-Small Cell lung cancer



Prognostic significance of high CD155 expression on progression-free survival and overall survival of the whole cohort (A-B), group without driver mutations (C-D) and subset with driver mutations (E-F). CD155, Cluster of Differentiation 155. HR, hazard ratio. mOS, median overall survival. mPFS, median progression-free survival. CI, confidence interval. PFS was calculated from diagnosis to progression to first-line treatment. OS was determined by the period between diagnosis and death for any cause. Log-rank test was performed to determine statistical differences between Kaplan-Meyer curves as always as p values were less than 0.

EP.06C PATHOLOGY AND BIOMARKERS - COHORT
SATURDAY, SEPTEMBER 7, 2024 - 11:58 - 11:59

EP.06C.01 KRAS Q61H Mutation Defines a Distinct Clinicopathological Entity of Lung Adenocarcinomas in East Asian Patients

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Introduction: KRAS mutations play an important role in the pathogenesis of lung adenocarcinoma, occurring in 20-35% of cases in the Western population. However, the incidence of KRAS mutations in East Asian patients is lower, and the clinicopathologic characteristics of KRAS-mutant lung adenocarcinoma have not been well studied.

Methods: Among a total of 1364 non-small cell lung cancer patients that underwent broad-panel targeted next-generation sequencing, the clinicopathologic and molecular characteristics of a total of 176 invasive lung adenocarcinomas (non-mucinous type n=122; mucinous type n=54) harboring oncogenic KRAS mutations were investigated.

Results: Patients harboring the KRAS Q61H mutation were identified in 10.2% (18/176) of cases. The presence of the Q61H mutation was significantly associated with worse overall survival in multivariate analysis compared to other variants (p=0.017). It was also associated with shorter progression-free survival in patients treated with first-line chemo-immunotherapy (p=0.007). KRAS Q61H mutations frequently co-occurred with STK11 mutations (p=0.023) and were associated with lower PD-L1 expression (p=0.003). Histologically, Q61H mutations were predominantly found in the non-mucinous subtype (p=0.037).

Conclusions: The KRAS Q61H mutation defines a distinct clinicopathological class of lung adenocarcinomas in East Asian patients, especially associated with worse prognosis.

Keywords: lung adenocarcinoma, KRAS Q61H, poor prognosis

EP.06C PATHOLOGY AND BIOMARKERS - COHORT
SATURDAY, SEPTEMBER 7, 2024 - 11:58 - 11:59

EP.06C.02 Clinical Features and Survival Outcome of Lung Invasive Mucinous Adenocarcinoma: A Real-World Analysis of 387,197 Patients

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Introduction: Pulmonary invasive mucinous adenocarcinoma (IMA) is known for its unique characteristics compared to non-IMA. In this study, we investigate clinical outcomes and prognostic factors from the Surveillance, Epidemiology, and End Results (SEER) database.

Methods: The clinical information of patients with IMA and non-IMA was extracted from SEER 17 registries from 2000 to 2020. The Kaplan-Meier was used to compare the differences in overall survival (OS). Univariate and multivariate Cox-proportional hazard regression analyses were further performed to investigate the independent prognostic factors for OS.

Results: A total of 387,197 patients diagnosed with IMA (4.0%, n=14,453) or non-IMA (96.0%, n=372,744) were included in the study. The IMA group demonstrated a higher rate in female group (p<0.001) and bilateral parenchymal involvement (p<0.001), while showing lower rate of nodal involvement (p<0.001) and distant metastasis (p<0.001). The IMA group presented a favorable a 5-year OS than non-IMA (31.7% vs 23.5%, p<0.001). In contrast, the distant SEER stage of IMA exhibited worse outcome (p<0.001, Figure.1). In multivariate Cox analysis for OS, both tumor types had similar risk factors such as age, sex, SEER stage, chemotherapy and radiation (Table 1). Notably, while both groups demonstrated a favorable outcome following chemotherapy, the effect was less in IMA than in non-IMA (HR: 0.782 [0.736-0.823] vs 0.571 [0.561-0.572], p<0.001).

Conclusions: Overall, IMA showed better clinical outcome compared to non-IMA from SEER database analysis. However, IMA with advanced stage exhibited opposite results. IMA seemed to derive less benefit from chemotherapy than non-IMA.

Keywords: Pulmonary Invasive Mucinous Adenocarcinoma (IMA), Independent prognostic factors, the Surveillance, Epidemiology, and End Results

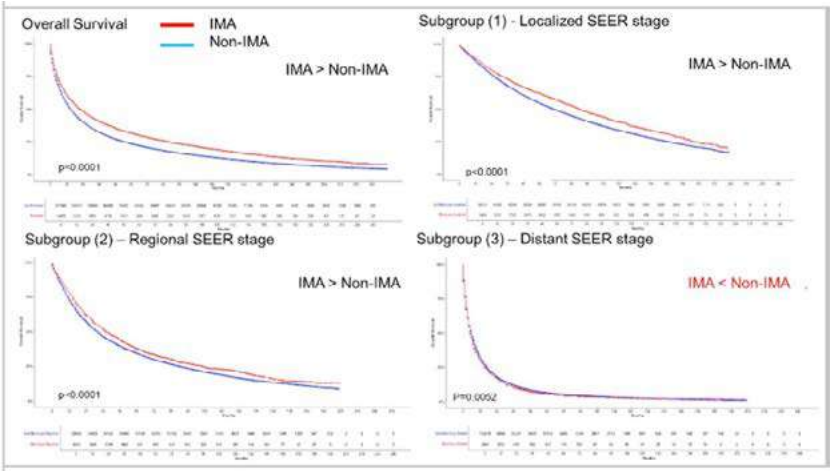

Table 1. **Multivariate risk factor analysis for overall survival according to tumor types**

Clinical Variables		IMA		Non-IMA	
		HR (95% CI)	p-value	HR (95% CI)	p-value
Age	<60				
	60-69	1.281 (1.191-1.372)	<0.001	1.092 (1.076-1.104)	<0.001
	70-79	1.521 (1.413-1.624)	<0.001	1.252 (1.238-1.272)	<0.001
	>80	1.771 (1.628-1.913)	<0.001	1.451 (1.431-1.474)	<0.001
Sex	Male	Ref			
	Female	0.792 (0.757-0.832)	<0.001	0.782 (0.769-0.783)	<0.001
Race	White	Ref			
	Black	1.052 (0.970-1.136)	<0.001	1.022 (1.006-1.035)	<0.001
	Other	0.722 (0.651-0.787)	<0.001	0.742 (0.732-0.756(	<0.001
SEER Stage	Localized	Ref			
	Regional	1.841 (1.719-1.979)	<0.001	1.962 (1.932-1.988)	<0.001
	Distant	4.062 (3.774-4.372)	<0.001	3.921 (3.862-3.974)	<0.001
Chemotherapy	No	Ref			
	Yes	0.782 (0.736-0.823)	<0.001	0.571 (0.561-0.572)	<0.001
Surgery	No	Ref			
	Yes	0.362 (0.337-0.384)	<0.001	0.362 (0.354-0.364)	<0.001
Radiation	No	Ref			
	Yes	1.132 (1.042-1.236)	0.004	0.951 (0.933-0.961)	<0.001

IMA, invasive mucinous adenocarcinoma; non-IMA, invasive non-mucinous adenocarcinoma

EP.06C PATHOLOGY AND BIOMARKERS - COHORT
SATURDAY, SEPTEMBER 7, 2024 - 11:58 - 11:59

EP.06C.03 Clinicopathological Analysis of Each EGFR Status in Surgically Resected Lung Adenocarcinoma: A Real-World Study (CReGYT-01 EGFR)

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Introduction: Biological characteristics of each epidermal growth factor receptor (EGFR) mutational subtype is suggested to be different from one another. However, the correlation between EGFR mutational subtypes and histological predominance of lung adenocarcinoma using the recently-launched International Association for the Study of Lung Cancer (IASLC) grading system remains uncertain. This study aimed to clarify the clinicopathological characteristics of each EGFR subtype in surgically resected lung adenocarcinoma.

Methods: This is a retrospective multicentre study conducted by 21 institutions in Japan from January 2015 to December 2018. Among 4181 patients with lung adenocarcinoma, we enrolled 2248 patients who underwent complete anatomical radical resection and confirmed EGFR mutational status and histological predominant subtype. We collected clinicopathological characteristics including age, gender, smoking history, performance status (PS), presence of ground glass opacity (GGO), consolidation tumor ratio (CTR), predominant subtype, IASLC grade, pN status, ly, v, pl, spread through air spaces (STAS), pathological invasiveness and compared them between wild type vs. all EGFR mutations, L858R vs. 19del, common vs uncommon mutations, and 20ins vs. common mutations (L8585R or 19del).

Results: One-thousand-seventy-nine cases had EGFR mutation (48%). Among them, 518, 428, and 133 cases harbored L858R, 19del, uncommon EGFR mutations, respectively. In uncommon mutations, 20ins (n = 42, 4 %) was the most frequent, followed by G719X (n = 26, 2 %) and L861Q (n = 25, 2 %). Tumors harboring EGFR mutation had less pathological invasiveness ($p < 0.001$) including lymph node metastasis ($p = 0.004$.), ly ($p = 0.020$), v ($p < 0.001$), and pl ($p = 0.002$) than those harboring wild type. L858R mutations were more frequent in GGO, lepidic predominant, and IASLC grade 1 than 19del mutations. There were no clinicopathological differences between common and uncommon EGFR mutations except that ever smoker are more frequent in patients with uncommon mutations compared to common mutations. In comparisons of 20ins vs. L858R and 20ins vs 19del, no statistically significant differences were observed, however, tumors with 20ins were found to have worse PS than each common mutation.

Conclusions: Clinicopathological difference in each subtype of EGFR was revealed. Tumors with L858R had less pathological invasiveness and higher prevalence of IASLC grade 1 than those with 19del. No statistical difference were observed in pathological features between common mutations and uncommon mutations nor 20ins and each common mutation.

Keywords: lung adenocarcinoma, EGFR, clinicopathological characteristics

EP.06C PATHOLOGY AND BIOMARKERS - COHORT
SATURDAY, SEPTEMBER 7, 2024 - 11:58 - 11:59

EP.06C.04 Impact of TP53/EGFR Mutations in Advanced-Stage NSCLC: LATAM Population

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Introduction: NSCLC is one of the most frequent mortality cause worldwide. Nowadays its treatment it's strong correlated with driver mutation and the inmune environment. Despite well known driver mutations, not all patients achieve the same response when we expose them to the same treatment, this observation guide us to find other nondriver mutation that potentially could affect the response and have an impact in the overall survival finally. One of this mutation is TP53 who plays a crucial role in cell cycle and tumorigenesis, EGFR is a common mutation in Latam, its incidence could be as high as 40% depending of the region. However, there is a lack of information about the behavior of this alteration in our population. The aim of our study is to determined if the double mutation of tp53 and EGFR has an impact in our population.

Methods: The study retrospectively reviewed 462 Latin patients with advanced lung cancer from 2 oncological centers: Clinica Aliada (Peru), and Instituto Nacional de Cancerologia - INCA (Mexico) from January 2015 to December 2022. The exclusion criteria were as follows: loss to follow-up (n = 37), and absence of detailed NGS information (n = 33). Finally, a total of 356 patients with wild-type TP53 or mutant TP53 reported on NGS panels met the inclusion criteria in the present study and just 90 patients of those have EGFR mutation. The study was reviewed and approved by the Ethics Committee of each department.

Results: Patient characteristics 63.8% were female, median age was 58 (range 27-88), majority were smokers (53.9%). TP53 mutated in 62.9%, PD-L1 expression: 50.6% negative, 38% positive, 11.2% undetermined. EGFR: most frequent alteration was deletion 19 (52.2%), followed by L858R (21.1%) and insertion 20 (9%) Median number of co-mutations was 3 (range 1-12). 90% of the total patients received treatment, of those the response rate (RR) was 57.8%. The overall survival (OS) for the whole group was 38.5 moths (CI 95%) for the TP53 mutated was only 28.7 m vs 57.18 for the wild type group ($p < 0.005$). There was no difference accordance tu PD l1 expression. The PFS media for the whole group was 14.7 months (CI: 95%), we found no difference between the mutated (12.8m) and wild type group (17.2) ($p = 0.5$). No significant difference in PFS based on PD-L1 expression ($p = 0.5$).

Conclusions: TP53 was the most frequent mutation associate with EGFR in LATAM population. There is a significant impact in OS for those with TP53 but not in PFS.PD-L1 expression does not seem to be a significant predictor of survival or progression-free survival in this group.

Keywords: EGFR, TP53, latam

EP.06C PATHOLOGY AND BIOMARKERS - COHORT
SATURDAY, SEPTEMBER 7, 2024 - 11:58 - 11:59

EP.06C.05 Impact of TP53 Mutation in Advanced NSCLC in LATAM

T. Runciman[1], C. Carracedo[1], O. Arrieta[2], G. Cruz-Rico[2], [1]Clinica Aliada, Lima/PE ,[2]INCAN, Ciudad de Mexico/MX

Introduction: A frequent mutation found in patients with lung cancer is TP53.Due to the diversity of molecular patterns in Latin American, it is important to determine if the presence of the TP53 mutation has any impact on the overall survival.

Methods: The study retrospectively reviewed 462 patients with advanced lung cancer from 2 oncological centers: Clinica Aliada (Peru), and INCAN (Mexico) from Jan 2015 to Dec 2022. 356 met the inclusion criteria. Statistical analyses were performed using Stata v.17.0. All tests were two-sided, and p-values less than 0.05 were considered statistically significant.

Results: The median follow-up was 5 y, 154 patients died during this period . A total of 149 patients (41.7%) carried TP53 mutations. Among this group, most of the patients were male (63.7 %).The majority had a driver mutation (81.3%). The majority have more than 4 molecular alterations detected beside TP53 (64.7% vs 35.3%, p<0.001).There were 214 patients where TMB could be evaluated, of these 88.8 % had an expression < or equal to 8Mb, having an expression of the TP53 mutation in 39.5% of the cases. In those with a TMB >8Mb, 70.8% had the TP53 mutation.According with PD-L1 and tp53 we did not find any difference.TP53 mutation was present in 149 patients (41.7%), the majority were missense mutations (93). The most frequent missense mutations were on exon 6 (n=29), followed by exon 4 and 8 . As for nonsense mutation, exon 5 was the most frequent (n=21). TP53 mutation was strongly related to the EGFR mutation, found in up to 69% of the total of this group.According to TP53 status, we found a median of 21.5 months for the group with mutant - TP53 and 46.5 months for the w-TP53 group (p<0.001) (Fig. 2A). The mortality HR of the TP53 mutation was 2.01 times the mortality HR of wild type (HR: 2.01; 95% CI: 1.44 - 2.81; p-value <0.001). Those who presented an increased number of mutations had worse OS: 0-1 vs 2-3 (HR: 2.02, CI 95% 1.27-3.2, P: 0.003) vs 4-11 (HR: 2.45, CI 95% 1.51- 3.97, P< 0.001). According to driver mutations, those with EGFR and KRAS had a worse OS if they had tp53 mutated. Since EGFR was the most frequent driver mutation, we also analyzed the OS in these patients finding a worse OS (20.5m vs NR) in patients with tp53 mutated, no difference was found according deletion exon 19 or other type of EGFR mutation. For the KRAS mutation, a detrimental of 9 months in OS was found (33.5 vs 24.5m). PFS For the tp53 wild-type, was 38 m vs NR in the mutant group.We did not find any difference according to tp53 mutational status and EGFR mutation, however, it was only 19 moths for those who have exon-19 deletion vs NR in other EGFR alterations.

Conclusions: TP53 mutant was associated with a worse prognostic in the general population but especially in EGFR mutation with a higher prevalence in contrast with other populations.

Keywords: tp53, Latam, NSCLC

EP.06C PATHOLOGY AND BIOMARKERS - COHORT
SATURDAY, SEPTEMBER 7, 2024 - 11:58 - 11:59

EP.06C.06 Outcome and Clinical Profile of Common and Uncommon EGFR Mutations in NSCLC: Retrospective Analysis from an Argentinean Cancer Center

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Introduction: The subtype of EGFR mutation is the strongest predictive biomarker to TKI response in patients with non-small cell lung cancer (NSCLC). The heterogeneity of these mutations and their association with different clinical and prognostic characteristics still remain an active area of research.

Methods: A retrospective analysis was conducted on patients with EGFR mutations, evaluating their clinical characteristics, specific EGFR mutations, and treatment outcome as an update of previous reported data from our population (JTO 2017, 12 S492, Abst P1.02-010).

Results: Between 2015 and 2023, we identified 484 metastatic NSCLC who had successful analysis for EGFR exons 18-21 mutations by PCR tests. A total of 91 patients (19%) had EGFR mutations. Exon 19 deletions and L858R mutation in exon 21 were detected in 51% (47/91) and 30% (27/91), respectively. Uncommon EGFR mutations were detected in 19% (17/90) of cases; exon 18 G719X was the most prevalent 14% (13/90), followed by Exon 20 INS (2%), L861Q (2%) and S7681 (1%). The median age of the whole group was 64 years (range: 34-85 years), with a female predominance (69%) in patients with common mutations and a male predominance (64%) in those with uncommon mutations. The median PFS to first line treatment was 11 months and 6.2 months for common and uncommon mutations respectively and OS was 28.4 months and 11.3 months, respectively. In multivariate analysis, male sex (HR = 2.35, 95% CI: 1.21-4.57, p = 0.01) and uncommon EGFR mutations (HR = 2.14, 95% CI: 0.97-4.73, p = 0.05) were associated with poor prognosis. Patients with uncommon EGFR mutations had a significantly higher prevalence of ever-smokers (88% vs. 24%, p = 0.001) and more synchronous central nervous system (CNS) metastases compared to those with common mutations (33% vs. 4.5%, p = 0.039).

Conclusions: Our population showed a positive correlation between smoking status and uncommon EGFR mutations in patients with NSCLC as previously described. The poorer survival observed in patients with uncommon mutations and higher incidence of synchronous CNS metastases underscores the need for and adequate diagnosis and personalized treatment strategies for this group

Keywords: EGFR mutation, Non-small cell lung cancer, Prognosis

EP.06C PATHOLOGY AND BIOMARKERS - COHORT
SATURDAY, SEPTEMBER 7, 2024 - 11:58 - 11:59

EP.06C.07 Impact of a Diagnostic Bronchoscopy Service with Embedded Reflex Molecular Testing within an Oncology Centre in Patients with Lung Cancer.

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Introduction: Oncologists require PD-L1 and molecular testing results to initiate treatment for patients with metastatic NSCLC. In the diagnostic journey, delays are introduced following the initial biopsy, as often the histopathology Lab awaits instructions for PD-L1 and molecular testing, whilst further delays are due to the time that the pulmonary physician takes to refer to the oncologist, and the delay in the oncologist to see the patient and to request molecular testing. Often these delays result in a TurnAround Time (TAT) in excess of 4 weeks, where optimal practice should be within 2 weeks. Other issues relate to the quality of the paraffin embedded tissue to allow RNA sequencing. For these reasons, the Bronchiomics study, with a diagnostic bronchoscopy service was set up in a tertiary Oncology center aiming to speed up the diagnostic pathway for patients with suspected Lung Cancer.

Methods: At bronchoscopy a fresh tissue sample was sent directly to a molecular Laboratory (Karaiskakio Foundation) accompanied by blood for liquid biopsy, whilst another sample was sent for histology to the Nicosia General Hospital (NGH), with instructions to undertake PD-L1 testing and NGS on paraffin embedded tissue once a diagnosis of LC was made. The study was enacted at the end of October 2023, and 36 patients with suspected lung cancer were enrolled between October 2023 and March 2024.

Results: 29 males and 7 female patients, median age 67 years were enrolled. Lung adenocarcinoma was diagnosed in 10 patients, squamous in 8 patients, SCLC in 5 patients, other types of cancer in 4, whilst 9 samples showed no cancer. The median time from bronchoscopy to histology result was 6 days, to PD-L1 result 11 days, to liquid bx result 7.5 days for the fast assay and 13 days for the comprehensive liquid panel, to NGS result from fresh tissue 17 days and NGS result from paraffin embedded tissue 14 days. For consecutively referred patients to the Oncology center between September and October 2023, prior to the initiation of the Bronchiomics study, median time from bx/bscopy to histology result was 5 days, to PD-L1 result 28.5 days, to fast liquid biopsy result 17.5 days, to comprehensive liquid NGS result 25.5 days and to solid tissue NGS result 36.5 days.

Conclusions: The Bronchiomics study and initiation of reflex testing decreased the median time from bx/bscopy to receipt of molecular results significantly and brought the TAT close to 2 weeks.

Keywords: molecular, testing, turnaround

Median time in days

	Bronchiomics Study	Prior to study
Bx to Histology	6	5
Bx to PD-L1	11	28,5
Bx to Fast Liquid	7.5	17.5
Bx to comp Liquid NGS	13	25.5
Bx to fresh tissue NGS	17	N/A
Bx to tissue NGS	14	36,5

EP.06C PATHOLOGY AND BIOMARKERS - COHORT
SATURDAY, SEPTEMBER 7, 2024 - 11:58 - 11:59

EP.06C.08 Presentations and Outcomes of Pulmonary Carcinosarcoma: Results of Comparing Pulmonary Carcinosarcoma and Primary Lung Sarcoma

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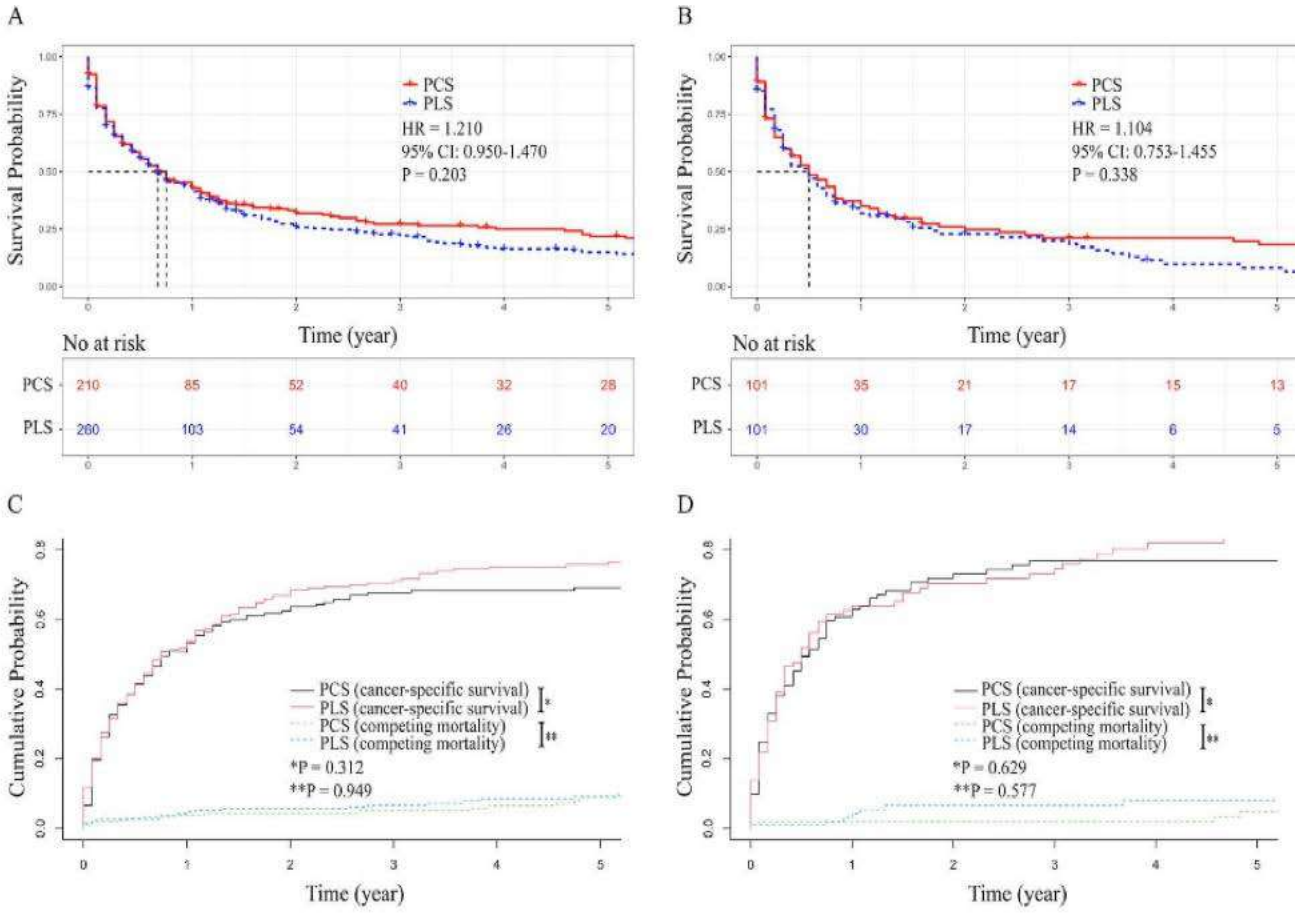
Introduction: We investigated the presentation and survival outcomes of pulmonary carcinosarcoma (PCS) with the purpose of obtaining a clearer picture of this rare disease.

Methods: Eligible PCS and primary lung sarcoma (PLS) cases were extracted from the Surveillance, Epidemiology, and End Results (SEER) database. A least absolute shrinkage and selection operator (LASSO) penalized Cox regression model was performed to identify prognostic indicators. Kaplan-Meier method with a log-rank test was used to compare overall survival (OS). Competing risk analysis with a Fine-Gray's test was used to analyze cancer-specific survival (CSS). Propensity score matching (PSM) was used to minimize selection bias.

Results: 210 PCS cases and 260 PLS cases were included in this study. Regarding PCS, the incidence was 0.05%, and poorly differentiated/undifferentiated tumors accounted for a large proportion of the entire cohort (51.0%). In contrast to PLS, more PCS cases were older and involved with lymph node metastasis. Receiving surgery, receiving chemotherapy and non-metastasis status were identified as favorable prognostic factors of PCS patients' survivals. The survival curves displayed that the OS and CSS of PCS patients nearly overlapped with those of PLS patients both before and after PSM (all P > 0.05).

Conclusions: PCS was a rare and aggressive tumor. PCS patients could benefit from surgical resection and chemotherapy. In addition, the survival rate of this disease was comparable to that of PLS.

Keywords: pulmonary carcinosarcoma, primary lung sarcoma, prognosis



EP.06D PATHOLOGY AND BIOMARKERS - CTDNA
SATURDAY, SEPTEMBER 7, 2024 - 11:58 - 11:59

EP.06D.01 Prognostic Evaluation by Using ctDNA in Patients with EGFR Mutated Resectable Lung Cancer

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Introduction: The detection of circulating Circulating tumor DNA (ctDNA) has been examined as a predictor of postoperative recurrence and survival in lung cancer patients.

Our research objective is investigating ctDNA detection and prognosis in EGFR mutated lung cancer.

Methods: We retrospectively examined patient background, EGFR mutation status, DFS, OS, and preoperative ctDNA in lung cancer patients who underwent surgery at Kanazawa University Hospital between January 2017 and May 2020, in whom preoperative chemotherapy was not administered. We extracted ctDNA from plasma (4ml) within 7 days before surgery using QIAamp Circulating Nucleic Acid Kid® (Qiagen). ctDNA from NSCLC patients with EGFR mutations (cobas EGFR Mutation Detection Kit) are analyzed by Digital Droplet PCR PrimePCR TM ddPCR TM Assay BIO-RAD.

Results: 285 patients were enrolled, and 93 patients were detected EGFR mutations in tissue. Plasma ctDNA was detected in 16 of 56 patients with tissue-confirmed L858R and in 7 of 32 patients with tissue-confirmed exon 19 deletions. 2-year DFS was 92.2% for ctDNA negative and 78.9% for ctDNA positive. In tissue EGFR mutated lung cancer patients, the patients who have ctDNA in plasma tested before surgery has shorter DFS compared with patients who without ctDNA in plasma.

Conclusions: In EGFR- mutated NSCLC, ctDNA positivity measured within a week before surgery correlated with shorter DFS and OS suggesting a good indication of adjuvant Osimertinib in this population.

EP.06D PATHOLOGY AND BIOMARKERS - CTDNA
SATURDAY, SEPTEMBER 7, 2024 - 11:58 - 11:59

EP.06D.02 Plasma-Derived Circulating Tumor DNA in Patients with Advanced EGFR-Positive Exon 20 NSCLC Treated With Osimertinib

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Introduction: Plasma-derived circulating tumor DNA (ctDNA) is promising in monitoring responses and detecting resistance mechanisms in non-small cell lung cancer (NSCLC). NSCLC patients with EGFR exon 20 mutations (EGFRex20+) treated with high-dose Osimertinib (160 mg) showed modest anti-tumor activity (28% confirmed response rate) and acceptable toxicity. In this pilot study we aim to identify molecular response and resistance mechanisms using ctDNA collected during treatment.

Methods: Twenty-five EGFRex20+, p.(T790M) negative, NSCLC patients with WHO PS 0-2, received high-dose Osimertinib QD until progression or unacceptable toxicity. Cell free DNA collected at baseline, six weeks (T6), and progression was analyzed with the next generation sequencing (NGS) based Guardant360 CDx (73 gene panel). Molecular profiles of samples at progression were compared with matched pretreatment (baseline) samples to find resistance mechanisms to Osimertinib. A secondary objective is whether changes in ctDNA levels of the EGFRex20+ variant, at T6 and progression, compared to baseline, are associated with progression.

Results: Baseline ctDNA was analyzed in twenty patients. EGFRex20+ variant concordance between tumor biopsy NGS and ctDNA was found in 13/20 patients (65%). Fourteen patients underwent ctDNA profiling at all timepoints. All patients in this subset had either partial response (responder, n=6) or stable disease (non-responder, n=8) according to RECIST 1.1. No statistical correlation was found between changing ctDNA levels and overall response to osimertinib treatment in this subset. 9/14 patients showed an EGFRex20+ variant decrease six weeks post-therapy initiation, of which eight patients showed a decrease of tumor shrinkage at the same time (median shrinkage of target lesions -20%, IQR -36% to -11,5%). Eight patients showed an increase of the EGFRex20+ variant at disease progression (either growth of tumor [n = 5, median increase of target lesions 36%, IQR 27% to 155%] or overall deterioration/growth of non-target lesions [n = 3]). Two patients lacked the EGFRex20+ variant in ctDNA at baseline, but this variant was observed upon disease progression. Variants potentially associated with treatment resistance were identified in several genes at progression in 11/18 patients (61%): SNV (n=14), insertion (n=2) and gene-fusion (n=1). We found three variants that were previously related with resistance: TP53 (n=2) and EGFR p(C797S) (n=1).

Conclusions: This pilot study using a unique cohort of EGFRex20+ NSCLC patients treated with high dose Osimertinib highlights the complexity of variant dynamics during treatment and disease progression, suggesting a potential link between changed levels of variants detected at progression. Potential resistance mechanisms were shown in 11/18 patients using ctDNA.

Keywords: ctDNA, EGFR exon 20, resistance

EP.06D PATHOLOGY AND BIOMARKERS - CTDNA
SATURDAY, SEPTEMBER 7, 2024 - 11:58 - 11:59

EP.06D.03 Concurrent Liquid and Tissue Biopsy from Same Laboratory Increases On-Label Alteration Detection with Faster Turnaround Time

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Introduction: Next generation sequencing (NGS) is necessary to identify targetable alterations in advanced stage non-small cell lung cancer (NSCLC). Liquid biopsy via circulating tumor DNA (ctDNA) has demonstrated high concordance to tissue biopsy in newly diagnosed NSCLC with a marked decrease in turnaround time (TAT). Recent guideline language supports combination liquid and tissue testing in either the concurrent or reflex setting. As such, we examined concurrent liquid and tissue testing trends in patients with NSCLC.

Methods: We queried the Guardant Health database (4/2022-11/2023) for advanced lung cancer samples with an ordered liquid (Guardant360®) and tissue biopsy (Guardant360 TissueNext®) to create two cohorts: 1. "liquid and tissue" - both biopsies collected within 6 months of each other and reported (N=1,200), and 2. "tissue NC" - liquid biopsy reported, but tissue not completed (NC) (N=2,389). Frequencies of on-label alterations and reasons for tissue NC were analyzed. TAT was quantified as the difference between date of sample received and reported and analyzed with an unpaired t-test.

Results: The liquid and tissue cohort identified an on-label alteration in 24% of patients via liquid biopsy and in 33% of patients via tissue, with a concordance >96% in all on-label alterations. Both assays demonstrated fast turnaround time (TAT), but liquid biopsy had a median of 8 fewer days than tissue (6 vs. 14 days) ($p<0.0001$). In the tissue NC cohort, liquid biopsy identified an on-label alteration in 26% of patients, also with a median TAT of 6 days. Reasons for tissue biopsy NC were listed for 31% of patients. The most common reason for tissue NC was quality not sufficient or not meeting internal requirements (QNS) (25.2%). QNS rates largely reduced over time, i.e. <19% after June 2023. Yet, liquid biopsy detected on-label alterations in 21% of patients with tissue QNS samples. Additionally, 2.1% of tissue NC samples were cancelled at the request of the clinician/patient, and liquid biopsy detected an on-label alteration in 24% of such samples.

Conclusions: In this dataset, concurrent liquid and tissue biopsy identified an on-label alteration in ~1/4 of patients with high concordance. Liquid biopsy demonstrated faster TAT than tissue. These data support the updated guideline language and demonstrate that concurrent testing captures the greatest number of on-label alterations with faster time to results, which is especially important given risk of tissue QNS. Additionally, there are other alterations detected by these assays that provide prognostic information and opportunities to enroll patients in clinical trials that may expand actionability of test results.

Keywords: Concurrent Testing, Liquid Biopsy, On-Label Alterations

EP.06D PATHOLOGY AND BIOMARKERS - CTDNA
SATURDAY, SEPTEMBER 7, 2024 - 11:58 - 11:59

EP.06D.04 Prognostic Value of Variant Allele Frequency in Circulating Tumor DNA for Survival Outcomes in Metastatic Non-Small Cell Lung Cancer

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Introduction: Through the analysis of plasma circulating tumor DNA (ctDNA), liquid biopsy has emerged as a non-invasive method of identifying tumor-derived somatic mutations, serving as an adjunct to tissue genotyping. Variant allele frequency (VAF) of ctDNA is a measure of the proportion of ctDNA molecules harboring specific tumor-derived mutations within a genetic locus. This study focuses on the prognostic potential of ctDNA VAF to predict survival outcomes in patients with metastatic non-small cell lung cancer (NSCLC). By examining the association between ctDNA VAF levels and patient survival, we aim to assess the utility of ctDNA VAF as a non-invasive prognostic biomarker in metastatic NSCLC.

Methods: Our retrospective study included patients at a single center who underwent liquid biopsies using the Guardant360 platform between January 2018 and March 2024. Eligible patients were those with confirmed non-small cell lung cancer (NSCLC) via tissue biopsy and metastatic disease identified on imaging. We collected demographic data, including age at diagnosis, race, ethnicity, smoking status, the presence of brain metastasis at diagnosis, and histologic sub-type. Analysis of ctDNA VAF was done utilizing Guardant360 liquid biopsy reports. Alterations with a VAF greater than 40% were excluded to omit potential germline mutations, focusing instead on somatic mutations. For each individual patient, we added the VAF of each somatic mutation to obtain the total VAF in that particular patient. Patients were then stratified into two separate groups based on total VAF levels, defined as either high (≥1%) or low (<1%) total VAF. Overall survival (OS) data were subsequently gathered. To assess survival outcomes, we employed Kaplan-Meier curves and Cox proportional hazards models, adjusting for relevant covariates.

Results: Our analysis included 293 patients, of whom 214 had a reported VAF, revealing 62 (28.9%) patients with a low VAF (mean VAF of 0.4%) and 152 (71.03%) with a high VAF (mean VAF of 16.5%). Demographic comparisons between the two groups showed no significant imbalance between either group. We observed a statistically significant difference in OS rates. Patients with a high VAF (n=74) exhibited a median OS of 5.16 months, whereas those with a low VAF (n=24) demonstrated a more favorable median OS of 10.25 months (p-value < 0.01). Adjusting for variables such as smoking history, brain metastasis presence, and cancer histology through the Cox proportional hazards model revealed a lower hazard ratio for death in patients with a low VAF (HR: 0.485, 95% CI: 0.289 to 0.814, p<0.01). A subsequent sub-analysis, which included only patients who received systemic therapy, immunotherapy, or targeted therapy, reaffirmed these findings, with median OS rates of 9.0 months for high VAF and 10.5 months for low VAF patients (p-value = 0.02).

Conclusions: Our study demonstrates an association between high VAF level in ctDNA and shorter OS among patients with metastatic NSCLC. Our findings highlight the potential role for utilizing ctDNA VAF as a prognostic biomarker. Further studies are needed to assess the benefit of integrating analysis of ctDNA VAF into clinical practice to better predict patient outcomes and tailor treatment plans.

Keywords: ctDNA, biomarker, NSCLC

EP.06D PATHOLOGY AND BIOMARKERS - CTDNA
SATURDAY, SEPTEMBER 7, 2024 - 11:58 - 11:59

EP.06D.05 The Prognostic Role of the Dynamic Changes in the Plasma ctDNA Levels in Advanced NSCLC after IO Initiation: A Meta-Analysis

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Introduction: Studying the dynamic changes in ctDNA concentrations via liquid biopsy in the peripheral blood of patients with advanced NSCLC receiving immunotherapy constitutes a new and highly promising biomarker. Unfortunately, the primary research in that field is plagued by methodological variability, thus limiting its capability of producing solid conclusions. The current study stands as a systematic review and meta-analysis of the present-day literature, aspiring to elucidate the prognostic importance of the longitudinal kinetics of the ctDNA concentration in the peripheral blood of patients with advanced NSCLC shortly after immunotherapy initiation.

Methods: A systematic review of the current literature (written in English) was performed via certified and international databases (PUBMED, Scopus, Web of Science, Cochrane Library, ClinicalTrials.gov) until September 2023. The Hazard Ratio (HR) from articles (approved based on pre-specified criteria) was recorded and used to assess the correlation between the reduction in ctDNA concentration with median disease-free survival (mDFS) and the median overall survival (mOS, primary endpoint) and the median disease-free survival (mDFS, secondary endpoint) in patients with advanced NSCLC receiving immunotherapy.

Results: 17 studies with 1437 patients were selected. Reduced concentration of ctDNA three to twelve weeks after immunotherapy initiation was positively correlated with a statistically significant improvement in the median OS [Hedges q = 0,32, OR = 1.79 - 95% CI (1.39 - 2.26), p < 0.001] and the median DFS [Hedges q = 0,26, OR = 1.60 - 95% CI (1.24 - 2.10), p < 0.001]. Further statistical analysis, performed in the patients' subgroup that completely eradicated ctDNA levels from peripheral blood, showcased a similar statistically significant benefit in the mOS [Hedges q = 0.26, OR = 1.60 - 95% CI (1.04 - 2.43), p = 0.03], and a (non-statistically significant) benefit in the mDFS [Hedges q = 0,31, OR = 1.76 - 95% CI (1.27 - 3.97), p = 0,17]. Absence of consensus regarding the precise cut-off values for properly defining the ctDNA concentration reduction (complete vs. partial reduction, different accepted percentage changes in the case of partial reduction) was noted.

Conclusions: The longitudinal study of ctDNA concentration in the peripheral blood of patients with advanced NSCLC receiving immunotherapy can provide valuable prognostic information. However, conducting prospective multicentre studies with strict methodological planning and joint consensus on any possible grey areas is required for this biomarker to become a clinical reality.

Keywords: ctDNA, NSCLC, Biomarker

EP.06E PATHOLOGY AND BIOMARKERS - IO
SATURDAY, SEPTEMBER 7, 2024 - 11:58 - 11:59

EP.06E.01 Preexisting CD153+CD4+ T Cells Cause Lung Specific Toxicity via Type 3 Immunity without Kidnapping Efficacy in Immunotherapy

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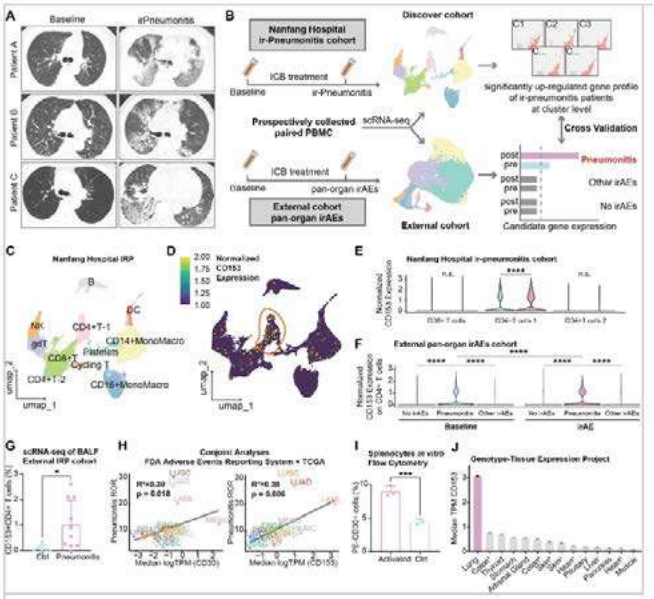
Introduction: Temporal and spatial unpredictability, and ligature with efficacy represent two puzzles about immune-related adverse events (irAEs) of immune checkpoint blockade (ICB) in cancers. Immunotherapy-related pneumonitis (IRP) often causes cessation of ICB and even death. However, the understanding of IRP is still in its infancy.

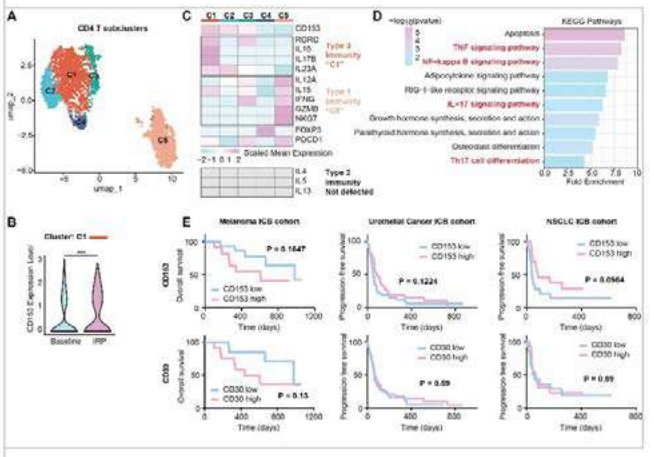
Methods: Single-cell RNA sequencing (scRNA-seq) was employed to profile 6 samples of paired PBMC at baseline and grade 2-3 IRP from three patients. Candidate genes were identified, followed by validation with a pan-organ irAEs cohort and an IRP cohort. Analysis of real-world pharmacovigilance big data, TCGA, flow cytometry, and Genotype-Tissue Expression Project (GTE-x) were performed to investigate the roles of candidate genes in IRP. Biological functions of candidate phenotype were determined by pathways enrichment. Three independent ICB cohorts were applied to evaluate the effect of candidate genes on ICB efficacy.

Results: Conjoint scRNA-seq analysis of our own and two external cohorts identified CD153 as a predictor of IRP, whose expression was exclusively on CD4+ T cells. Pre-existing CD153+CD4+ T cells forecast toxicity after ICB specifically in lungs, rather than in other organs. Integrative analysis of pharmacovigilance big data with TCGA, and GTE-x also revealed a significantly positive relationship between IRP and CD153, with the same observed on CD30, ligand of CD153. Furthermore, flow cytometry of in vitro stimulated primary splenocytes confirmed up-regulated CD30 levels upon immune activation. Further scRNA-seq analysis of CD4+ T cells identified a proinflammatory subpopulation expressing high levels of CD153 and canonical markers of type 3 immunity, which mainly shaped autoinflammatory disorders. Levels of CD153 or CD30 did not interfere with ICB efficacy in three independent ICB cohorts.

Conclusions: Preexisting CD153+CD4+ T cells might be a bonafide predictor of ICB toxicity specifically in lungs, while blockade of CD153 or type 3 immunity might be a feasible intervention uncoupling ICB toxicity and efficacy.

Keywords: immunotherapy-related pneumonitis, immunotherapy, CD153





EP.06E PATHOLOGY AND BIOMARKERS - IO
SATURDAY, SEPTEMBER 7, 2024 - 11:58 - 11:59

EP.06E.02 Integrated Analysis of Prognosis and Immune Characterization of COMMD3 In Lung Squamous Cell Carcinoma

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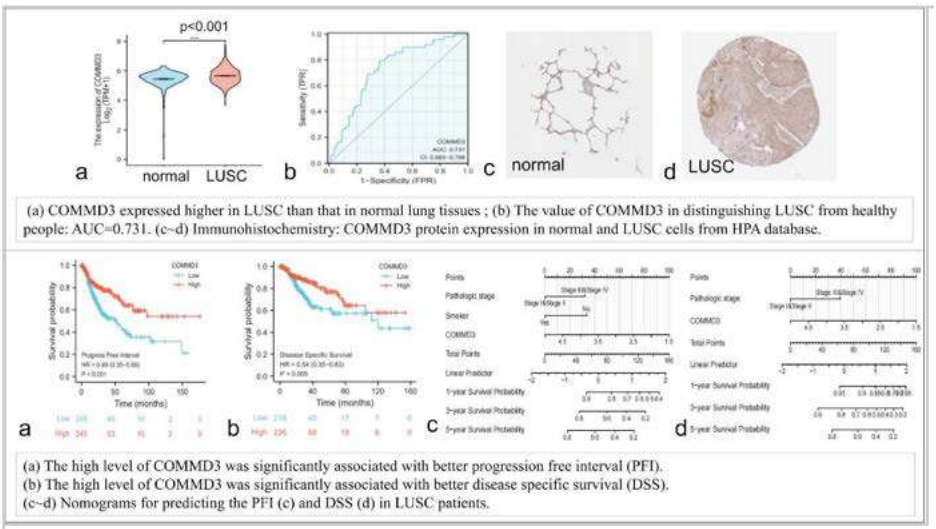
Introduction: The copper metabolism MURR1 domain protein (COMMD) has been known to play roles in tumorigenesis, progression and metastasis in tumor cells. However, the characters of COMMD3 in lung squamous cell carcinoma (LUSC) are still unclear.

Methods: The transcription level of COMMD3 was analyzed using TCGA database, and the value of COMMD3 in distinguishing LUSC from healthy people was analyzed via ROC analysis. Human Protein Atlas database was used to display the immunohistochemistry results of COMMD3. The prognostic value of COMMD3 was analyzed using Kaplan-Meier (KM) analysis. Via R software 'rms' package, the nomogram was developed to predict the 1, 3, 5-year progression free interval (PFI) and disease specific survival (DSS). Limma package in R software was used to analyze the COMMD3 expression-correlated differentially expressed genes (DEGs). The Gene ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analysis were performed via ClusterProfiler package. The relationship between COMMD3 and immune infiltration was analyzed via GSVA package.

Results: The COMMD3 was found to be significantly upregulated in LUSC than that in normal lung tissues, and the AUC was 0.731 for distinguishing LUSC from healthy people. The high level of COMMD3 was significantly associated with better prognosis including PFI and DSS. Nomograms were developed to predict PFI and DSS in LUSC patients. In addition,the 207 DEGs including 161 up-regulated genes and 46 down-regulated genes were found, and the first five up-regulated genes (AMER2, SOX1-OT, PNMA5, ADGRG7, DEFA5) and down-regulated genes (TKTL1, AC105177.1, SPANXB1, TGM6, GPHB5) were displayed. The COMMD3 expression was correlated with immune cells infiltration, Tcm cells were the most negatively correlated with COMMD3 (r=-0.221, p<0.001) and T helper cells were the most positively correlated with COMMD3 (r=0.228, p<0.001).

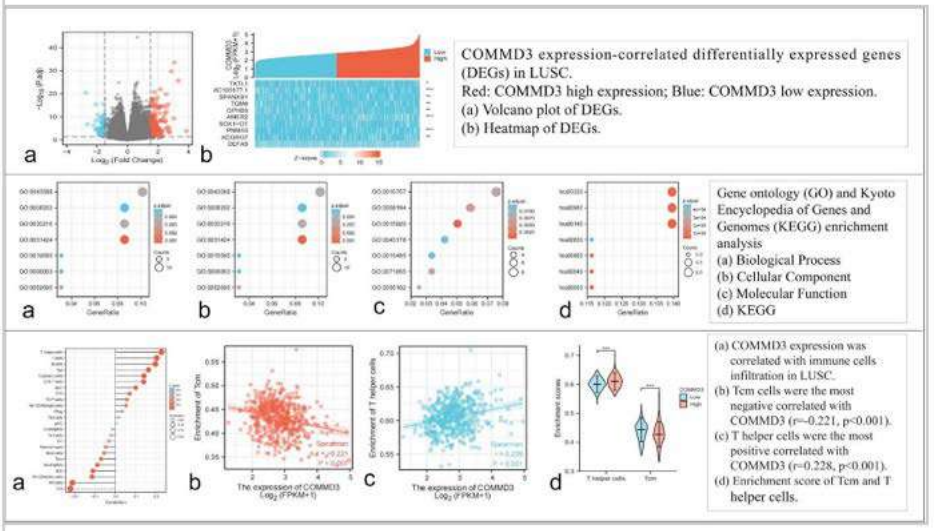
Conclusions: COMMD3 may have important roles in immune infiltration and may serve as a prognostic biomarker in LUSC patients.

Keywords: COMMD3, lung squamous cell carcinoma



(a) COMMD3 expressed higher in LUSC than that in normal lung tissues ; (b) The value of COMMD3 in distinguishing LUSC from healthy people: AUC=0.731. (c~d) Immunohistochemistry: COMMD3 protein expression in normal and LUSC cells from HPA database.

(a) The high level of COMMD3 was significantly associated with better progression free interval (PFI).
(b) The high level of COMMD3 was significantly associated with better disease specific survival (DSS).
(c~d) Nomograms for predicting the PFI (c) and DSS (d) in LUSC patients.



COMMD3 expression-correlated differentially expressed genes (DEGs) in LUSC.
Red: COMMD3 high expression; Blue: COMMD3 low expression.
(a) Volcano plot of DEGs.
(b) Heatmap of DEGs.

Gene ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analysis
(a) Biological Process
(b) Cellular Component
(c) Molecular Function
(d) KEGG

(a) COMMD3 expression was correlated with immune cells infiltration in LUSC.
(b) Tcm cells were the most negative correlated with COMMD3 (r=-0.221, p<0.001).
(c) T helper cells were the most positive correlated with COMMD3 (r=0.228, p<0.001).
(d) Enrichment score of Tcm and T helper cells.

EP.06E PATHOLOGY AND BIOMARKERS - IO
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EP.06E.03 Body Composition and Inflammation Index-Based Nomograms to Assess the Outcomes of Patients with NSCLC Receiving Chemoimmunotherapy

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Introduction: It has been debatable about impact of body composition on the outcome of chemo-immunotherapy in advanced non-small cell lung cancer(NSCLC). This study sought to explore the predictive value of pretreatment CT-derived body composition indices, inflammatory indices and nutritional indices evaluated by peripheral blood in patients with advanced NSCLC treated with chemo-immunotherapy, so as to identify vulnerable patients for improving outcomes for these patients.

Methods: Patients with NSCLC receiving chemo-immunotherapy between March 2017 and March 2019 were included in this retrospective analysis. Nomograms were created using LASSO Cox regression. The concordance index (C-index), calibration plots, decision curve analysis (DCA)were used to evaluate the nomograms' performance.

Results: According to LASSO regression, systemic immune-inflammation index (SII), platelet to lymphocyte ratio (PLR), prognostic nutrition index (PNI), visceral Adipose Index (VAI), total Adipose Index (TAI), skeletal muscle density (SMD) were screened out as interfering factors for PFS, while SII, VAI, SMD, sarcobesity were significantly associated with OS. The C-index for the nomograms of PFS and OS were 0.668 and 0.753, respectively. The calibration curves indicated excellent agreement between the predicted and actual survival outcomes of 6- and 9-month PFS and 12- and 18-month OS. Patients with sarcobesity had worse OS (20.233m,95%CI 15.221-25.246) compared to non-sarcobesity patients (36.833m, 95%CI 10.392-63.275, P < 0.001), while the difference was not reflected in patients classified according to sarcopenia. Subsequent analysis revealed that patients with high SII, high VAI and low SMD had worst PFS and OS than patients with low SII,low VAI and high SMD (PFS:HR 6.012,95% CI 2.681-13.484, P<0.001; OS:HR 16.903,95% CI 5.314-53.763, P<0.001).

Conclusions: Increased sarcobesity index was risk factor for survival outcomes, while sarcopenia was not. A comprehensive analysis of body composition (visceral adipose index:VAI and skeletal muscle index: SMD) and inflammation index (SII)may contribute to prognostic stratification of patients with advance NSCLC receiving chemo-immunotherapy as first-line.

Keywords: Body composition, Inflammation index, Sarcobesity

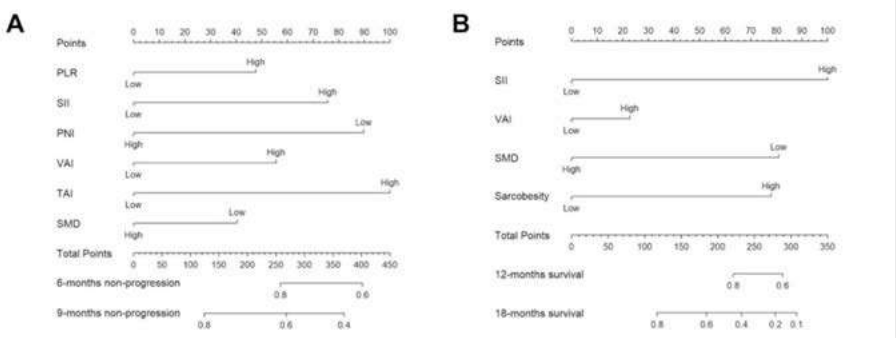

Figure 1 Predictive nomograms. (A) 6-and 9-month probability of Non-progression; (B)12- and 18-month survival probability; PLR, platelet to lymphocyte ratio; SII, systemic immune-inflammation index; PNI, prognostic nutrition index; VAI, Visceral Adipose Index; TAI, Total Adipose Index; SMD, skeletal muscle density.

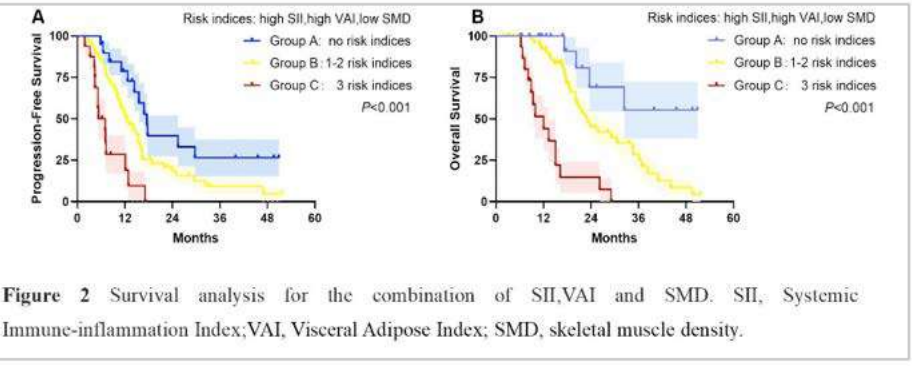

Figure 2 Survival analysis for the combination of SII,VAI and SMD. SII, Systemic Immune-inflammation Index;VAI, Visceral Adipose Index; SMD, skeletal muscle density.

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EP.06E.04 Insight Into the Significance of CD8+ Tumor-Infiltrating Lymphocytes in Lung Adenocarcinoma

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Introduction: Although there are great expectations regarding the use of tumor-infiltrating lymphocytes (TILs) to predict effects of immunotherapies and prognosis, knowledge about TILs remains insufficient for clinical application. In this study, we focused on CD8+ T cells, which are the most promising candidate biomarker among TILs, and investigated the clinical significance of CD8+TILs in lung adenocarcinoma (LAC) with a more objective method using a digital pathology scoring software program.

Methods: Among patients who underwent surgical resection of LAC in 2011-2017, those with pathological stage IB-III were immunohistochemically studied to evaluate CD8+TILs in the tumor stroma. The impact of CD8+TILs on relapse-free survival was analyzed with Kaplan-Meier survival analysis and multivariate analysis using a Cox proportional hazards model/Fine-Gray model. Furthermore, we examined the association between the number of CD8+TILs in the tumor stroma and the efficacy of immune checkpoint inhibitors (ICIs) in patients who received ICIs at the time of postoperative recurrence using swimmer plot.

Results: The multivariate analysis showed that large and intermediate numbers, but not small numbers, of CD8+TILs in the tumor stroma may be related to a more favorable prognosis (large vs. small: HR, 0.66; 95% CI, 0.36-1.20, P=0.17; intermediate vs. small: HR, 0.70; 95% CI, 0.39-1.23, P=0.21). However, an exploratory study showed that even among groups with intermediate to large number group of CD8+TILs, there is population with poor prognosis. The swimmer plots showed that the larger number of CD8+TILs in the tumor stroma tended to be associated with the better progression-free survival (PFS) and overall survival (OS).

Conclusions: Our study provided partial but important information on the significance of CD8+TILs in LAC. To use CD8+TILs as biomarkers, in addition to the number of CD8+TILs, it seemed necessary to assess the functional status of CD8+TILs. Therefore, we need to identify the molecules indicating dysfunctional CD8+ T cells and to establish a simplified pathological detection method of them.

Keywords: biomarker, tumor-infiltrating lymphocytes, lung cancer

EP.06E PATHOLOGY AND BIOMARKERS - IO
SATURDAY, SEPTEMBER 7, 2024 - 11:58 - 11:59

EP.06E.05 Is Diffusion-Weighted Imaging Able to Indicate Pathological Response in NSCLC after Neo-Adjuvant Immuno-Chemotherapy?

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Introduction: About one third of non-small cell lung cancer (NSCLC) patients show an excellent histopathological response to neo-adjuvant immuno-chemotherapy leading to better prognosis. Nonetheless, this leaves two third non-complete responders raising the need for reliable markers to predict treatment response. Preliminary studies using advanced multiparametric MRI parameters were effective in predicting histopathological response. These parameters, however, are not included in routine MRI protocols. Therefore, the aim of our study was to evaluate whether standard care MRI using diffusion-weighted imaging (DWI) can discriminate between complete pathological response (cPR) and non-cPR.

Methods: This study is part of a large prospective single-center study which enrolled 14 (5 male, 9 female) operable NSCLC patients who received three cycles of neo-adjuvant immuno-chemotherapy. Images were obtained with a 3 T MR scanner including a DWI sequence within six weeks prior to surgery. Tumor lesions >1 cm were included in the analysis. Three independent readers defined regions of interest on the apparent diffusion coefficient (ADC) map. The histological results were retrieved from patients' records. Patients were assigned to either cPR or non-CPR groups. The median of measured ADC values was recorded and the differences between cPR and non-cPR groups were evaluated using an unpaired T-test.

Results: Six patients had a cPR and eight patients a non-cPR, respectively. Both, minimal and average ADC values did not show any statistically significant differences between cPR and non-cPR (median_min: 628.5 (IQR 307.5), median_ave: 1174 (IQR 507.5) and (median_min: 546.5 (IQR 263), median_ave: 1126 (IQR 352)), p= 0.796; p= 0.393 (Figure 1). The tumor size was not significantly different between the two groups (median: 29mm (IQR 20) vs. 37mm (IQR 24)), p=0,415.

Conclusions: The preliminary results of our pilot study indicate that ADC does not discriminate between cPR and non-cPR in operable NSCLC after neo-adjuvant immuno-chemotherapy.

Keywords: NSCLC, neo-adjuvant immuno-chemotherapy, DWI MRI

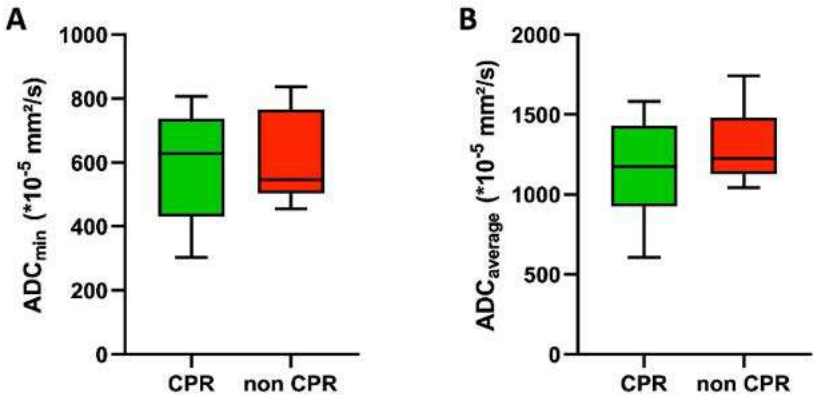

Figure 1. Minimal (A) and average (B) ADC values of patients with cPR and non-cPR.

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EP.06E.06 Elucidating the Interplay Between Oncogenic Fusions and the Tumor Immune Microenvironment in Lung Adenocarcinoma

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Introduction: In non-small cell lung cancer, particularly in lung adenocarcinoma, fusion mutations of driver genes were associated with a higher degree of malignancy. The patients with fusion mutations tended to be more prevalent in later stages of tumor development, correlating with a higher rate of lymph node metastasis, vascular invasion, or an increased likelihood of brain metastases. Although targeted therapy was the preferred treatment for lung cancer driven by fusion mutations, with ALK rearrangements showing less benefit from PD-1/PD-L1 inhibitors, an open stance was maintained towards immunotherapy for other fusion-driven mutations (such as ROS1, RET, NTRK, etc.). Therefore, research into the immune microenvironment of tumors driven by fusion mutations warranted further exploration.

Methods: Tumor samples from lung adenocarcinoma patients with oncogenic fusions (N = 21) and non-targetable mutations (N = 21) were analyzed. The formalin-fixed, paraffin-embedded slides, they were stained using the Opal multiplex immunohistochemistry (mIHC) Detection Kit (Akoya), targeting 11 markers in two seven-color panels. Tumor and stromal areas were identified by cytokeratin (CK) and DAPI staining. Results, showing immune cell percentages of total cells, provided insights into cell subpopulation distributions in tumor and stroma.

Results: In patients with oncogenic fusions, ALK rearrangements constituted 47.62% (n=10), RET rearrangements accounted for 19.05% (n=4), and NRG1 rearrangements made up 14.28% (n=3). The remaining fusions, including ROS1, FGFR1, FGFR3, and BRAF, each represented a single case. In the population with oncogenic fusions, there were no statistically significant differences in the distributions of all 13 immune cell subpopulations within tumor and stromal areas. This consistency was maintained even when specifically examining the ALK rearranged subgroup, with no significant differences found between the areas. However, in the population with non-targetable mutations, the proportions of CD68+/CD163- macrophages, PD-1+ cells, and CD20+ cells were significantly lower in the tumor areas compared to the stromal areas (p=0.018, p=0.021, and p=0.00014, respectively). Comparing the immune microenvironments of the oncogenic fusion population to those with non-targetable mutations, an interesting finding was that CD56 dim NK cells were more abundant in the tumor areas of the oncogenic fusion group (p=0.0035). Furthermore, FoxP3+ cells were more concentrated in both tumor and stroma areas in the oncogenic fusion group (p=0.0059 and p=0.033, respectively).

Conclusions: In patients harboring oncogenic fusions, the immune cell landscape exhibits uniformity across both tumor and stromal regions, particularly in those with ALK rearrangements. This stands in stark contrast to patients with non-targetable mutations, where specific immune cells are notably less abundant within tumor environments. Significantly, the oncogenic fusion cohort demonstrates an increased presence of CD56 dim NK cells and FoxP3+ cells, indicating unique immunological profiles distinct from those observed in non-targetable mutations.

Keywords: oncogenic fusions, lung adenocarcinoma, tumor immune microenvironment

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EP.06E.07 Geospatial and Molecular Characterization of Tumor Immune Cell Infiltration in NSCLC

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Introduction: Non-small cell lung cancer (NSCLC) is the leading cause of cancer mortality worldwide. Molecular testing has identified an increasing number of NSCLC associated genes, but their exact roles are not well understood. Examining tumor immune cell infiltration as a function of altered RNA expression and a patients' residential address can help characterize both the tumor-immune interface and environmental effects that may contribute to genetic changes and treatment response in NSCLC. We hypothesize that tumor immune infiltration in NSCLC is related to altered RNA expression secondary to residential environmental factors.

Methods: RNA sequencing was performed by TEMPUS labs on patients with NSCLC at a single academic institution (UI Health) and residential zip codes were collected on all patients and used to explore the relationship between tumor immune infiltration and altered RNA expression.

Results: 144 NSCLC FFPE tumor samples were studied. We found that a number of genes were highly associated with increased tumor immune cell infiltration (figure 1). Additionally, we found that tumor immune cell infiltration patterns differed depending on a patient's geospatial region (zip code).

Conclusions: Our study suggests altered RNA expression likely impacts tumor immune infiltration in NSCLC or vice versa. Initial findings warrant further investigation into the specific genes and environmental factors contributing to altered immune landscapes within NSCLC tumors and their potential relationship to treatment efficacy. Future studies are needed to elucidate the complex interplay between genetics, environment, and immune response in NSCLC progression and treatment outcomes.

Keywords: non-small cell lung cancer, immune infiltration, RNA sequencing

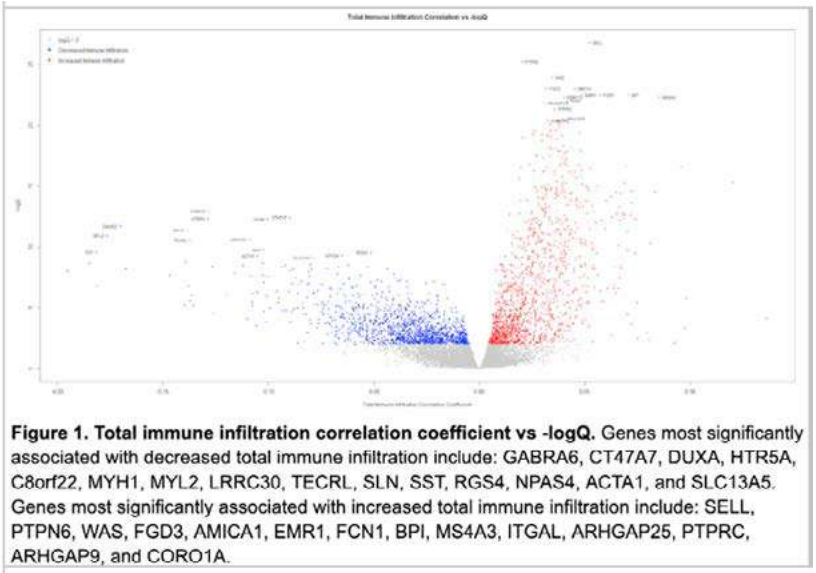

Figure 1. Total immune infiltration correlation coefficient vs -logQ. Genes most significantly associated with decreased total immune infiltration include: GABRA6, CT47A7, DUXA, HTR5A, C8orf22, MYH1, MYL2, LRRC30, TECRL, SLN, SST, RGS4, NPAS4, ACTA1, and SLC13A5. Genes most significantly associated with increased total immune infiltration include: SELL, PTPN6, WAS, FGD3, AMICA1, EMR1, FCN1, BPI, MS4A3, ITGAL, ARHGAP25, PTPRC, ARHGAP9, and CORO1A.

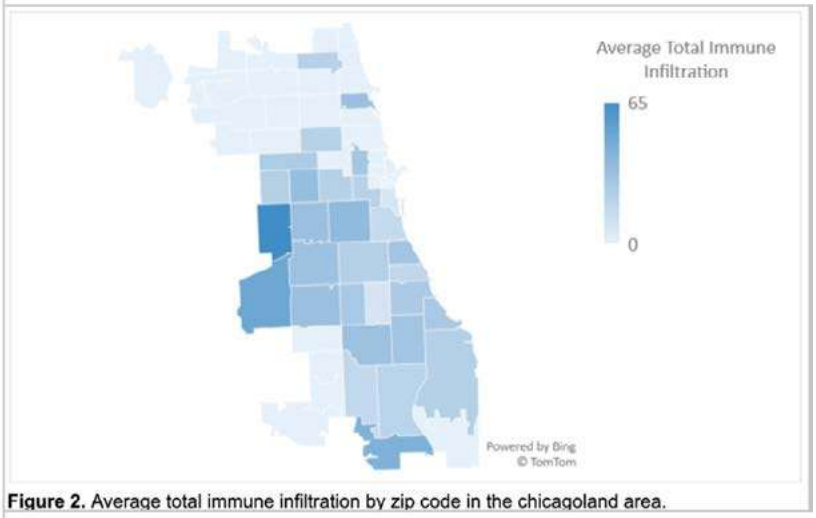

Figure 2. Average total immune infiltration by zip code in the chicagoland area.

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EP.06E.08 Clinical Significance of JPH4 and Correlation with the Immune Microenvironment of Lung Adenocarcinoma

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Introduction: To investigate the expression of JPH4 in lung adenocarcinoma, its correlation with clinicopathologic features and its potential prognostic significance, as well as its regulation of the tumor microenvironment.

Methods: Based on TIMER and GEPIA databases, we analyzed the differences in JPH4 expression in lung adenocarcinoma and paracarcinoma tissues, which were validated by immunohistochemistry (IHC), Western blot, and RT-qPCR. Differences in overall survival between high and low JPH4 expression groups and correlation with clinical information were analyzed using TCGA database. Cox proportional risk regression analysis showed independent prognostic significance of JPH4. GSEA enrichment analysis of JPH4 was performed to explore its potential biological functions and mechanisms. The role of JPH4 in regulating the immune microenvironment of lung adenocarcinoma was also explored based on the TIMER database and immune infiltration algorithms such as ssGSEA and ESTIMATE. The relationship between JPH4 and common immune checkpoints was also analyzed.

Results: TIMER and GEPIA databases showed that the expression of JPH4 was significantly lower in lung adenocarcinoma, and IHC, Western blotting and RT-qPCR experiments confirmed that the expression of JPH4 in lung adenocarcinoma tissues was also significantly lower than that in Para cancerous lung tissues. Based on public databases and clinical samples, survival analysis showed that high expression of JPH4 was associated with favorable prognosis of lung adenocarcinoma; secondly, there were significant differences in the expression of JPH4 in different clinical stages, and the higher the T and stage, the more downregulated the expression of JPH4 was. Cox multifactorial analysis showed that JPH4 could be used as an independent favorable prognostic factor for lung adenocarcinoma (HR=0.634, P=0.03). JPH4 mRNA expression was significantly positively correlated with the degree of immune cell infiltration, and deletion of JPH4 copy number at the arm level decreased the degree of immune cell infiltration. JPH4 was also significantly positively correlated with immune checkpoints.

Conclusions: JPH4 was significantly downregulated and associated with poor prognosis in lung adenocarcinoma. The mRNA level of JPH4 affected the microenvironmental homeostasis of lung adenocarcinoma and mediated an increase in the level of anti-tumor immune cell infiltration, such as CD8+ T cells, which inhibited the development of lung adenocarcinoma. It suggests that JPH4 is an independent prognostic protective factor and is associated with anti-tumor immunity in lung adenocarcinoma and can be used as a prognostic marker.

Keywords: JPH4, Lung Adenocarcinoma, Immune Microenvironment

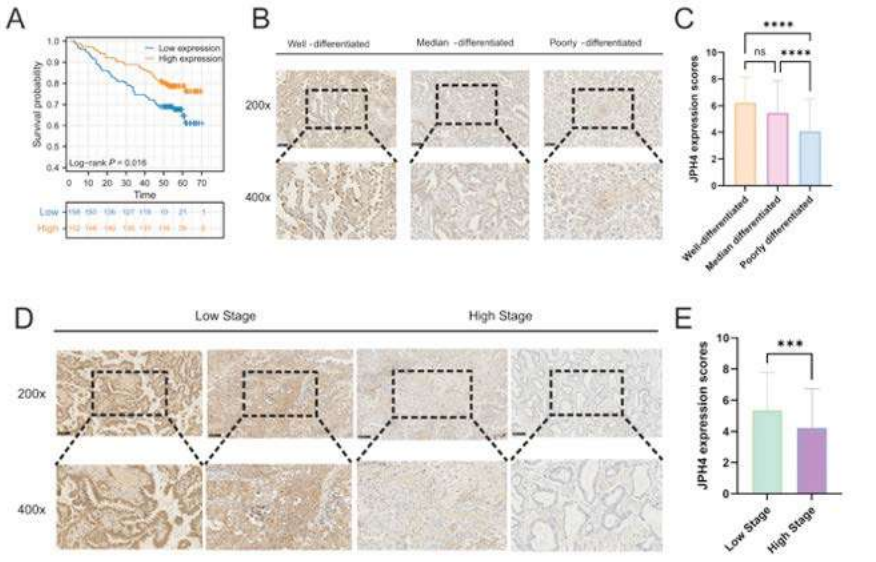

Figure. Prognostic significance of JPH4 and its differential expression among different clinical subgroups. (A): Kaplan-Meier curves of overall survival in JPH4 high and low expression groups. (B-C): JPH4 expression in different differentiated subtypes of lung adenocarcinoma. (D-E):Expression levels and statistical results of JPH4 in lung adenocarcinoma in high (stage III and IV) and low (stage I and II) stages.

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EP.06E.09 Spatial Multiomics Analysis Reveals AT2 Cells Inhibit B Cells of TLS in Pre-invasive Lung Adenocarcinoma after Neoadjuvant Immunotherapy

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Introduction: The incidence of multiple primary lung cancers (MPLCs) is increasing gradually, especially multiple subsolid nodules (SSNs). In addition to surgery, other treatments such as immunotherapy combined with chemotherapy are not effective for multiple SSNs, and the mechanism is unknown. Here, we conducted spatial multi-omics analysis to explore molecular characteristics that influence immunotherapy efficacy.

Methods: We performed whole exome sequencing, transcriptome sequencing, and imaging mass cytometry (IMC) testing for all resected lesions of a 61-year-old MPLC patient. There were four pulmonary lesions, among which the primary nodule (PT) was solid, and the rest were SSNs. After neoadjuvant immunotherapy, PT and right lower paratracheal lymph nodes (R4LN) had reached pathologic complete response (pCR); however, SSNs including two minimally invasive adenocarcinoma (MIA) and one atypical adenomatous hyperplasia (AAH), were unresponsive and remained stable in size.

Results: HE staining revealed the presence of multiple tertiary lymphoid structures (TLSs) in all nodules, implying that therapeutic response also occurred within the SSNs. Genomics and transcriptomics showed that SSNs harbored more copy number alterations and significantly involved in cell-substrate adhesion pathway, indicating genomic instability and immune evasion related to worse immune response. Multiplexed IMC for functional metaclusters displayed there was no significant difference in CD20-labeled TLS among different responding lesions, while AT2 cells were significantly enriched in SSNs. Further analysis of the spatial cell neighborhood (CNs) showed nonresponding SSNs hold higher AT2 positive niche (CN2) and responding nodules enriched AT2 negative CN (CN8), suggesting AT2 cells play a key immunosuppressive role by interacting with surrounding cells. Analysis inside and outside TLS found that mature B cells in TLSs and AT2 cells outside TLSs had accordant spatial distribution, which further proved that inhibitory effect of AT2 on B cells in TLSs resulting in poor immunotherapy effect. Our previous single-cell sequencing results reconfirmed that AT2 interacts more strongly with B cells in nonresponding nodules and exerts immunosuppressive effects via MIF ligands. In addition, other therapeutic clusters and interactions were also revealed, such as memory T cells appear to play a positive role in immune efficacy.

Conclusions: We provide a new insight into the immunosuppressive function of AT2 cells on B cells within TLS in the case of poor immune response of SSN lesions, bringing new targets for multiple SSNs treatment.

Keywords: Multiple primary lung cancers, Tertiary lymphoid structures, Cellular interaction

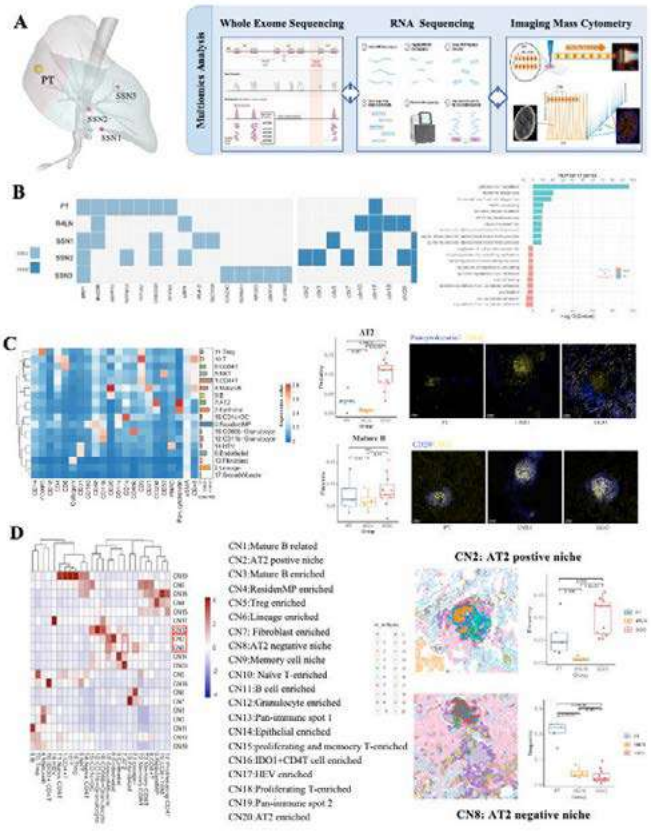

Figure Overview of results. (A) Schematic view of the study design. (B) Genomic and and transcriptional landscape in different lesions. (C) Metacluster analysis and comparation among lesions with different response. (D) Functional cell neighbors definition and interaction profiles related immunoefficacy.

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EP.06F.01 Survival Benefits of NGS in Advanced Lung Adenocarcinoma Vary by Populations and Timing of Examination

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Introduction: Despite the widespread application of next-generation sequencing (NGS) in advanced lung adenocarcinoma, its impact on survival and the most suitable timing for the examination remains uncertain. Our study aimed to analyze the impact of mutation-targeted treatment following NGS examination on survival, considering different populations and various timing of examination.

Methods: This retrospective hospital-based cohort study screened advanced lung adenocarcinoma patients who underwent tissue or liquid NGS testing between December 2018 and January 2024. Patients were followed up until death or the end of the study (29 Feb 2024). We categorized these patients into four groups according to the timing of NGS examination: Group 1: treatment-naïve, upfront NGS; Group 2: Treatment-naïve, exclusionary EGFR/ALK/ROS1; Group 3: post-treatment, no known EGFR/ALK/ROS1; Group 4: known driver mutation and post-tyrosine kinase inhibitor treatment.

Results: A total of 528 patients who underwent NGS examination were screened. After exclusion 104 patients (not of advanced lung cancer, and histology indicating non-lung adenocarcinoma), 424 patients with advanced lung adenocarcinoma (tissue biopsy 211 and liquid biopsy 213) were included. There were 128, 126, 90, and 80 patients in Group 1, 2, 3, and 4, respectively. In Group 1, 2, 3, and 4, targetable mutations were identified in 76.6%, 49.2%, 41.1%, and 33.3% of the patients, respectively ($P < 0.001$). Mutation-targeted treatments were applied in 68.0%, 15.1%, 27.8%, and 22.5% of the patients, respectively ($P < 0.001$). In each group, the top two most frequently detected targetable mutations were: Group 1 (EGFR 54.7%, ALK 6.3%); Group 2 (METex14 skipping or METamp 13.5%, HER2 mutation 13.5%); Group 3 (EGFR 21.1%, HER2 mutation 7.8%); Group 4 (EGFR T790M 13.6%, MET amplification 11.1%). Patients receiving mutation-targeted treatments exhibited significantly longer overall survival (OS), with a median of 59.9 months, compared to those not receiving such treatments, who had a median survival of 43.1 months (aHR 0.54 [95% CI 0.37-0.79], $P = 0.001$). However, the survival benefits varied between the four groups, with the profoundest benefit among the treatment naïve upfront NGS population (Group 1, not reached [NR] vs. 40.4 months, $P = 0.028$). The median OS for patients with mutation-targeted treatments was also significantly longer among Group 2 patients (19.2 vs. 12.4 months, $P = 0.049$). The median post-NGS survival for patients receiving mutation-targeted treatments were numerically longer than those without treatments in Group 3 (49.9 vs. 38.1 months, $P = 0.684$) and Group 4 (NR vs. 19.3 months, $P = 0.377$).

Conclusions: Our research shows that the proportion and types of targetable mutations identified through NGS testing as well as the survival benefits vary among different populations and timing of examination. However, regardless of when the examination takes place, individuals who are identified with targetable mutations and undergo mutation-targeted treatments tend to experience longer survival compared to those who do not undergo such treatment.

Keywords: Next-generation sequencing, Advanced lung adenocarcinoma, Survival

EP.06F PATHOLOGY AND BIOMARKERS - NGS
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EP.06F.02 Enhancing Clinical Utility: Oncomine Dx Target Test Augments Biomarker Detection in Advanced Non-Small-Cell Lung Cancer

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Introduction: Despite considerable progress in targeted therapies for advanced non-small-cell lung cancer (NSCLC), there remains controversy surrounding the integration and utilty of single gene tests alongside next-generation sequencing (NGS) within clinical diagnostic platforms for identifying critical biomarkers. This controversy arises primarily from tissue limitations and reimbursement challenges.

Methods: In this study, we investigated the impact of integrating the upfront Oncomine Dx Target Test (ODxTT) and single gene tests (SGTs) into routine clinical practice by analyzing data before and after implementation. Our analysis compared the performance of ODxTT alongside concurrent SGTs in cohort 1 (n = 458) over a three-year period. We juxtaposed this evaluation with SGTs exclusively conducted during the same timeframe in cohort 2 (n = 1850) and against cohort 3 (n = 1968), which exclusively underwent SGTs before the integration of ODxTT over the identical period. Notably, all cohorts underwent single gene tests targeting EGFR, ALK, and ROS1 mutations.

Results: The ODxTT demonstrated a success rate of 98.7% (452/458), while single gene tests in both cohort 2 and cohort 3 achieved a success rate of 99.7%. Among the cases analyzed with ODxTT, 51.5% (233 out of 452) revealed clinically significant biomarkers. Notably, ODxTT detected clinically significant genes not identified by simultaneous SGTs, including RET fusion (1.3%), BRAF V600E (1.7%), MET exon 14 skipping (1.1%), as well as KRAS G12C (2.8%), PIK3CA (2.4%), ERBB2 (0.4%), FGFR3 (0.2%), NRAS (0.4%), and MAP2K1 (0.4%). Both EGFR and ROS1 were evaluated by ODxTT and SGT. The incidence of EGFR exon 20 insertion (0.9%) tended to be higher, while ROS1 (4.8%) was significantly more frequently detected in ODxTT compared to SGT. However, the rates of EGFR T790M and rare EGFR variants did not exhibit significant differences between ODxTT and SGT.

Conclusions: The integration of ODxTT alongside single gene tests provides significant additional information without compromising the performance of single gene tests. With ODxTT's high success rate, this integration expands the scope of comprehensive therapeutic strategies for advanced lung cancer.

Keywords: Oncomine Dx Target Test, Lung Cancer, Single gene test

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EP.06F.03 Analysis of Copy Number Variations of MET, EGFR and ERBB2 Genes in a Lung Cancer Patient Series: Comparison of FISH with NGS

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Introduction: Amplification of MET, EGFR and ERBB2 genes plays an important role in the development of non-small-cell lung cancer (NSCLC), which can also mediate primary and secondary resistance to EGFR tyrosine kinase inhibitors. Fluorescence in situ hybridization (FISH) is the standard method for detecting gene amplification and Next Generation Sequencing (NGS)-based molecular profiling of advanced NSCLC patients is strongly recommended by scientific agencies including the European Society for Medical Oncology (ESMO). Meanwhile, the role of NGS in identifiyng amplification remains uncertain. The aim of this study was to validate and compare Copy Number Variations (CNVs) of MET, EGFR and ERBB2 genes detected by a NGS 50 genes panel with those obtained by a FISH assay.

Methods: Thirthy-four patients diagnosed with advanced NSCLC were included. FISH and NGS were conducted. In this study MET, EGFR and ERBB2 were classified as positive by FISH (FISH positive) when Gene Copy Number (GCN) was >5, regardless of chromosome signals. A chromosomal copy number >4 was considered polysomy. MET, EGFR and ERBB2 were classified as positive by NGS when CNV was ≥4. The Oncomine Precison Assay gene panel and the Genexus integrated sequencer (Thermo Fisher Scientific) were used for NGS analysis.

Results: Thirteen of 34 patients (38%) were FISH MET positive: 11 (85%) had polysomy and 2 (15%) were dysomic. Twenty-one FISH negative cases were all dysomic. NGS accurately identified the MET gene status in all dysomic cases, while 82% of patients in the polysomic FISH scenario had a CNV <4 by NGS analysis. Thirty-eight percent of cases were FISH EGFR positive: 31% had polysomy and 69% were dysomic. Notably 67% of discordant cases between FISH and NGS fell into the polysomic FISH setting, as observed for the MET gene. Regarding ERBB2 gene, 26% of cases were FISH positive. We observed that, unlike the MET and EGFR genes, only a few cases were polysomic (15%) and all showed a FISH GCN >5 and a NGS CNV <4. The row agreement between FISH and NGS for MET, EGFR and ERBB2 genes was: 74%, 79% and 78% respectively.

Conclusions: In the dysomic context, the two methods agree in detecting both normal and alterated gene copy number cases. Since polysomy cannot be detected by NGS using a 50 genes diagnostic panel, observed discrepancies are confined to the polysomic setting. It is important to point out that, unlike conventional gene amplification assessment, which considers positivity by ratio (GCN/chromosome CN), we only evaluated positivity by GCN, which is why the high percentage of positive FISH cases reported in this study. Finally, FISH remains the gold standard for differentiating polysomy from normal copy number and amplification.

Keywords: Copy Number Variations, MET, EGFR, ERBB2, NGS & FISH

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EP.06F.04 The Characteristics of Plasma Sample NGS Analysis in the Detection of Lung Cancer Driver Genes

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Introduction: The detection of driver mutations is critically important in the treatment of non-small cell lung cancer (NSCLC), with tissue specimens being usually used for this purpose. However, the use of plasma specimens is rapidly gaining popularity. The advantages of NGS analysis using plasma samples include the low invasiveness and convenience of sample collection, as well as a shorter turn around time. Nonetheless, it remains unclear to what extent plasma samples can substitute tissue specimens. We investigated the characteristics of plasma sample NGS analysis in clinical practice through a multicenter institutional study.

Methods: A prospective observational study was conducted at six facilities in Japan, enrolling cases suspected of advanced lung cancer planned for pathological diagnosis and driver gene screening. Clinical presentation, presence of driver mutations, their detection methods, and PD-L1 status were extracted from electronic medical records. At the time of diagnostic procedure, 14 ml of blood was collected for RNA and DNA extraction from plasma and subsequent NGS analysis using the Genexus system and Oncomine Precision Assay, all performed automatically.

Results: From June 2022 to September 2023, 303 cases were registered, with 261 cases diagnosed as NSCLC. The median age was 71 years (range 26-90), with 164 males and 97 females. Performance status (PS) 0/1/2/3/4: 81/149/21/5/4, never smoker/current or former: 69/162, cStage I/II/III/IVA/IVB/recurrence/unknown: 15/7/52/66/108/13/1, Adenocarcinoma/Squamous/NSCLC: 183/54/24. Driver mutations were present/absent/unknown in 116/134/11 cases, with/without tissue specimen multiplex driver gene testing in 214/47 cases (table). EGFR and ALK mutations were detected in 13 and 3 cases, respectively, without multiplex testing. PD-L1 <1%/1-49%/≥50%/Unknown: 69/76/72/44. For cases excluding post-surgical recurrence, the median time from specimen collection to confirmation of genetic aberration was 20 days (range 5-744). NGS analysis of plasma samples was available in 226 cases, with the identical driver mutations detected in 60 cases as in tissue specimens. The agreement was less frequent for fusions than mutations (55.9% vs 34.8%). In 7 cases, driver gene were detected only in plasma samples. The median time from plasma sample collection to result was 8 days (range 2-26).

Conclusions: Detection of driver genes through NGS analysis of plasma samples was possible in approximately half (51.7%) of the cases compared to tissue samples, but results were obtained more quickly. Only a few driver mutations were detected exclusively in plasma samples.

Keywords: Driver Gene, cell free DNA, NGS analysis

Characteristics of detected driver genes by NGS analysis

	Tissue	Plasma
EGFR	63	37
ALK	11	2
ROS1	8	4
BRAF	5	3
MET	8	3
RET	4	3
KRAS-G12C	13	9
HER2	4	6

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EP.06F.05 External Quality Assessment Results of Third-party NGS Laboratories in China for the Detection of Rare Mutations in Lung Cancer

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Introduction: Rare mutations in lung cancer are defined as mutations with an incidence of less than 5%, and multiple variant forms have been identified. With the progress of drug development, the reliable detection of rare mutations has attracted more and more attention from clinical practice. For third-party laboratories with NGS platforms, their ability to detect rare mutations in lung cancer needs to be tested.

Methods: Ten standards were prepared from cell lines, including variants with drugs approved or in the late development stage such as EGFR 20 insertion, MET 14 skipping, MET amplification, HER2 mutation, RET fusion, and BRAF mutation, and titrated to 5% mutation frequency to mimic tissue samples (5 samples) and 1% mutation frequency to mimic plasma samples (5 samples). The genotype of each standard was verified by ddPCR and NGS, respectively. The registration is freely open to all third-party laboratories with NGS platforms. Standards were distributed to laboratories that signed the informed consent and were required to be tested using NGS methods to report functional variants of EGFR, MET, HER2, RET, and BRAF. The results of each laboratory were evaluated and scored based on variant calling and interpretation. Laboratories were considered to pass the assessment if all variants were reported accurately in all mimic samples.

Results: A total of 30 third-party laboratories participated in this evaluation, of which 29 reported valid results. Regarding the variant calling, the pass rate of mimic tissue samples was 72.4% (21/29), and that of mimic plasma samples was 65.5% (19/29). For various targets, participants had the highest error rate for detection of MET amplification (tissue 5/29 including 1 false positive, plasma 6/29), followed by MET 14 skipping (tissue 2/29, plasma 4/29, all errors occurred in the mutation: c.2888-35_2888-17del), and relatively lower error rates for RET fusion (tissue 1/29, plasma 2/29) and BRAF mutation (tissue 1/29, plasma 1/29); both EGFR and HER2 mutations were accurately identified. Regarding variant interpretation, the percentage of laboratories with no error in mimic tissue samples was 55.2% (16/29) and that of mimic plasma samples was 51.7% (15/29). Participants had the highest error rate for the interpretation of MET amplification (11/29), followed by BRAF mutations (5/29), EGFR 20 insertion (3/29), MET 14 skipping (2/19), HER2 mutations (2/29), and RET fusions (1/29). Overall, the number of laboratories that reported no error in both variant calling and interpretation was 13 in mimic tissue samples and 11 in mimic plasma samples.

Conclusions: Overall, about 70% of participants passed the assessment for the detection of rare mutations in lung cancer. Results showed that more calling errors were found in variant types of amplification and fusion, and mimic plasma samples than mimic tissue samples. In addition, only about 50% of participants received a perfect score on variants interpretation, suggesting laboratories should pay more attention to the update of the interpretation database. In conclusion, third-party NGS laboratories must participate in quality assessment regularly.

Keywords: Rare mutations, Next-generation sequencing, External quality assessment

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EP.06F.06 Concurrent DNA and RNA NGS Testing to Characterize Rare Fusions in Advanced NSCLC Patients

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Introduction: Therapy directed at molecular actionable variants improves survival in patients with advanced NSCLC and is standard of care. Although there is familiarity with common fusion targets such as ALK, ROS1, and RET, there is growing evidence that emerging rare fusion targets in advanced NSCLC are likely promising targets for matched therapies that also may lead to improved outcomes. Here we report the prevalence of rare BRAF, NRG1, and EGFR fusions, and their co-occurrence with other NCCN recommended actionable NSCLC targets, using concurrent DNA-RNA NGS testing in a real-world patient cohort.

Methods: Deidentified records were extracted from the Tempus multimodal database, consisting of 5,546 advanced (Stage IIIB-IV) patients with a primary diagnosis of adenocarcinoma NSCLC who underwent solid-tumor testing with both DNA-seq and RNA-seq (Tempus xT and xR assays, respectively). Concurrent RNA-NGS and DNA-NGS pipelines were run separately and manually reviewed as part of the Tempus clinical workflow. Fusion partners with the highest read support are reported. NCCN-recommended testing for targeted variants analyzed included ALK, RET, ROS1, and NTRK1/2/3 fusions, MET exon 14 skipping variants, EGFR pathogenic single nucleotide variants (SNVs)/indels (e.g., exon 19 deletions), BRAF V600E, and KRAS G12C.

Results: The overall prevalence of rare fusions in our cohort was 0.6% (n=32): 0.3% (n=18) BRAF, 0.2% (n=9) NRG1, and 0.1% (n=5) EGFR. Fifty percent (n=16) of the rare fusions were detected solely by RNA-seq—including 66.7% (n=12) of BRAF, 22.2% (n=2) of NRG1, and 40% (n=2) of EGFR. Of the 32 NSCLC patients with rare fusions detected, 31% (n=10) harbored an NCCN NSCLC guideline-recommended co-variant. This frequency varied by fusion type: 50% (9/18) of BRAF, 11% (1/9) of NRG1, and 0% of EGFR. All patients with a BRAF fusion and NCCN-recommended co-variant (n=9) had EGFR exon 19 deletions [n=9]; two of these patients had additional T790M variants. Seven out of 8 patients with co-occurrence of BRAF fusions and EGFR SNV/indels, with concomitant treatment information, were treated with EGFR-targeted therapy prior to sequencing, implicating the clonal emergence of BRAF fusions as a possible resistance mechanism to anti-EGFR therapy.

Conclusions: Concurrent DNA-RNA NGS improved the detection rate of emerging rare fusion variants in advanced NSCLC patients compared to DNA-NGS, doubling the number of rare fusions detected and eligible patients that may benefit from targeted therapy. Importantly, co-occurrence of rare fusions and EGFR classical activating mutations in patients pre-treated with anti-EGFR therapy suggests a potential resistance mechanism and consideration of upfront, dual mutation, targeted treatment to improve outcomes. Further clinical studies are needed to validate the best treatment options for these patients with rare fusions.

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EP.06F.07 Comparison Between EGFR PCR Alone and NGS with Gene Fusion PCR for Detecting Oncogenic Driver Alteration in Thai NSCLC Patients

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Introduction: Targeted therapies have significantly improved the prognosis for NSCLC patients with oncogenic driver alterations. Thus, molecular testing results are essential to determining the systemic treatment option. EGFR mutation is the most common altered oncogene among Thai NSCLC patients. This mutation can be detected using PCR and NGS. While EGFR PCR offers faster turnaround time (TAT) and lower costs, it does not identify other less common actionable alterations. Conversely, NGS provides comprehensive mutation detection at the expense of longer TAT and higher costs. Since EGFR TKI is the only targeted therapy reimbursable for all Thai patients, EGFR PCR alone is the most commonly used test for NSCLC patients in Thailand. Here, we evaluated the concordance of EGFR test results between PCR and NGS and analyzed their TAT. Moreover, we examined the benefit of concurrent NGS and gene fusion-panel PCR to detect other actionable alterations.

Methods: We conducted a retrospective analysis of 155 NSCLC patients who were treated at Siriraj Hospital and Siriraj Piyamaharajkarun Hospital in Bangkok, Thailand, from November 2021 to August 2023 and had concurrent EGFR PCR, gene fusion-panel PCR, and targeted NGS results. Tumor tissue was tested using cobas EGFR mutation test v2, Idylla GeneFusion assay, and QIAact Lung DNA UMI Panel or QIAact AIT UMI Panel (sequenced with Qiagen GeneRead NGS system) or QIAseq targeted DNA-AIT panel (sequenced with MiSeq), respectively. Data were analyzed using SPSS Version 29.0.2.0.

Results: EGFR PCR detected EGFR mutation in 53.5% (83/155) of cases (Table). All EGFR PCR-positive cases were also detected by NGS, although one case with exon 19 deletion was identified as L747P by NGS. Among EGFR PCR-negative cases, NGS detected uncommon EGFR mutations (L861R/L833F, A750FS, G779F) in 3 cases. Cohen's kappa coefficient for EGFR mutation detection between PCR and NGS was 0.96 [95%CI 0.917 to 1.005]. NGS and gene fusion-panel PCR recognized an additional 37/155 cases (23.9%) harboring other oncogenic driver alterations (Table). Median (SD) TAT for EGFR PCR, gene fusion-panel PCR, and targeted NGS were 7.1 (3.8), 7.1 (3.8), and 19.0 (4.7) days, respectively.

Conclusions: Sensitizing EGFR mutation was found in 49.7% of NSCLC patients in Thailand. EGFR test results were highly concordant between PCR and NGS. However, NGS had a 12-day longer TAT compared to EGFR PCR. Gene fusion-panel PCR and NGS identified an additional 11.6% of patients harboring actionable alterations who may benefit from FDA-approved targeted therapies.

Keywords: EGFR, PCR, NGS

Mutation detected by EGFR PCR	Number of cases (%)	Remarks
Total EGFR mutation	83 (53.5)	
- Exon 19 deletion	37 (23.9)	
- L858R	40 (25.8)	
- L858R with T790M	2 (1.3)	1 de novo T790M, 1 acquired T790M
- Exon 19 deletion with T790M	1 (0.6)	de novo T790M
- G719X	2 (1.3)	
- Exon 20 insertion	1 (0.6)	
Other oncogenic driver alterations detected by gene fusion-PCR and targeted NGS in EGFR PCR-negative patients	Number of cases (%)	
KRAS G12C mutation	2 (1.3)	
KRAS non-G12C mutation	16 (10.3)	
ALK fusion	5 (3.2)	
ROS-1 fusion	3 (1.9)	
MET exon 14 skipping mutation	3 (1.9)	
HER-2 mutation	3 (1.9)	
BRAF V600E	1 (0.6)	
BRAF non-V600E	3 (1.9)	
RET fusion	1 (0.6)	

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EP.06F.08 Cancer Evolution Analysis for Lung Carcinomas with Multiple Driver Mutations

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Introduction: Driver gene mutations in non-small cell lung cancer (NSCLC) are generally considered to be mutually exclusive. However, rare cases have been reported in which multiple driver mutations within the same tumor or multiple tumors within the same individual harbor different driver mutations.

Methods: In this study, we report on NSCLC cases in which multiple driver mutations were detected in the same individual and discuss their clinical significance and implications for treatment using RNA sequencing for cancer evolution analysis.

Results: Case 1. 77-year-old male, suspected N1 lung adenocarcinoma, planned neoadjuvant therapy. However, surgery and adjuvant therapy using EGFR TKI were planned because the biopsied specimen harbored the EGFR L858R mutation. Left upper lobectomy was performed, and postoperative pathology was T3N0M0 adenocarcinoma and showed EGFR L858R+KRAS G12C. Adjuvant therapy with CDDP+VNR was performed after surgery. Case 2. 59-year-old female, 8mm ground-glass opacity in the right middle lobe, suspected early-stage lung cancer, and the tumor was resected. Pathological diagnosis was adenocarcinoma, pT1aN0M0, pStageIA1, with EGFR Exon19del + KRAS G12C in the same tumor. Case 3. 72-year-old male, cT1N1M0 squamous cell carcinoma. Neoadjuvant therapy was performed. However, the tumor was unresectable due to PD. EGFR G810S mutation + G857W mutation + KRAS G12C mutation were detected in a biopsied specimen from the tumor. Case 4. 64-year-old female, multiple adenocarcinomas, pT1cN0M0, pStage IA3, underwent right upper lobectomy. EGFR Exon19 del mutation + MET Exon14del mutation was detected in different tumors in the same individual.

Conclusions: Genetic mutations in lung cancer have traditionally been considered mutually exclusive. However, owing to the recent increased use of multiplex testing using next-generation sequencing (NGS), lung cancer cases with multiple driver mutations in the same individual have been reported. In this study, we reviewed NSCLC cases positive for multiple driver gene mutations based on NGS testing and discussed the mechanisms of driver mutations on cancer development and progression. We reported a cancer evolution analysis of four lung cancer cases with multiple driver mutations.

Keywords: Cancer Evolution Analysis, RNA Sequence, Gene Mutation

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EP.06F.09 Epidemiological Profile of Patients with Non-Small Cell Lung Cancer Treated at Oncologia D' or Bahia from January 2018 to December 2022.

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Introduction: Lung cancer is one of the most prevalent tumors in the world and responsible for the highest mortality among neoplasms. Its epidemiological and anatomopathological profile has been changing over the years and with the advancement of precision medicine, the treatment of non-small cell lung cancer is no longer based solely on chemotherapy and has become more individualized and with based on specific molecular changes and programmed death ligand-1 (PDL-1) status. The presence of driver mutations varies according to different geographic regions and patient profiles, therefore, it is extremely important to define the epidemiological and molecular profile of patients treated in our region.

Methods: After approval by the local ethics committee, a retrospective, cross-sectional, descriptive study was carried out, collecting data from medical records of patients diagnosed with non-small cell lung cancer undergoing treatment in at least one of the units of the Oncologia D´or Bahia from January/2018 to December/2022.

Results: The medical records of 422 patients were analyzed and 160 patients were included in the study. The patients were mostly women (56.25%), smokers (55%) and with an median age on the diagnostic of 67,5 years. The most common histology was non-squamous (81.25%), followed by squamous cell carcinoma (15.6%). Around 50% of the patients were diagnosed in EC IV and most patients did not have an indication for curative thoracic surgery at the time of diagnosis (59.3%). Regarding molecular characteristics, 15% of patients had PDL1 between 1-49%, 10% had high PDL1 expression (≥50%) and 17.5% of patients were PDL1 negative. The most common driver mutations found in the studied population were EGFR (23%), followed by ALK (3.75%), MET (3.1%), KRAS G12C (2.5%), ROS-1 (2.5%) , HER-2 (1.25%) and RET (0.62%). Statistical analysis is being carried out to evaluate the correlation between age, smoking, site of metastases and the presence or absence of PDL1 expression and driver mutations.

Conclusions: The data found in this work is similar to other Brazilian studies on the epidemiological profile of patients with non-small cell lung câncer.

Keywords: Non-Small Cell Lung Cancer, Epidemiology, Molecular

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EP.06G.01 Prognostic Significance of Purinergic Receptor- and Ectonucleotidase- Expression in NSCLC Tumor Cells and Stroma

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Introduction: Purines are not merely a source of energy but have the ability to act as extracellular signal molecules and activators of immune cells. Therefore, the purinergic system regulates the antineoplastic immune response and plays an important role in the development and progression of solid tumors. The purinergic system is controlled by two key players: purinergic receptors and ectonucleotidases. This study investigates how their expression in the tumor cells and the tumor microenvironment interferes with the tumor biology and prognosis.

Methods: In this retrospective cohort study, we analyzed tumor tissue samples of 142 patients diagnosed with NSCLC. Tissue microarrays were created and stained immunohistochemically to detect the expression of the purinergic receptors and ectonucleotidases. A histochemical H-score was used to divide the tissue into high and low expressing phenotypes in tumor cells and stroma. These phenotypes were then correlated with the clinical and pathological data. The purpose of this study was to determine whether the expression of the purinergic receptors P2X4/P2X7 and the ectonucleotidases CD39/CD73 correlates with the overall (OS) and progression-free survival (PFS). As a secondary endpoint it was analyzed how different expression patterns influence clinical parameters like tumor size, pack years, metastasis or SUVmax.

Results: Higher levels of the purinergic receptor P2X4 in the tumor cells correlated with a prolonged PFS (p=0.036; HR 2.11 [1.05-4.22]). Similarly, an overexpression of CD39 on the malignant cells is a favorable prognostic factor (PFS p=0.007; HR 1.89 [1.19-2.99]; OS p=0.009; HR 2.08 [1.2-3.61]). On the contrary, a lower expression of CD73 in the tumor is associated with an extended PFS (p=0.004; HR 0.43 [0.24-0.77]) and OS (p=0.035; HR 0.55 [0.32-0.96]). In the stroma cells, higher levels of both CD39 (p=0.008; HR 2.2 [1.23-3.94]) and CD73 (CD73 p=0.03; HR 3.58 [1.13-11.4]) correlate significantly with a longer PFS. An association between an overexpression of CD39 and a smaller tumor size (p=0.016), a lower SUVmax(p=0.035) and a reduced tendency to metastasize (p=0.006) and relapse (p=0.003) could be observed.

Conclusions: This study demonstrates a correlation of the purinergic system with the tumor biology and survival in NSCLC. Notably, ectonucleotidases can be identified as factors with a high prognostic and biological impact. From a pathophysiological point of view, an overexpression of CD39 and low CD73 levels lead to higher concentrations of purinergic metabolites and activate the antineoplastic immune response. This mechanism explains the observed impact on PFS and OS of the respective expression patterns.

Keywords: NSCLC, purinergic system, immunotherapy

EP.06G.02 Profiling the Metastatic Potential of Non-Small Cell Lung Cancer Patients Based on TP53 Classification

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Introduction: Non-small cell lung cancer (NSCLC) is known for its high metastatic potential, yet the precise genetic profile metastatic potential remains elusive. In this study, our aim was to characterize the molecular features contributing to metastatic potential, focusing on TP53 classification.

Methods: In the present study, 2736 treatment-naïve patients diagnosed with stage I to stage IV NSCLC were enrolled. Tissue samples from targeted lesions underwent processing using next-generation sequencing (NGS) technology. The NGS platform utilized was a commercially available gene panel comprising 68 cancer-related genes (Burning Rock Biotech, Guangzhou, China). We performed an analysis to assess the association between TP53 mutation frequency and histopathological types to characterize potential molecular features. Additionally, we investigated the disparities between TP53 (-) and TP53 (+) patients. Finally, we initiated the development of a TP53-based classification system for metastatic features.

Results: In this cohort, 48% of patients were diagnosed with invasive LUAD, 11% with LUAD, 9% with LUSC, and the remaining patients were diagnosed with other pathological subtypes, including microinvasive LUAD (7%), LUAD in situ (6%), and LUAD + LUSC (3%). Among patients diagnosed with LUAD in situ, microinvasive LUAD, and invasive mucous LUAD, the percentages of TP53 (+) patients were 1%, 6%, and 13%, respectively, defining them as the TP53 (Low) cohort. For those diagnosed with acinar invasive LUAD, invasive LUAD, and LUAD, the percentages of TP53 (+) patients were 30%, 32%, and 55%, respectively, defining them as the TP53 (Medium) cohort. Patients diagnosed with poorly differentiated LUAD, metastatic LUAD, and LUAD + LUSC had percentages of TP53 (+) patients at 68%, 70%, and 74%, respectively, defining them as the TP53 (High) cohort. Finally, patients diagnosed with non-keratinized LUSC, keratinized LUSC, and LUSC had percentages of TP53 (+) patients at 78%, 89%, and 95%, respectively, defining them as the LUSC cohort. These findings suggest that pathological subtypes with high malignancy harbor a higher frequency of TP53 mutation. Further analysis indicates that specific TP53 co-mutations, such as RB1+ATM, KRAS+STK11, EGFR+KRAS, contribute to increased metastatic potential in LUAD, while specific TP53 co-mutations, such as PIK3CA+CDKN2A, FGFR1+FGF4, contribute to increased metastatic potential in LUSC.

Conclusions: Collectively, this study suggests that differences in driver gene patterns potentially play a crucial role in increasing metastatic potential. The acquisition of tumor metastatic potential may be closely associated with these co-mutations, particularly in TP53 (+) patients.

Keywords: NSCLC, TP53 mutation, Metastatic features

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EP.06G.03 Newly WHO Reporting System for Lung Cytopathology: Reproducibility Test of the Diagnosis

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Introduction: Diagnosis of lung cancer and management of patients requires histological or cytopathological diagnosis. In particular, cytopathological specimens of lung cancer may be collected even when tissue cannot be obtained, and can be used for cytopathological and genetic diagnosis. However, until now, there has been no universal cytopathological category classification for lung cancer. Therefore, the Japanese Lung Cancer Society (JLCS) and the Japanese Society of Clinical Cytology (JSCC) jointly proposed four cytopathological categories: "negative for malignancy," "atypical cells," "suspicious for malignancy," and "malignancy. The WHO Reporting System for Lung Cytopathology in 2022 added "Insufficient/Inadequate/Non-diagnostic" to these four categories and proposed the following five categories: "Insufficient/Inadequate/non-diagnostic", "benign", "atypical ", "suspicious for malignancy," and "malignant". In order to disseminate this classification widely, we evaluated the reproducibility of the category through tutorial, and investigated the issues and problems with the category.

Methods: Forty-two cases were selected from the case that had been collected for previous studies to create this classification, and a diagnostic and tutorial system was created and reviewed through web-based first diagnosis, tutorial, and second diagnosis. Participants were recruited through the website of JLCC and by e-mail. One 100x and one 400x photograph centered on the lesion to be diagnosed in each case was shown. The questions were: 4 choices for the category under the new criteria (benign, atypical, suspicious for malignancy, malignant), 7 choices for the presumed pathological diagnosis (benign tumor, inflammatory change, adenocarcinoma, squamous cell carcinoma, small cell carcinoma, large cell neuroendocrine carcinoma, other), and 4 choices for the first and second decision bases (cell cluster, cytoplasm, nuclei, other). The results were analyzed and compared between first and second diagnosis by t-test using calculating the average number/rate of correct or incorrect answers for 42 cases per participant and for 105 participants per case in both diagnoses. χ-square test was used to identify cases with diagnostic difficulties and cases with high tutorial effect, and to explore the problems.

Results: There were 105 participants with the average number of correct answers by category being 16 (16/42: 38.1%) for the first diagnosis and 20.3 (20.3/42: 48.3%) for the second diagnosis, with a significant increasing ($p < 0.001$). The analysis was divided into seven presumed pathological diagnosis, 105 participants had average number and rate of correct answers of 20.3 (20.3/42:48.3%) in the first diagnosis and 25.1 (25.1/42:59.8%) in the second diagnosis, significantly increasing with $p < 0.001$. The average number/rate of correct answers per case for the 42 cases was 40.2 (40.2/105:38%) in the first diagnosis and 51.5 (51.5/105:49%) in the second diagnosis, which increased significantly ($p=0.0147$). Four cases that were difficult to match even after tutorial and 3 cases that were highly effective in tutorial were presented. The most important basis for diagnosis was nuclear findings in both diagnoses.

Conclusions: It is necessary to educate and disseminate appropriate diagnostic criteria so that this report form can be used accurately. In particular, it is necessary to devise ways to have patients with ambiguous findings, those with poor characteristic morphology correctly diagnosed with cancer.

Keywords: WHO Reporting System for Lung Cytopathology, Reproducibility testing, Five categories

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EP.06G.04 Clinicopathological Differences between EGFR Mutated and EGFR Wild-Type Lung Adenocarcinoma with Papillary Predominant Pattern

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Introduction: We aimed to reveal the clinicopathological differences between epidermal growth factor receptor (EGFR)-mutated and wild-type (WT) lung adenocarcinoma (LUAD) focusing on the predominant subtype.

Methods: This study included 352 with EGFR mutation and 370 with WT patients in consecutive stage I LUAD classified by the predominant subtype, and their clinicopathological characteristics and prognosis were analyzed. Using the Cancer Genome Atlas Program (TCGA) cohort, we analyzed differences in gene expression between EGFR mutation and WT groups. Furthermore, we performed immunohistochemical evaluations for 46 with EGFR mutation and 47 with WT patients in consecutive stage I papillary predominant adenocarcinoma (PPA).

Results: Compared to the PPA with WT [n = 115], those with EGFR mutation [n = 99] exhibited smaller invasive size ($p = 0.03$) and less frequent vessel invasion ($p < 0.01$). However, PPA with EGFR mutation showed significantly worse 5-ys recurrence-free survival (RFS) rates compared to those with WT (70.6% versus 83.3%, $p = 0.03$). Contrarily, no significant differences were observed in other predominant subtypes. In the TCGA cohort, PPA with EGFR mutation tended to show higher expression of galectin-3, which is associated with tumor metastasis and resistance to anoikis, compared to those with WT ($p = 0.06$). Immunohistochemical evaluation revealed that galectin-3 expression was significantly higher in PPA with EGFR mutation than in those with WT ($p < 0.01$).

Conclusions: The prognosis for PPA with EGFR mutation proved to be less favorable compared to that with WT, which might be due to a higher expression level of galectin-3.

Keywords: Papillary predominant lung adenocarcinoma, Galectin-3, Anoikis

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EP.06G.05 Molecular Characteristics of Pulmonary Lymphoepithelioma-Like Carcinoma in the Chinese Population

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Introduction: Pulmonary lymphoepithelioma-like carcinoma (PLELC) is a rare and distinct subtype of non-small cell lung cancer often with better clinical outcomes than other subtypes. It usually affects young, non-smoking, Asian populations and is associated with Epstein-Barr virus (EBV) infection. The molecular characteristics of PLELC are relatively vague due to its rarity, which may limit the treatment of this rare malignancy.

Methods: We retrospectively studied the Next-generation sequencing (NGS) data (733-gene panel) of tumor tissue specimens from 26 PLELC patients over the past 3 years. All samples were obtained by surgical resection or aspiration biopsy. Microsatellite instability and EBV infection were also detected by NGS.

Results: In 26 PLELC patients performed NGS, the median age was 48.5 years and 69.2% were female. Genomic analysis revealed that 61.5% (16/26) of the patients exhibited gene alterations with no typical driver mutations, predominantly in the form of copy number variations (CNVs, 9/26) and single nucleotide variations (SNVs, 9/26). There was no statistical difference in age between patients with and without gene alterations (median: 48.5 vs 52.5 years,p=0.672, Mann-Whitney U test). Among the genes with copy number gains, the 11q13 amplicon (CCND1/ FGF19/ FGF4/ FGF3) showed the highest frequency (11.5%, 3/26), along with KRAS (11.5%, 3/26) and CCND2 (11.5%, 3/26). SNVs were identified in TP53, CYLD, CBFB, NRAS, AXIN1, PIK3CA, BMPR1A, NFKBIA in 34.6% (9/26) of PLELC patients, in addition to an ATM insertion. No gene arrangement variation was detected. One PLELC patient presented solely with a germline pathogenic deletion mutation in BAP1 which predisposed to various cancers, without any coinciding somatic gene alterations, indicating a possible genetic risk. There were no patients with microsatellite instability (MSI) and 22 patients were found to be positive for EBV.

Conclusions: The study demonstrates a notable frequency of copy number variations at 11q13, KRAS, and CCND2 in PLELC. Exploring the molecular features of PLELC enhances our comprehension of its underlying biology, thereby advancing the diagnosis and precise management of this uncommon malignancy.

Keywords: Molecular characteristics, PLELC, Copy number variations

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EP.06G.06 Molecular Profiling of Separate Primary Non Small Cell Lung Cancers

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Introduction: Reflex NGS testing for all NSCLC tumors is standard at our institution. Tumors with same histological diagnosis and different molecular profiles may be considered separate primary lung cancers.

Methods: Retrospective review of NSCLC cases at our institution with more than one tumor molecular profile report. The molecular profile is an in-house NGS assay detecting DNA and RNA alterations in over 60 genes including known driver mutations (EGFR, ALK fusion, KRAS, MET amplification) and other genes relevant to solid tumors (TP53).

Results: Fifty-five (55) paired specimens with separate molecular profile reports were identified (total of 110 specimens). Adenocarcinoma was the most common histologic diagnosis. Squamous histology was present in 14 pairs, and 5 pairs had discordant histology. At least one alteration in TP53 was detected in 73% of specimens (40/55) and represented the most common alteration. In 15 cases, the TP53 mutations were at different loci. In 18 cases, only one of the paired samples carried a TP53 mutation. KRAS was the next most common alteration, mostly discordant between pairs. 7/55 paired samples had KRAS mutation at the same gene but different loci. Only 4% (2/55) of the pairs had the same KRAS alteration, and also had discordant TP53 alterations.

Conclusions: Molecular profiling with NGS should be performed on multifocal tumors. Most tumors have different molecular profiles despite same histology, suggesting separate primary lung cancers with distinct clonal evolution.

Keywords: molecular profile, NSCLC

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EP.06G.08 Clinicopathologic and Molecular Features of SWI/SNF-Deficient Thoracic Tumors

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Introduction: Recently identified subtype known as SWI/SNF (Switch/Sucrose Non-Fermenting) defective tumors has emerged. SMARCA2 and SMARCA4 are two catalytic subunits essential for the function of the SWI/SNF complex. Particularly, inactivating mutations in the SMARCA4 gene result in a loss of expression of the catalytic subunit BRG1 and establish a critical link to tumorigenesis.

Methods: Immunohistochemical, second-generation sequencing technology, and statistical methods were applied to analyze the clinicopathological, and genomic features and prognosis of SWI/SNF-deficient thoracic tumors.

Results: Using the expression of keratin and SMARCA2 as classification criteria, we classified the cases into SMARCA4-deficient non-small cell lung cancers and thoracic SMARCA4-deficient undifferentiated tumors. A minority (15/37) exhibited the common morphological features of highly moderately differentiated adenocarcinomas, which was the same as the 12 cases of isolated deletion tumors in the SMARCA2 gene, and the majority of cases (22/37) exhibited poorly differentiated or undifferentiated morphology. In addition, 10 cases were classified as " thoracic SMARCA4-deficient undifferentiated tumor with rhabdomyosarcoma-like tumor cells, with a few exhibiting epithelioid cell histomorphology. By X-tile, we analyzed the IRS and prognostic correlation of SMARCA4 in 485 cases, with an optimal cutoff value of 5 (P=0.00011). In our study, those with SMARCA4-deficient non-small cell lung cancers demonstrated a better prognosis compared to those with thoracic SMARCA4-deficient undifferentiated tumors (P=0.0219). Furthermore, patients exhibiting moderately to highly differentiated morphology showed improved prognoses (p = 0.0004), as did those who received immunotherapy (p = 0.036. In contrast to SMARCA4-deficient tumors, only one patient of the 12 SMARCA2-deficient tumors with preserved SMARCA4 expression received chemotherapy but had a good prognosis.

Conclusions: SMARCA4 could be a new predictor of lung tumor prognosis.

Keywords: SMARCA4, Thoracic Tumor, SWI/SNF-deficient

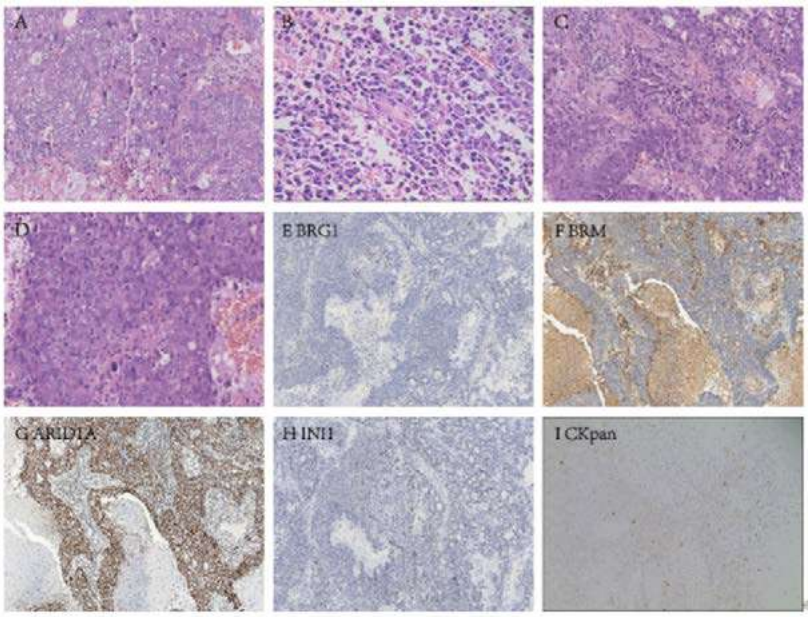

FIGURE 2. Histologic and immunohistologic features of SD-TSTs. The tumor cells were solid or glandular in arrangement, with epithelioid cells, large size, abundant cytoplasm, eosinophilic, and obvious nucleoli. (A) The tumor cells were rhabdoid in shape and some of them were polygonal. (B) Lymphocytic infiltration is seen in the interstitium of the tumor. (C) The nuclei of tumor cells are obvious, with loss of adhesion and pathological nuclear division images easily seen. (D) SMARCA4 expression was negative in tumor cells and positive in the nuclei of the stromal lymphocytes. (E) SD-TSTs showed negative expression of SMARCA2 in the nuclei of tumor cells. (F) Most of the tumor cells were positive for BAF250A in the nucleus. (G) Most of the tumor cells were positive for SMARCB1 in the nucleus. (H) Negative expression or diminished expression of pan-CK. (I)

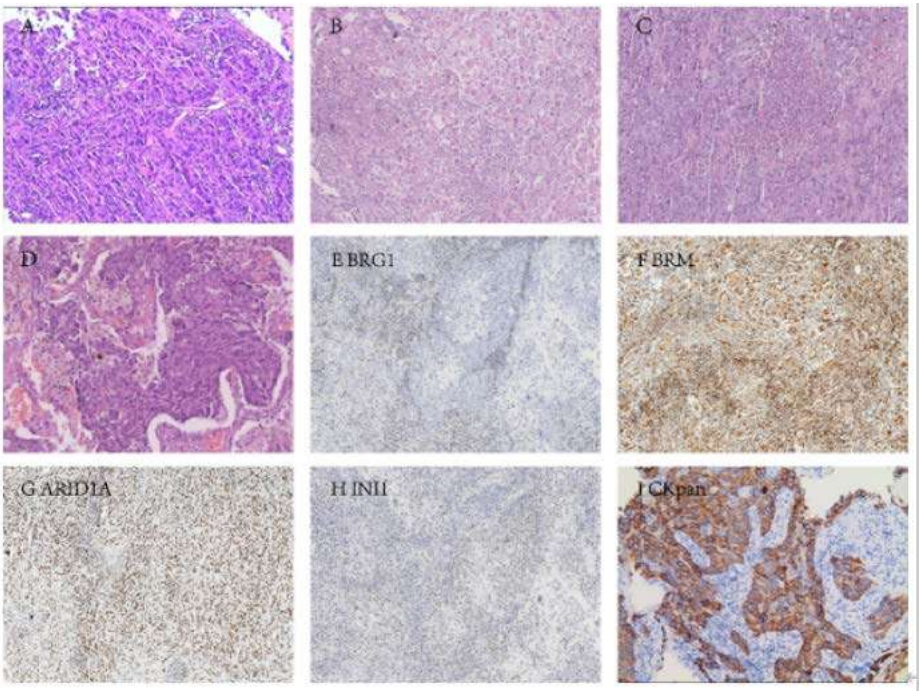

FIGURE 1. Histologic and immunohistologic features of SD-NSCC. The tumor cells were solid and glandular in arrangement, with epithelioid morphology, large cell volume, abundant cytoplasm, and eosinophilic. (A) Classic rhabdoid cells. (B) A large number of lymphocytic infiltrates were seen in the interstitium. (C) Focal clear cytoplasm and vesicular chromatin, pathologic mitosis is easily seen. (D) SMARCA4 expression was negative in tumor cells and positive in the nuclei of the stromal lymphocytes. (E) SD-NSCC tumor cells were positive for SMARCA2 in the nucleus. (F)) Positive for BAF250A in the nucleus of tumor cells. (G) Positive for SMARCB1 in the nucleus of tumor cells. (H) Diffused positive expression for pan-CK (I)

EP.06G PATHOLOGY AND BIOMARKERS - PATHOLOGY
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EP.06G.09 Harnessing Real-World Data for Translational Research in Lung Cancer: MD Anderson Thoracic GEMINI Program

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Introduction: Lung cancer continues to be the foremost cause of cancer-related fatalities worldwide, with nearly 2 million lives lost each year. The majority of lung cancer patients receive standard-of-care (SOC) treatments. The treatment experiences of these patients including their diagnostic tasting, treatment-related side effects, tumor responses and overall survival, hold valuable information that can inform lung cancer therapy and shape future clinical trials. Unfortunately, this invaluable data is not consistently captured. To maximize the knowledge gained from each lung cancer patient treated at MD Anderson Cancer Center (MDACC), we have initiated the Thoracic GEnomic Marker-guided Therapy INItiative (GEMINI) program.

Methods: Following completion of consent procedures, we systematically gather comprehensive molecular, clinical, and demographic information (>850 data points per patient) from lung cancer patients seeking oncological care at MDACC. These data are meticulously curated by data specialists with specialized training in thoracic oncology. Additionally, optional peripheral blood samples are collected, and any remaining tumor specimens following clinical diagnosis and molecular profiling are carefully stored. During SOC biopsies, additional tissue samples are collected when deemed safe, for patient-derived xenograft models, primary cell lines or banked for translational research projects. Collaborating with information technology experts and data scientists, we are developing a user-friendly electronic medical record (EMR) interface to facilitate accurate and efficient review of molecular biomarkers. Furthermore, we are establishing a pipeline utilizing natural language processing (NLP) techniques, which will transform biomarker data from various sources into structured data.

Results: From 01/28/2014 to 04/04/2024, GEMINI database currently houses comprehensive clinical and molecular data from 12,981 lung cancer patients with prospective collection of 7,673 blood samples and 846 tumor tissues in addition to the remaining diagnostic specimens. Serving as a research platform across MD Anderson and other collaborating institutions, GEMINI has facilitated 120 projects, resulting in 115 impactful publications and 250 meeting abstracts. For instance, GEMIMI has served as the essential platform for a series of studies on Kras co-mutations and the impact of radiomics features on the benefit from immunotherapy in lung cancer patients. Importantly, many of these studies have served as critical rationale for numerous clinical trials that have led to the change of SOC. Additionally, leveraging artificial intelligence, we are implementing a continuous learning system that integrates both molecular biomarkers and clinical data, thereby enhancing the research process, improving data precision, and enabling comprehensive data analysis.

Conclusions: The MDACC Thoracic GEMINI program is a prospective initiative designed to systematically gather, archive, and analyze clinical, molecular, and demographic data from lung cancer patients. Databases like GEMINI serve as invaluable reservoirs of information for lung cancer investigations, contributing to enhanced patient outcomes and propelling advancements in personalized oncology therapy.

Keywords: Database, Translational research, Realworld

EP.06G PATHOLOGY AND BIOMARKERS - PATHOLOGY
SATURDAY, SEPTEMBER 7, 2024 - 11:58 - 11:59

EP.06G.10 Comprehensive Analysis of the Clinicopathological Features, Targetable Profle, and Prognosis of Mucinous Adenocarcinoma of the Lung

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Introduction: The clinicopathological or genetic features related to the prognosis of mucinous adenocarcinoma are unknown because of its rarity. The clinicopathological or targetable features were investigated for better management of patients with mucinous adenocarcinoma of the lung.

Methods: We comprehensively evaluated the clinicopathological and genetic features of 60 completely resected mucinous lung adenocarcinomas. Targetable genetic variants were explored using nCounter and polymerase chain reaction, PD-L1 and TTF-1 expression were evaluated using immunohistochemistry. We analyzed the prognostic impact using the Kaplan-Meier method and log-rank test.

Results: Of the 60 enrolled patients, 13 (21.7%) had adenocarcinoma in situ/minimally invasive adenocarcinoma, and 47(78.3%) had invasive mucinous adenocarcinoma (IMA). Fifteen patients (25%) showed a pneumonic appearance on computed tomography (CT). CD74-NRG1 fusion, EGFR mutations, and BRAF mutation were detected in three (5%), four (6.7%), and one (1.7%) patient(s), respectively. KRAS mutations were detected in 31 patients (51.7%). Two patients (3.5%) showed immunoreactivity for PD-L1. No in situ or minimally invasive cases recurred. IMA patients with pneumonic appearance had signifcantly worse recurrence-free survival (RFS) and overall survival (OS) ($p<0.001$). Furthermore, IMA patients harboring KRAS mutations had worse RFS ($p=0.211$). Multivariate analysis revealed that radiological pneumonic appearance was signifcantly associated with lower RFS ($p<0.003$) and OS ($p=0.012$). KRAS mutations served as an unfavorable status for RFS ($p=0.043$).

Conclusions: Mucinous adenocarcinoma had a low frequency of targetable genetic variants and PD-L1 immunoreactivity; however, KRAS mutations were frequent. Pneumonic appearance on CT imaging and KRAS mutations were clinicopathological features associated with a worse prognosis.

Keywords: lung cancer, mucinous adenocarcinoma, KRAS mutation

EP.06G PATHOLOGY AND BIOMARKERS - PATHOLOGY
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EP.06G.11 Effects of Gut Microbiota and Metabolites on Peritoneal Metastasis of Non-Small Cell Lung Cancer

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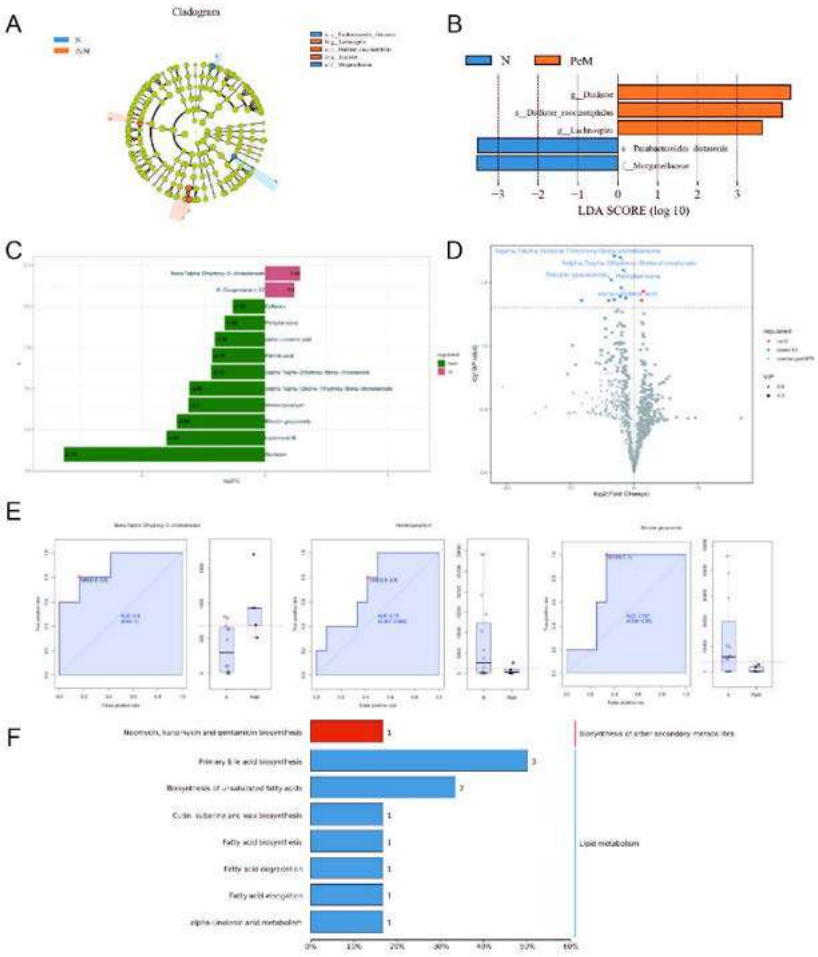
Introduction: Peritoneal metastasis (PM) is a rare metastasis of non-small cell lung cancer (NCLC), and patients with PM have a poor prognosis. Previous studies have shown that gut microbiota and its metabolites are closely related to lung cancer. At present, the relationship between gut microbiota and its metabolites and PM of NCLC still needs further investigation.

Methods: The study included 17 newly diagnosed NCLC patients and collected their baseline stool samples prior to treatment. Patients were divided into N group and PeM group according to the presence or absence of PM at diagnosis. Metagenomic sequencing and metabolomics detection were performed on fecal samples from the two groups to compare the differences in gut microbiota and metabolites between the two groups, analyze related metabolic pathways, and search for potential biomarkers.

Results: Among the enrolled NCLC patients, 5 patients had PM and 12 patients had no PM. The analysis found that there were significant differences in gut microbiota and metabolites between the two groups. Compared with patients in the group N, the abundance of Dialister, Dialister_succinatiphilus and Lachnospira in the PeM group increased, while the abundance of Parabacteroides_ distasonis and Morganellaceae decreased. In PeM group, metabolites such as 3beta,7alpha-Dihydroxy-5-cholestenoates were up-regulated, while metabolites such as Bilirubin glucuronide and Harderoporphyrin were down-regulated. By using the Kyoto Encyclopedia of Genes and Genomes (KEGG) database to enrich the differential metabolites, it is found that the pathway related to lipid metabolism has the most significant difference, including primary bile acid biosynthesis, biosynthesis of unsaturated fatty acids, fatty acid biosynthesis, fatty acid degradation, etc.

Conclusions: This study shows that there are statistical differences in the gut microbiota and metabolites of NCLC patients with or without PM, which may provide new ideas for the prediction, diagnosis, treatment and prognosis assessment of NCLC patients with PM.

Keywords: NCLC, Peritoneal metastasis, Gut microbiota and metabolites



EP.06G PATHOLOGY AND BIOMARKERS - PATHOLOGY
SATURDAY, SEPTEMBER 7, 2024 - 11:58 - 11:59

EP.06G.12 The Fibrosis Around the Pulmonary Artery Is Associated with Difficulty in Dissection During Surgery after Systemic Therapy

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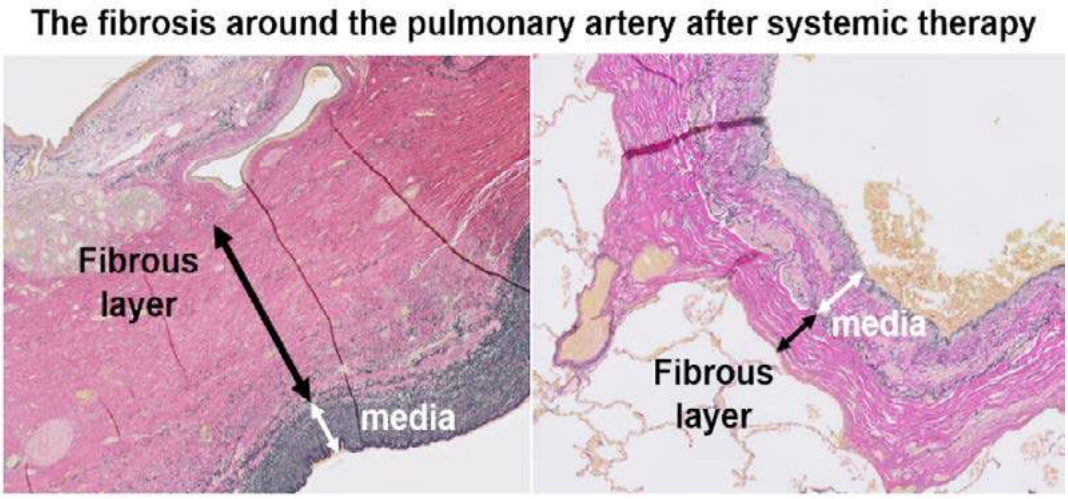
Introduction: The number of surgeries after systemic therapy for lung cancer is increasing. The difficulty of dissection of the Pulmonary Artery (PA) is a serious problem. Large vessels and airways in the tumor bed have been reported to develop therapy-related proliferative fibrosis in the surrounding area after systemic treatment. We investigated the correlation between fibrosis around the PA and difficulty in dissection.

Methods: Six patients who underwent anatomical lung resection after systemic therapy for lung cancer were included. The pathologist (H. N.) identified the proximal part of the PA adjacent to the tumor or metastatic lymph nodes in the resected specimen and assessed using hematoxylin and eosin staining and Elastica van Gieson staining. The thickness of the fibrous layer around the PA was measured and its ratio to the thickness of the media was calculated. The association between perivascular fibrotic change and difficulty in dissecting the sheath of the PA during surgery was analyzed.

Results: Of the six patients, two underwent surgery after neoadjuvant therapy (one bilobectomy after pembrolizumab plus chemotherapy and one lobectomy with nivolumab plus chemotherapy) and four underwent surgery as salvage surgery after systemic therapy (three lobectomies after targeted therapy for ALK rearrangement and one lobectomy after targeted therapy for EGFR mutation). The operation time was 214 ± 70 min and the blood loss was 120 ± 130 mL. Complete resection was obtained in all cases. In one case, we could not dissect the PA from the surrounding parenchyma, and we dissected them together using a stapling device. There was no mortality. Pathological CR was observed in two cases after treatment using immune checkpoint inhibitors. Perivascular fibrous layer around the PA was observed in all cases, and its thickness varied between cases. The ratio of the thickness of the fibrous layer to the media was significantly higher in the four cases in which the pulmonary artery sheath was difficult to dissect than in the other two cases. (2.85 ± 1.19 vs. 0.81 ± 0.04, p = 0.042). We did not find a constant association between the type of systemic treatment and the thickness of the fibrous layer.

Conclusions: The fibrosis around the PA was associated with difficulty in dissection during anatomical lung resection after preoperative systemic treatment. Further research is needed to determine whether the fibrosis arised in the tumor bed and whether radiological findings can predict a thickening of the fibrous layer.

Keywords: mitsue6482S, mitsuekawahara, a19921122



EP.06G PATHOLOGY AND BIOMARKERS - PATHOLOGY
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EP.06G.13 TP53 Somatic Mutation and its Association with Clinicopathological Parameters and Long-Term Clinical Outcome in Non-Squamous NSCLC Patients

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Introduction: Remarkable advances in molecular profiling of non-small cell lung carcinoma (NSCLC), a leading cause of global cancer-related mortality, have led to improvements in long-term clinical outcomes. However, a better comprehension of resistance mechanisms in this heterogeneous disease may add benefit to daily practice. Beyond its well-recognized role in carcinogenesis, p53 alterations emerge as an important resistance mechanism and may guide treatment decisions. In this cohort, we aimed to investigate the prevalence of TP53 somatic mutations among non-squamous (ns) NSCLC patients and their association with clinical features and relevant long-term clinical outcomes.

Methods: We retrospectively collected clinicopathological data from advanced nsNSCLC patients whose full molecular panel, including TP53 mutation, was ordered by an assistant oncologist in a Brazilian referral private center between January 2021 and January 2024. Those harboring STK11 and KEAP-1, recognized as resistance mutations, were excluded. Treatment decisions were made according to local practice. The Cox Regression Model assessed their independent association with long-term outcomes, such as progression-free survival (PFS) and overall survival (OS). Shapiro-Wilk tested normality, with significance assumed at $p < 0.05$.

Results: In this cohort, 39 patients were included. The median age at diagnosis was 64.1 years (SD ±11.95), and adenocarcinoma was the predominant histologic subtype (98.0%). CNS (38.0%) and bones (46.0%) were common metastasis sites. Molecular analyses revealed PD-L1 positivity in 56.4%, TMB < 10 in 74.3%, EGFR mutation in 28.2%, ALK translocation in 7.6%, and somatic TP53 mutations in 64.1% of cases. Co-existing TP53 and RAS mutations were found in 15% of patients. Among patients with targetable mutations (n=12), only 41.6% received the recommended treatment upfront, while 58.3% had their treatment transitioned. Considering the entire cohort, PFS was 13.2 months, and OS was 16.3 months. After adjustment for clinicopathological variables, radiotherapy directed to the primary tumor increased the risk of disease progression by 5.6 times (p=0.01). Unusual site metastases and TMB ≥10 were associated with poor OS (3.1 times, p = 0.04, and 6.89 times, p = 0.01, respectively). Regarding molecular parameters, TP53 somatic mutation seemed to be associated with poor OS (OR 1.8), in univariate analysis, among patients with targetable molecular alteration. However, none of the studied molecular variables were independently associated with relevant clinical outcomes in the multivariate model.

Conclusions: This study assessed the nsNSCLC molecular complexity and its possible role in resistance mechanisms. Somatic TP53 mutations were prevalent among this population and may be associated with poor clinical outcomes, but unequivocal evidence could not be demonstrated. Our findings point towards an association between this mutation and poor clinical responses to tyrosine-kinase inhibitors, but not for immunotherapy, suggesting a possible role in resistance mechanisms. However, further investigation is necessary.

Keywords: Non-small cell lung carcinoma (NSCLC), TP53 somatic mutations, Clinical outcomes

EP.06G PATHOLOGY AND BIOMARKERS - PATHOLOGY
SATURDAY, SEPTEMBER 7, 2024 - 11:58 - 11:59

EP.06G.14 Discovery of Immune-Related Long Noncoding RNA Signatures in Lung Adenocarcinoma

D. Hu, UCLA, Los Angeles/CA/USA

Introduction: Lung adenocarcinoma (LUAD) represents a significant category of lung and bronchus cancers, categorized under non-small cell lung cancer. Unlike squamous cell lung cancer, LUAD is predominantly observed in younger women, individuals with a history of smoking, and within Asian demographics. It mainly originates from the epithelium of the bronchial mucosa, with a smaller proportion stemming from the mucous glands of the larger bronchi. This study focuses on identifying and assessing immune-related long non-coding RNAs (lncRNAs) as potential prognostic biomarkers in LUAD.

Methods: We downloaded lncRNA expression profiles for LUAD from The Cancer Genome Atlas (TCGA) and immune-related genes from the Immunology Database and Analysis Portal (ImmPort). Pearson correlation analysis was conducted to reveal immune-associated lncRNAs. The TCGA LUAD patient cohort was randomly segregated into training and testing groups. Within the training group, both univariate and multivariate Cox regression analyses identified significant immune-related lncRNAs, subsequently verified through Cox regression, principal component analysis (PCA), and receiver operating characteristic (ROC) analysis in the testing group.

Results: Seven immune-related signature lncRNAs with prognostic significance in LUAD were identified. Both univariate and multivariate Cox regression analyses indicated the risk score derived from our seven-lncRNA model as a significant survival indicator, compared to other clinical-pathological factors (age, gender, stage, N, T). Kaplan-Meier survival analysis showed significantly enhanced overall survival in the low-risk group versus the high-risk group across both training and testing cohorts. ROC analysis revealed the AUCs for 5-year overall survival within the range of 0.81-0.89 for training, testing, and the combined cohorts. PCA further evidenced significant divergence in immune status between the high-risk and low-risk groups.

Conclusions: We established a prognostic model in LUAD based on seven immune-related signature lncRNAs. This model may have clinical significance and could contribute to the advancement of tailored immunotherapy approaches for LUAD.

Keywords: Lung adenocarcinoma, Long non-coding RNA, Immune-related biomarkers

EP.06G PATHOLOGY AND BIOMARKERS - PATHOLOGY
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EP.06G.15 Rapid Immunohistochemistry of Microsatellite Instability Using Non-Contact Alternating Current Electric Field Mixing

K. Imai, H. Nanjo, Y. Wakamatsu, S. Takashima, T. Matsuo, S. Kuriyama, H. Suzuki, R. Demura, H. Iwai, S. Shibano, Y. Minamiya, Akita University Graduate School of Medicine, Akita/JP

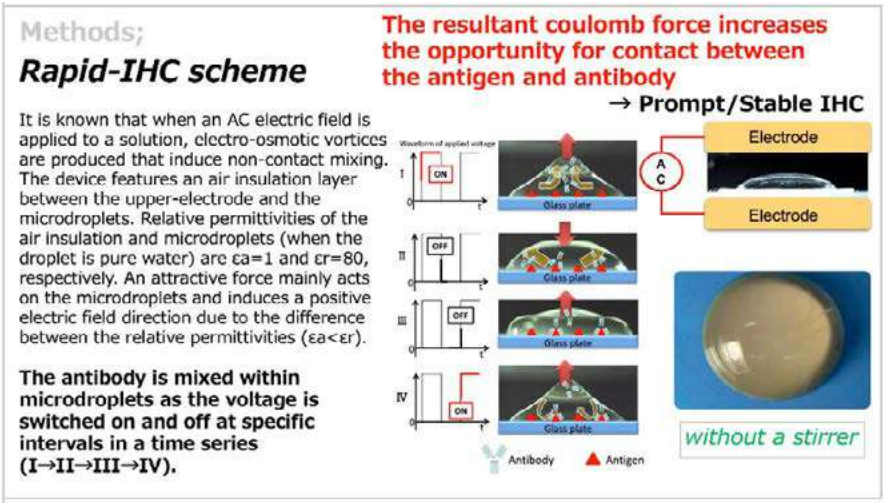
Introduction: Tumors caused by failure of the DNA mismatch repair system generally show microsatellite instability (MSI). High-frequency MSI cancers have been shown to be more susceptible to Immuno-Oncology therapies. The aim of this study was to evaluate the clinical reliability of a new rapid immunohistochemistry (IHC) technique for assessing the molecular status intraoperatively, through detection of tumoral deficient mismatch repair protein (dMMR; MLH1, MSH2, MSH6, and PMS2) expression.

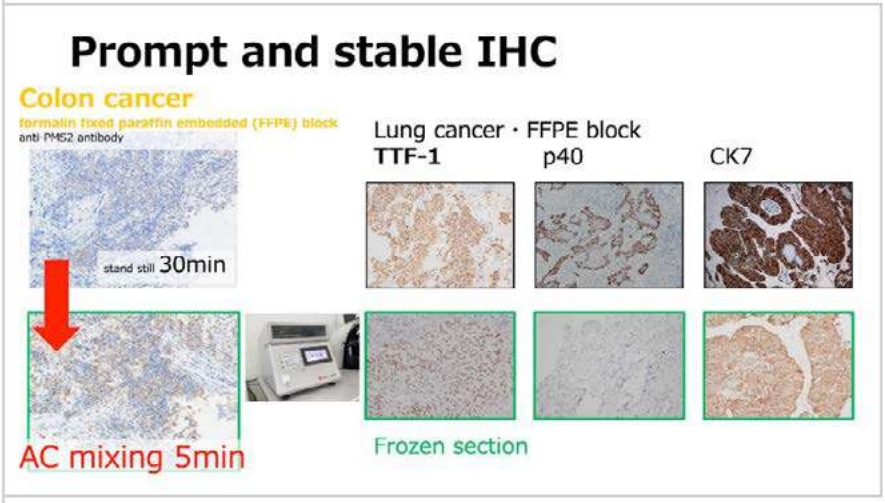
Methods: The rapid IHC method uses non-contact alternating current (AC) mixing to achieve more rapid/stable staining within a minimum of 13 min during surgery (Figures 1 and 2). Three deficient mismatch repair (dMMR)-IHC patients (with Lynch syndrome, 16 formalin-fixed paraffin-embedded (FFPE) samples) and 6 dMMR-IHC deficient patients (6 FFPE samples) in our group hospitals were deemed eligible for establishing MSI-IHC protocol. Of 25 patients obtained the MSI result by MSI Analysis System as companion diagnostics between January 2021 and February 2024, the accuracy of the dMMR diagnoses from frozen sections/FFPE of thoracic/pulmonary tumors are compared between the conventional and rapid AC mixing IHC.

Results: The Rapid-IHC protocol was established with primary antibody 10min / secondary antibody 5min (HRP labeled) using AC mixing for all 4 dMMR antibodies. The concordance of MSI-IHCs staining between the conventional and rapid IHC was achieved 100%. dMMR-High FS/FFPE samples (including a patient with pulmonary sarcoma) were wholly matched.

Conclusions: Rapid MSI-IHC with AC mixing could potentially serve as a clinical tool for intraoperative determination of tumor molecular status. AC mixing technology will contribute to improving pathological diagnostic capability through the development of original/innovative rapid IHC.

Keywords: microsatellite instability, non-contact AC electric field mixing, immunohistochemistry





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EP.06G.16 Pleural Fluid EGFR Mutation Testing in 10 Patients with Advanced Lung Adenocarcinoma with Pleural Effusion

Y. Kim, Y.J. Lee, J.H. Ha, Y.J. Hong, Incheon St. Mary's hospital, Incheon/KR

Introduction: Many studies have documented the utility of malignant pleural effusion (MPE) for detecting EGFR mutations. Reports suggest that MPE supernatant samples could serve as a viable alternative liquid biopsy specimen. These samples contain a higher concentration of tumor-derived DNA compared to plasma samples and are easier to obtain from patients with advanced lung cancer who have MPE.

Methods: From June 2023 to March 2024, we collected pleural fluid to detect EGFR mutations from 11 patients who were suspected to have MPE at Incheon St. Mary's hospital. Among these, we retrospectively reviewed the EGFR positivity, types of mutations, level of circulating free DNA (cfDNA) in pleural fluid, serum, and tissue samples from 10 patients who were diagnosed as lung cancer with MPE.

Results: EGFR mutation tests were performed on the pleural fluid of a total of 11 patients, among whom 10 were diagnosed with lung cancer and 1 was diagnosed with pleural metastasis from colon adenocarcinoma. Among a total of 10 patients with lung cancer and MPE, 2 patients were negative for EGFR mutations in all three specimens-tissue, serum, and fluid. Four patients were positive in all three specimen types. Two patients had positive results in both tissue and pleural fluid, one patient was positive in tissue and serum only, and in one case, the patient was in the terminal stage, and EGFR mutation test could not be performed. Among the four patients who were positive for EGFR mutations in all three types of samples, 2 were found to have the Exon 19 deletion mutation, and 2 had the L858R mutation. In all these 4 patients, cfDNA levels in pleural fluid were found to be higher than those in serum. Notably, among those with the L858R mutation, one patient, who was diagnosed with progression disease due to newly developed MPE, tested negative for the T790M mutation in serum but positive for T790M in the pleural fluid EGFR mutation test.

Conclusions: Testing for EGFR mutations in MPE is efficient and reliable due to the accessibility of samples, quality of specimen considering higher concentration of tumor derived DNA, and it is especially useful for identifying resistance mutations such as T790M in patients with MPE progression disease. It holds promise for guiding treatment decisions in advanced lung cancer. There is anticipation for future work to increase the sample size or conduct prospective studies on this subject.

Keywords: EGFR mutation, Pleural effusion, Lung cancer

EGFR mutation results of three specimens in 10 patients

patient number	sex	age	Pleural fluid EGFR mutation (cfDNA)	Blood EGFR mutation (cfDNA)	Tissue EGFR mutation	Pathology
1	F	81	L858R (13.43)	-	L858R	Adenocarcinoma
2	M	54	-	L858R (12.34)	L858R	Adenocarcinoma
3	M	50	Ex19Del (18.11)	Ex19Del (11.8)	Ex19Del	Adenocarcinoma
4	F	71	-	-	-	Adenocarcinoma
5	M	78	-	-	-	Adenosquamous
6	F	67	L858R (17.34)	L858R (6.48)	L858R	Adenocarcinoma
7	M	80	Ex19Del (21.4)	Ex19Del (9.49)	Ex19Del	Adenocarcinoma
8	F	94	-	-	Not analyzed	Adenocarcinoma
9	M	88	L858R (13.67)	-	L858R	Adenocarcinoma
10	F	79	T790M (15.46), L858R (15.14)	L858R (8.62)	L858R	Adenocarcinoma

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SATURDAY, SEPTEMBER 7, 2024 - 11:58 - 11:59

EP.06G.17 A Clinical Conundrum: Lung Cancer in the Breast

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Introduction: Most patients with lung cancer present with advanced disease. Rarely, lung cancer can metastasize to the breast and be confounded with primary breast carcinoma. To date, only case reports or small series have been published on this topic. Our study provides the largest comprehensive review of the current literature to highlight common key clinical and histopathologic features in this unique patient population.

Methods: A search using the PubMed database for studies published from 1962 to 2024 was performed using the following keywords: "lung cancer", "non-small cell lung cancer", "lung adenocarcinoma", "lung squamous cell", "small cell lung cancer", "lung neuroendocrine", "metastasis to breast", "metastasize to breast", "breast", "metastasize". A secondary search using the references of relevant studies was performed for additional articles. The inclusion criteria consisted of studies of lung cancer with breast metastasis. Articles were excluded for any of the following criteria: 1) lung cancer with breast metastasis was not described, 2) abstracts without full texts were available, 3) insufficient clinical data reported, 4) non-original cases, 5) study was not published in a peer-reviewed journal, or 6) study was written in a non-English language.

Results: Our literature search produced 3268 unique articles. 359 full manuscripts were reviewed based on inclusion and exclusion criteria. 84 manuscripts were included comprising 146 total patients. A summary of patient demographics, clinical disease characteristics, tumor immunohistochemistry and biomarker profile, disease management, and clinical outcomes is described in Table 1. Adenocarcinoma was the predominant cancer type in the breast. 57/114 (50%) of patients had metachronous metastatic breast disease with an average identification time of 24 months from diagnosis of lung primary. The most common site of additional metastatic disease was bone in 32/75 patients (42.7%). Biomarker analysis was consistent with lung adenocarcinoma in most patients; however, markers typically associated with non-lung sites, namely breast and gastrointestinal origin, were positive in a minority of patients. 26/103 (25.2%) were initially managed as primary breast cancer with 24/26 patients undergoing breast resection. Excisional thoracic surgery was performed in 11/49 (22.4%) of patients, which included lobectomy, pneumonectomy, segmentectomy, and decortication. The overall mortality was 58.9%, with an average follow-up of 14.9 months.

Conclusions: Patients with lung cancer that have breast metastasis may be at high risk for misdiagnosis and inappropriate treatments including unnecessary surgery. Our study demonstrates that careful clinical consideration and thorough histopathologic evaluation is critical for accurate management and optimal prognosis for metastatic lung cancer.

Keywords: Lung cancer, Breast, Metastasis

Table 1.

Lung Cancer Breast Metastasis	Patients = 146
Demographics	
Male	15 (10.3%)
Female	131 (89.7%)
Age (Range)	55 (28-84)
Primary Lung Cancer	
ADCA	95 (65.1%)
SCC	4 (2.7%)
NEC	20 (13.7%)
SCLC	23 (15.8%)
Adenosquamous	1 (0.7%)
Carcinoma	2 (1.4%)
NSCLC	1 (0.7%)
Metachronous Breast Cancer	
Yes	57 (50%)
No	57 (50%)
NR	32
Average interval in months (range)	24 (2-87)
Misdiagnosed as Primary Breast Cancer	
Yes	26 (25.2%)
No	77 (74.8%)
NR	43
Survival	
Alive	30 (41.1%)
Dead	43 (58.9%)
NR	73
Follow Up	
Average	14.9 months
Range	<1 week-19 years

Immunohistochemistry					
TTF-1			**CK-7**		
Yes	96 (86.5%)		Yes	45 (91.8%)	
No	15 (13.5%)		No	4 (8.2%)	
NR	35		NR	97	
ER			**CK-20**		
Yes	7 (7.1%)		Yes	2 (7.7%)	
No	92 (92.9%)		No	24 (92.3%)	
NR	47		NR	120	
PR			**Napsin-A**		
Yes	2 (2.4%)		Yes	21 (67.7%)	
No	80 (97.6%)		No	10 (32.3%)	
NR	64		NR	115	
Her-2			**GATA3**		
Yes	2 (5.3%)		Yes	1 (3.7%)	
No	36 (94.7%)		No	26 (96.3%)	
NR	108		NR	119	
GCDFP15					
Yes	0 (0%)		NR	112	
No	34 (100%)				
Molecular Tests					
EGFR			**ROS1**		
Yes	15 (55.6%)		Yes	3 (60%)	
No	12 (44.4%)		No	2 (40%)	
NR	119		NR	141	
ALK					
Yes	6 (35.3%)				
No	11 (64.7%)				
NR	129				

Table 1. ADCA - Adenocarcinoma, SCLC - Small Cell Lung Cancer, NEC - Neuroendocrine Carcinoma, SCC - Squamous Cell Carcinoma, NSCLC - Non-small Cell Lung Cancer, NR - Not Reported. Percentages are based only on reported data.

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EP.06G.18 Lung Cancer with Pleural Dissemination is Potentially a Non-Shedding Tumor

H. Hong[1], J-T. Zhang[1], Y. Zhang[2], M. Song[2], X. Gao[3], H-J. Li[1], S-R. Cui[4], S. Dong[1], Y-L. Wu[1], W-Z. Zhong[1], [1]Guangdong Provincial People's Hospital (Guangdong Academy of Medical Sciences), Southern Medical University, Guangzhou/CN ,[2]Geneplus-Beijing Institute, Beijing/CN ,[3]State Key Laboratory of Microbial Resources, Institute of Microbiology, Chinese Academy of Science, Beijing/CN ,[4]Operational Research, Department of Industrial Engineering and Operations Research, Fu Foundation School of Engineering and Applied Science, New York/NY/USA

Introduction: Non-small cell lung cancer (NSCLC) with pleural dissemination (M1a) includes a subset of patients demonstrate an indolent biology and may benefit from surgical resection of the primary tumor. In this study, we aims to evaluate the prognostic value of circulating tumor DNA (ctDNA) in M1a patients after surgery.

Methods: In this study, we analyzed 12 preoperative and 80 postoperative blood sample from 29 M1a patients with serial ctDNA detection. Additionally, 25 preoperative and 151 postoperative serum carcinoembryonic antigen (CEA) results were collected for comparasion. The primary endpoint was progression-free survival (PFS).

Results: The overall ctDNA detection rate for M1a disease was 26.1% (24/92). As of 31 December, 2022, 17 patients had disease progression with a median PFS of 14.3 months, among whom three had detectable longitudinal ctDNA before progression. The sensitivity of longitudinal ctDNA was 17.6%. In contrast, six patients had an elevated CEA trend within 3 months after surgery and before progression. The sensitivity of the elevated CEA level trend after surgery was 35.3%. Patients with longitudinal undetectable and detectable ctDNA demonstrated with a similar PFS; by contrast, patients with a decreasing CEA trend within 3 months after surgery was associated with an improved PFS (HR 0.24, 95% CI: 0.06-0.99, P=0.007).

Conclusions: Overall, our findings indicate that M1a NSCLC may represent a "non-shedding" tumor. In M1a patients, ctDNA detection demonstrated a limited prognostic value, while serum CEA in these cases may perform as a more cost-effective biomarker for predicting disease progression.

Keywords: ctDNA, non-shedding, Pleural dissemination

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EP.06G.19 Characterization of Metabolomic Landscape in Underrepresented Patients with Lung Cancer

J.J. Pothen, A. Hulbert, A. Mallisetty, M.M. Pasquinelli, R.H. Nguyen, F. Weinberg, University of Illinois Chicago, Chicago/IL/USA

Introduction: Despite the high incidence of lung cancer, little is known about how differences in patient populations (e.g. geographic location and race) correlate with differences in metabolic pathways in lung malignancies. Understanding which pathways are enriched can provide further insight into how these demographic factors affect the malignancy's behavior, and ultimately lead to personalized, more effective therapies.

Methods: As part of an exploratory study, we collected plasma from 42 patients with confirmed lung cancer, and from 60 patients without a lung cancer diagnosis. Metabolomic profiling was performed using ultra-high performance liquid chromatography - mass spectrometry. Untargeted metabolomics analysis was performed using MetaboAnalyst 5.0 software to uncover patterns in individual metabolite expression. We used orthogonal partial least squares discriminant analysis to demonstrate significant differences in metabolite expression in malignant vs non-malignant (control) lung samples. We then sorted all metabolites by their Variable Importance in Projection (VIP) scores to determine which metabolites contribute most to the model, and therefore which have the greatest statistical difference between malignant and non-malignant samples.

Results: We found significant differences in metabolite enrichment between patients with lung cancer and those without cancer (Figure 1). Additionally, we found that specific amino acids such as cystine and amino acids important in arginine synthesis were decreased in patients with lung cancer compared to non-cancer patients (Figure 2).

Conclusions: Our metabolomic analysis demonstrates significant differences in metabolite expression and their associated pathways between lung cancer and non-lung cancer samples. Interestingly, we find decreased levels of certain amino acids, traditionally found to be in higher levels in cancer patients, in our patients with lung cancer. Further analysis will involve characterizing the anthropometric factors that may account for these differences. Additionally, we plan to focus on aggregating geospatial data to further identify neighborhood-level differences in metabolite enrichment in underrepresented patients with lung cancer.

Keywords: metabolomics, lung cancer, underrepresented

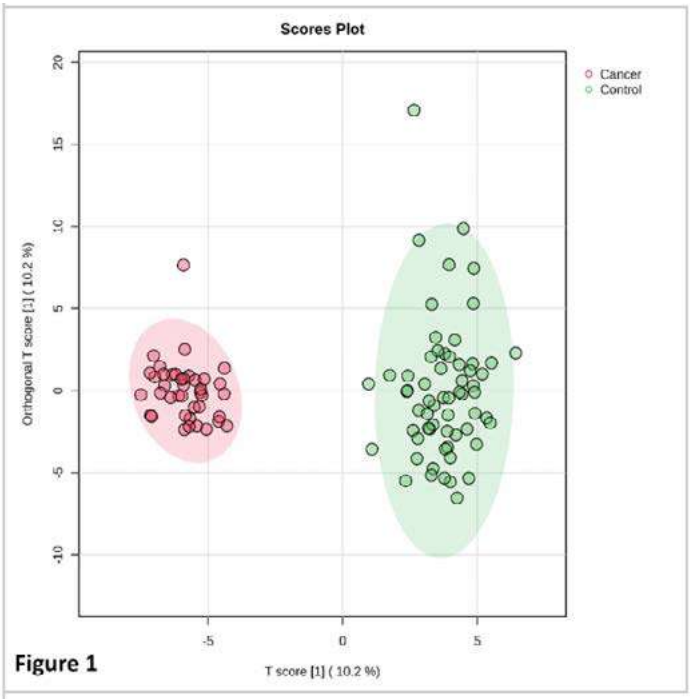

Figure 1

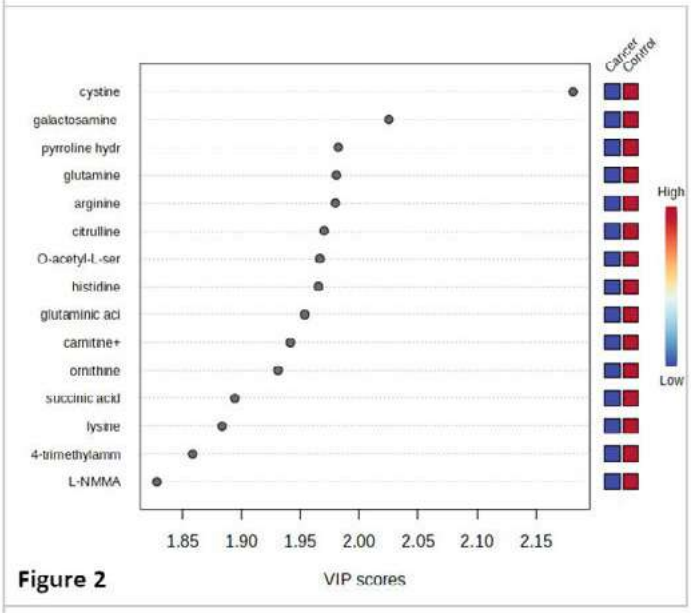

Figure 2

EP.06G.20 Advanced Squamous Cell Lung Carcinoma in Never Smokers: A Different Entity? Analysis from the Thoracic Tumor Registry in Spain (RTT)

M. Blanco[1], A. Collazo-Lorduy[1], M. Cobo[2], V. Calvo[1], M. Martínez- Cutillas[1], A. Cantero[2], D. Rodríguez-Abreu[3], E. Carcereny[4], J. Bosch-Barrera[5], M.R. García Campelo[6], R. López Castro[7], R. Bernabé[8], E. del Barco[9], A.L. Ortega[10], A. Sánchez[11], F. Aparisi-Aparisi[12], S. Vázquez[13], M. Guirado[14], J. Casal[15], K. Medina[16], S. Cerezo[17], C. Camps[18], J.L. Gonzalez-Larriba[19], M.A. Sala[20], B. Massutí[21], M. Dómine[22], B. Losada[23], A. Royuela[1], M. Provencio[1], [1]Hospital Universitario Puerta de Hierro-Majadahonda, Madrid/ES ,[2]Medical Oncology Intercenter Unit. Regional and Virgen de la Victoria University Hospitals. IBIMA., Málaga/ES ,[3]Hospital Universitario Insular de Gran Canaria, Gran Canaria/ES ,[4]Institut Català D'oncologia Badalona- Hospital Germans Trias I Pujol, B-Argo Group,, Badalona (Barcelona)/ES ,[5]Institut Català d'Oncologia, Hospital Universitari Dr. Josep Trueta and Precision Oncology Group (OncoGIR-Pro), Institut d'Investigacions Biomèdiques de Girona (IDIBGI), Girona/ES ,[6]Complexo Hospitalario Universitario A Coruña, A Coruña/ES ,[7]Hospital Clínico Universitario de Valladolid, Valladolid/ES ,[8]Hospital Universitario Virgen del Rocío, Sevilla/ES ,[9]Complejo Asistencial Universitario de Salamanca-IBSAL, Salamanca/ES ,[10]Hospital Universitario de Jaén, Jaén/ES ,[11]Hospital Provincial de Castellón, Castellón/ES ,[12]Hospital Universitari i Politècnic La Fe,, Valencia/ES ,[13]Hospital Universitario Lucus Augusti,, Lugo/ES ,[14]Hospital General Universitario de Elche, Elche/ES ,[15]Complexo Hospitalario Universitario de Vigo, Pontevedra/ES ,[16]Hospital Universitario Nuestra Señora De La Candelaria, Santa Cruz de Tenerife/ES ,[17]Hospital General La Mancha Centro, Alcazar de San Juan (Ciudad Real)/ES ,[18]Hospital General Universitario de Valencia, Valencia/ES ,[19]Hospital Clínico San Carlos, Madrid/ES ,[20]OSI Bilbao Basurto, Bilbao/ES ,[21]Hospital General Universitario Dr. Balmis de Alicante, Alicante/ES ,[22]Hospital Universitario Fundación Jiménez Díaz. IIS-FJD, Madrid/ES ,[23]Hospital Universitario de Fuenlabrada, Madrid/ES

Introduction: Squamous cell lung carcinoma (SQCLC) is a disease usually related to tobacco history, which may rarely be present in never smokers. There is little evidence about the clinical and molecular characteristics of this subgroup of patients, as well as their outcomes in terms of survival, with the majority of studies developed in Asian population.

Methods: our study aimed to retrospectively describe the epidemiological, clinical and molecular characteristics, as well as survival outcomes, of a Spanish cohort of non-smoking patients diagnosed with advanced SQCLC included in the Thoracic Tumor Registry (TTR) of the Spanish Lung Cancer Group, between February 2001 and December 2023. Differential characteristics between the non-smoker and the current/previous-smoker groups were analyzed.

Results: A total of 2351 patients with advanced SQCLC were included in our study, of which, 100 were never-smokers. The median age was similar between both groups (69.7 vs 67.8 years), with a higher percentage of women in the non-smoking group (63% vs 12.1%, P 0.001), as well as patients with history of cancer (26% vs 17.1% p = 0.017). No differences were found regarding occupational exposures. Performance status and symptoms at diagnoses were similar, but, subcutaneous, extrathoracic lymph nodes and central nervous system metastases were more frequent in non-smokers (4% vs 1.3%; p=0.02; 22% vs 12.7%; p=0.007; 16% vs 9.9% p=0.05, respectively). Molecular analyses were performed more frequently in the non-smoking group (82% vs 63%), including PDL1, but not all driver genes were analyzed in each patient. No molecular differences were found between both groups (table 1). There were no differences in the type of treatment received, nor in the number of patients who received any local treatment. With a median follow-up of 38.4 months, no differences were found in the progression free survival (5.7 vs 5.5 months, p = 0.85) or in the overall survival (10.9 vs 9.1 months, p = 0.64) between both groups.

Conclusions: Our study is one of the largest series of SQCLC in never-smokers in the European population. It is a rare entity, which is more frequent in women and in patients with history of cancer. There were no differences in terms of survival between never-smokers and current/previous-smokers. Our study could not find molecular differences between both groups, probably due to the heterogeneity in the genes tested and techniques applied across the TTR. However, further research is needed in the molecular aspects to better characterize this unusual disease.

Keywords: Advanced Squamous SCLC, non smokers, Thoracic Tumor Registry-Spanish Lung Cancer Group

	Non-smokers (n)	Current/previous smokers (n)
EGFR mutations	Total: 15 •Del19: 10 •Exon21: 2 •T790M: 1 •Ins20: 2 •Amplification: 0	Total: 18 •Del19: 10 •Exon21: 4 •T790M: 1 •Ins20: 2 •Amplification: 1
ALK rearrangements	2	4
KRAS mutations (G12C and non-G12C)	1	14
ROS1 rearrangements	1	2
MET alterations	Amplification: 1 Ex14 skipping: 2	Amplification: 0 Ex14 skipping: 1
PDL1 expression	Negative (<1%): 12 (20.7%) **Positive (≥1%): 44 (75.9%)** Unknown: 2 (3.5%)	Negative (<1%): 515 (39.5%) Positive (≥1%): 744 (57.1%) Unknown: 45 (3.5%)
HER2, BRAF and FGFR mutations RET and NTRK rearrangements	0	0

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EP.07A.01 Association Between Surgical Approach < Surgical Outcome in Lung Cancer Patients Undergoing Segmentectomy

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Introduction: Although segmentectomy tends to have a better overall survival for early stage lung cancers based on the results of randomized clinical trials, local recurrence rate following segmentectomy is higher than that following lobectomy. To perform a safe segmentectomy and reduce the local recurrence rate, an understanding of the 3-dimensional anatomy is essential. Segmentectomy performed through a thoracotomy (8-12 cm in length), the so-called hybrid approach, provides direct vision intraoperatively and is safe. Video-assisted thoracic surgery (VATS) provides a 2-dimensional view without direct vision. The purpose of this study was to compare short-term surgical outcomes and survival among patients who underwent segmentectomy for lung cancer using a hybrid approach compared to VATS.

Methods: This was a retrospective study using a prospectively collected database from two institutions. Patients with clinical T1N0M0-stage IA with the following characteristics underwent segmentectomy: patient request, poor performance status, and impaired respiratory function and/or severe co-morbidities. In one institution the hybrid approach was performed via an 8-cm thoracotomy, while VATS without direct vision was performed at the other institution. From June 2016 to December 2021, a total of 250 patients underwent segmentectomy for lung cancer. We evaluated 250 patients who underwent segmentectomy using the hybrid approach or VATS and compared the perioperative surgical outcomes and overall survival. Additionally, propensity score matching was performed to balance patient characteristics between the groups.

Results: Ninety-seven hybrid approaches and 153 VATSs were performed. The background of patients was similar in the groups, but the proportion of complex segmentectomies was higher in VATS (52.6% vs. 73.9%; P<0.001). The intraoperative and acute postoperative surgical outcomes in the hybrid approach and VATS, respectively, were as follows: median operative time, 146 and 167 min (P=0.006); median blood loss, 4 and 49 g (P<0.001); number of dissected lymph nodes, 4 and 2 (P=0.046); incidence of grade ≥2 postoperative complications, 18.6% and 13.2% (P=0.252); median duration of chest tube drainage, 2 and 1 d (P=0.008); median postoperative hospital stay, 4 and 4 d (P=0.832); and readmission within 30 d after discharge, 5.2% and 1.3% (P=0.113). There was 1 death within 30 d after surgery using VATS. The 5-year overall survival with the hybrid approach and VATS was 91.7% and 92.6%, respectively (P=0.408). After propensity score matching, the hybrid approach had a shorter operative time and less blood loss than VATS. The 5-year overall survival was 92.2% and 90.6%, for the hybrid approach and VATS, respectively (P=0.792).

Conclusions: The hybrid approach was associated with shorter operative times, less blood loss, and more dissected lymph nodes than VATS. There were no significant differences in perioperative surgical outcomes. Although the number of complex segmentectomies was higher in VATS than in the hybrid approach, the hybrid approach had superior intraoperative outcomes and similar survival compared to VATS.

Keywords: Lung cancer, Segmentectomy, VATS

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EP.07A.02 Staple Formation by Endostapler and Bronchial Wall Thickness in Pulmonary Lobectomy: Prospective Observational Study

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Introduction: We conducted a single-center, prospective observational study to evaluate staple formation according to cartridge type of endostapler and bronchial wall thickness, and the rate of postoperative complications in patients undergoing pulmonary lobectomy.

Methods: Eighty patients who were planned for lower lobectomy were enrolled (Figure 1). The bronchus was divided using endostapler (ECHELON FLEX™ Powered Plus Stapler). The cartridge (Gold, Green, or Black) was selected at the surgeon's discretion. After measuring the thickness of the bronchial stumps, the bronchial tissue was proteolysed and all staple formation was scored from 1 to 3 points, focusing on staple ends return, with 3 representing an approximately perfect B-shaped closure, 2 representing both staple ends slightly returning but not forming a B-shape, and 1 representing one or both staple ends not returning.

Results: Gold, Green and Black cartridges were used in 26, 49 and 5 patients respectively. Green/Black was used more frequently than Gold in patients with thicker bronchial stumps (p = 0.001). The mean staple formation score tended to be higher in patients used Green/Black than Gold (p = 0.087). The proportion of score 2 or higher was equivalent (p = 0.766). The proportion of score 3 was higher for patients used Green/Black than Gold (p < 0.001). Bronchial stump thickness was significantly correlated with gender (p < 0.001) and height (p = 0.001). In men, and women over 160 cm in height, the mean score of staple formation tended to be higher for patients used Green/Black cartridge than that used Gold cartridge (p = 0.068) (Figure 2). No postoperative bronchopleural fistula was observed.

Conclusions: Although each cartridge performed well ensuring tissue apposition and good clinical outcomes, the Green or Black cartridges appeared to be more appropriate for the lower bronchus, especially in men, and women over 160 cm in height.

Keywords: lung cancer, surgery, stapler

Figure 1

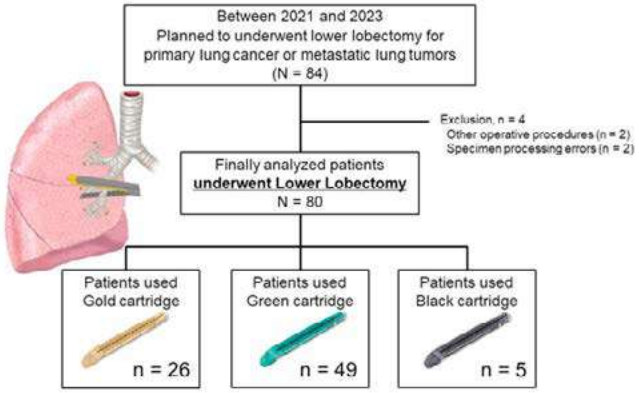
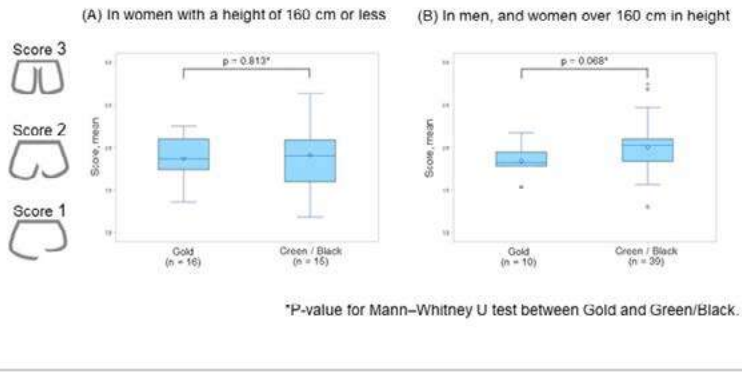


Figure 2



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EP.07A.03 Influence of Preoperative Percutaneous Transthoracic Lung Biopsy on Recurrence and Mortality after Surgery for Lung Cancer

E.J. Hwang, Seoul National University Hospital, Seoul/KR

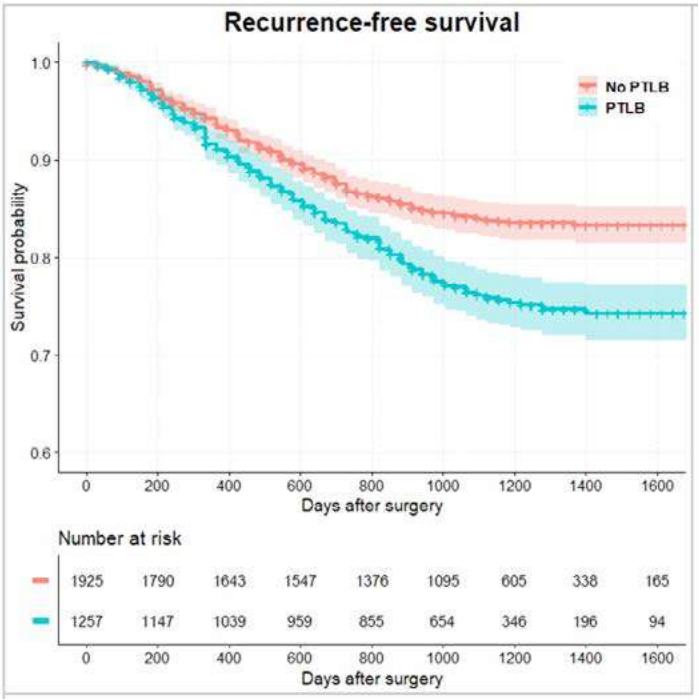
Introduction: Percutaneous transthoracic lung biopsy (PTLB) is a representative procedure for lung cancer diagnosis. There has been controversy regarding the association between preoperative PTLB and long-term risk of recurrence or mortality in surgically treated lung cancer patients.

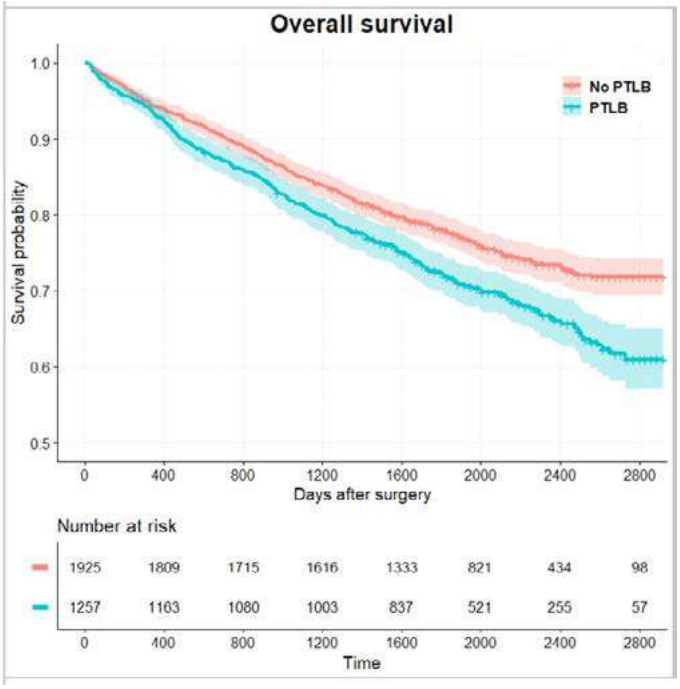
Methods: A public database from the Korea Central Cancer Registry was analyzed. The database comprised information regarding the diagnosis, stage, treatment, and outcomes of patients diagnosed with lung cancer in 51 institutions in South Korea. From the database, data from patients who underwent curative-intent surgery were included for the analysis, while patients with multiple primary lung cancers and patients who received neoadjuvant treatment were excluded. Restricted mean survival time (RMST) analyses were conducted to investigate the association between the conduction of preoperative PTLB and recurrence-free survival (RFS), lung cancer-specific survival, or overall survival (OS) after surgery. Age, sex, histologic classification, pathologic stage, type of surgery, and adjuvant treatment were considered confounding factors.

Results: Among 3,182 patients (1,975 men, mean age 64 years), 1,257 (39.5%) underwent preoperative PTLB. Patients who underwent preoperative PTLB exhibited significantly shorter RFS (P<.001; survival probability at 3-year after surgery, 76.4% vs. 84.2%), lung cancer-specific survival (P<.001; survival at 7-year after surgery, 69.1% vs. 78.7%), and OS (P<.001; survival at 7-year after surgery, 63.2% vs. 72.1%). After adjustment for potential confounding factors, conduction of preoperative PTLB was an independent factor for reduced RFS (RMST at 3-year after surgery, 964 vs. 992; P=.005), lung cancer-specific survival (RMST at 7-year after surgery, 2154 vs. 2215; P=.040), and OS (RMST at 7-year after surgery, 2083 vs. 2136; P=.045).

Conclusions: Preoperative PTLB was an independent factor for reduced RFS, lung cancer-specific survival, and OS in patients undergoing curative-intent surgery for lung cancer. Judicious decisions would be required for the conduction of preoperative PTLB in patients under suspicion of resectable lung cancer.

Keywords: Biopsy, Percutaneous lung biopsy, Preoperative diagnosis





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EP.07A.04 Risk Factor Analysis and Predictive Model for Air Leakage after Thoracoscopic Lung Wedge Resection

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Introduction: The rate of postoperative complications is low due to the wedge resection procedure does not involve the major structures. However, postoperative air leak is still common. There are no large-scale studies in this area. This study aimed to identify risk factors for air leakage (AL) after thoracoscopic lung wedge resection and to develop a predictive model to screen suitable patients for tube lessness.

Methods: Patients undergoing thoracoscopic pulmonary wedge resection at Fujian Medical University Union Hospital between January 2015 and December 2020 were included in this study. Univariate and multivariate logistic regression analyses were used to identify independent risk factors and establish the corresponding models. Concurrent data from two other centers were also collected as a validation set for external validation.

Results: A total of 2503 patients who met the selection criteria were enrolled. The overall incidence of AL was 11.34% (284/2503). The development data set included 2006 cases; columnar plots were drawn based on the results of the multifactorial logistic regression analysis. The final model included age>70, FEV1%<80%, nodule size, benignity/malignancy, and pleural adhesions(none, focal, diffuse). In the development data set, the C-index was 0.829. There were 497 cases in the external validation set, at this, the C-index was 0.833.

Conclusions: The prediction model of AL was performed well, and may be clinical useful to assessed AL and identify patients who can benefit from a tubeless strategy.

Keywords: postoperative air leak, predictive model, tubeless strategy

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EP.07A.05 Evolution of Use of Sublobar Resection in a US Population-Based Cohort Before and after Two Randomized Controlled Trials

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Introduction: We evaluated sublobar resection practices for early-stage non-small cell lung cancer (NSCLC) in a population-based cohort after two pivotal randomized controlled trials, JCOG 0802 and CALGB 140503, established similar outcomes to lobar resection.

Methods: We retrospectively analyzed patients with stage IA from 2009 to 2023 in the Mid-South Quality of Surgical Resection cohort, which includes 14 hospitals in Arkansas, Mississippi, and Tennessee regions and categorized eligible and ineligible patients based on the selection criteria from the JCOG 0802 and CALGB 140503 trials to ensure a representative comparison (Figure 1. CONSORT diagram). We assessed resection trends overall; and 2009 to 2019 (pre-) versus 2020 to 2023 (post-publication of JCOG 0802, the first published RCT), using the Cochran-Mantel-Haenszel test and logistic regression, including an interaction term for periodic impact analysis.

Results: Of 3,030 patients, 61% met trial eligibility; 6.5% underwent segmentectomy, 10.3% wedge resections. Sublobar resection use increased overall (Figure 2a) and among eligible patients (Figure 2b) (p<.0001 for both). Changes among ineligible patients remained insignificant (p=0.2609). Wedge and segmentectomy rates decreased gradually from 2009 to 2019, but then increased after 2019, more so in segmentectomy (Figure 2). Pre-JCOG 0802, patients were 50.8% less likely to have sublobar resections (OR=0.492, 95% CI: 0.338-0.718, p=0.0002) and the period-eligibility interaction was significant with 42.5% higher odds of undergoing sublobar resection post-JCOG 0802 (OR=1.425, 95% CI: 1.425-1244, p<.0001).

Conclusions: The utilization of sublobar resection for early-stage NSCLC has increased post-JCOG 0802 and CALGB 140503, especially segmentectomy. The increase has mostly been in appropriately selected patients. Use of sublobar resection among ineligible patients has not yet diminished, suggesting opportunity for improvement.

Keywords: Resection, NSCLC, Early Stage

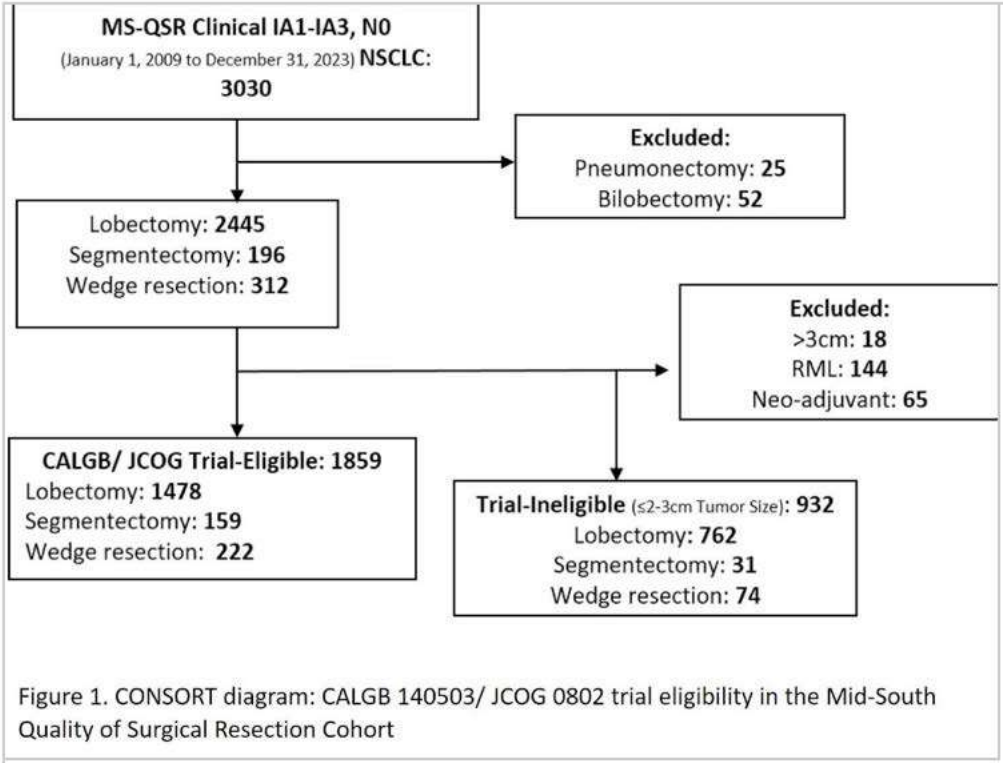

Figure 1. CONSORT diagram: CALGB 140503/ JCOG 0802 trial eligibility in the Mid-South Quality of Surgical Resection Cohort

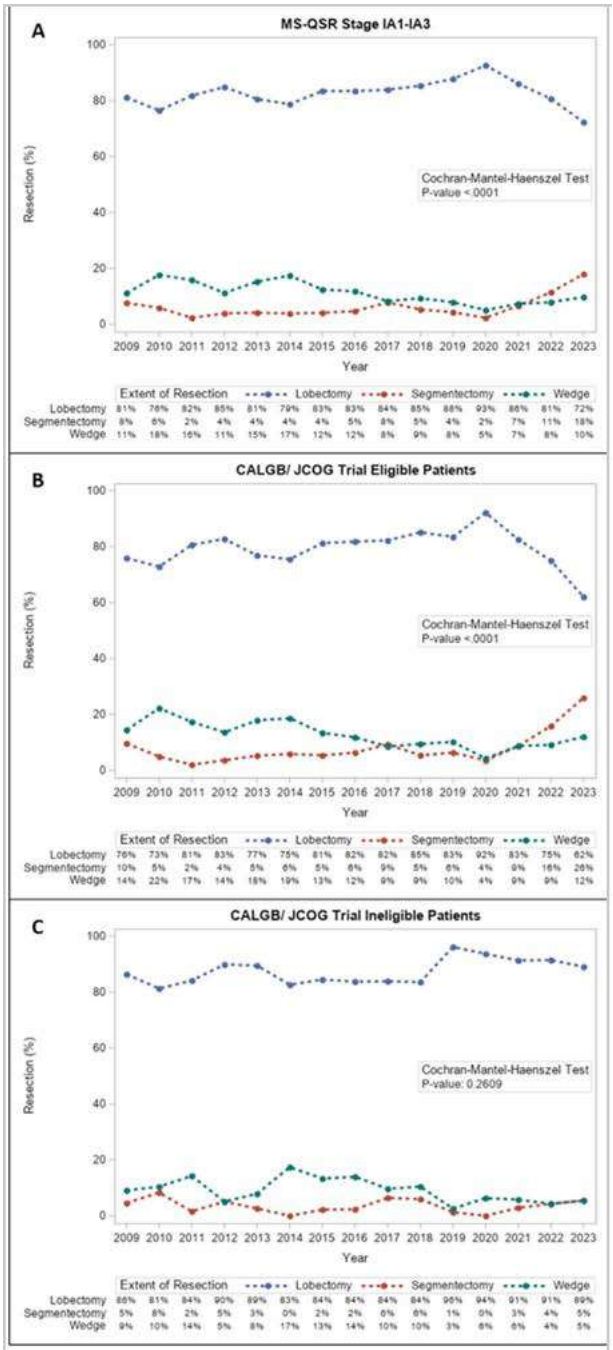

Figure 2. Trends in use of lobar vs. sublobar resection in the Mid-South Quality of Surgical Resection cohort: a.) All patients with Stage IA1-IA3 NSCLC; b.) CALGB 140503/ JCOG 0802 trial eligible patients; c.) Ineligible patients.

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EP.07A.06 Usefullness and Appropriate Indication of Intraoperative CT-Guided Marking Using O-Arm Based on Cancellation Rate

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Introduction: Improvements in imaging technology and lung cancer screening have led to an increased detection rate of small pulmonary tumors that include ground glass nodules (GGNs). These GGNs and small nodules are often difficult to find if they cannot be recognized from the lung surface. It is difficult to accurately predict preoperatively whether small nodules in the peripheral lung fields can be detected intraoperatively. We had percutaneous preoperative CT-guided marking with dye from 2007 to 2016, but discontinued it due to reports of air embolization. Since 2017, we have been performing intraoperative CT-guided marking using O-arms, and we would like to discuss the indications for marking based on the cancellation rate as well as the usefulness of the method.

Methods: Of the 3021 respiratory surgery cases from May 2017 to May 2023, 2007-2016 were considered the early period group and 2017-2023 the late period group. There were no significant differences in gender, age, tumor diameter, or solid component diameter between the groups.

Results: In the early group, 18 of 1447 patients (1.2%) underwent marking. In the late group, marking was planned in 75 of 1574 patients (4.8%), 17 were cancelled intraoperatively, and marking was performed in 58 patients (3.7%). In all cancelled cases, lesions could be detected intraoperatively. The number of markings was significantly higher in the late group (1 in the early group and 2.8 in the late group, $p<0.01$). 3.2 CT sessions were performed in the early group and 1.3 in the late group, significantly lower in the late group ($p<0.01$). The operation time for partial resection was significantly longer in the late group (102 minutes) than in the early group (75 minutes) ($p<0.01$), but there was no difference in the operation time for segmentectomy and lobectomy. Bleeding was 10 ml in the early group and 11 ml in the late group, with no difference. In the early group, 1 of 18 patients had to convert to open chest surgery due to lack of intraoperative dye confirmation, but in the late group, all patients were successfully marked. In the early group, pneumothorax occurred in 4 cases, which were immediately treated by surgery. In the late group, there were no complications caused by marking.

Conclusions: Compared to previous methods, the intraoperative marking method using O-arm was considered superior in terms of marking accuracy and complications. The intraoperative cancellation rate was 22%, and it was possible to determine intraoperatively that marking was unnecessary in 1/4 of the cases. On the other hand, the ability to easily cancel the marking increased the safety of lesion retrieval and allowed the surgeon to select the most appropriate indication for the lesion.

Keywords: Intraoperative CT-guided marking, O-arm, early lung cancer

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EP.07A.07 Comparison of Inpatient Opioid Use and Pain Control Following Thoracoscopic Segmentectomy Versus Lobectomy for Non-Small Cell Lung Cancer

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Introduction: Video-assisted thoracoscopic surgery (VATS) segmentectomy and lobectomy are common surgical approaches for non-small cell lung cancer (NSCLC). However, their impact on in-hospital opioid use and pain management remains uncertain. This study aims to compare postoperative opioid use and pain control between the two procedures.

Methods: Patients were extracted from the ongoing CN-PRO-Lung 3 longitudinal cohort study. Retrospective analysis included NSCLC patients underwent VATS segmentectomy or lobectomy from April 2021 to November 2022. Propensity score matching (PSM) matched patients 1:1 based on sex, age, BMI, smoking status, Charlson Comorbidity Index (CCI), and TNM staging. Data on opioid usage and postoperative symptoms (assessed by the PSA-Lung scale) were collected. Mixed effects model compared symptom scores on postoperative days 1 to 5.

Results: We found that during surgery, patients undergoing segmentectomy received a lower total dose of opioid medications compared to those undergoing lobectomy (86.55 [67.5-112.5] vs. 100 [77.55-126.9] mg, p < 0.0001). Postoperatively, patients in the segmentectomy group continued to have lower rates of opioid medication usage (55.67% vs. 71.18%, p < 0.0001) and lower total doses compared to the lobectomy group (24 [0-48] mg vs. 36.92 [0-74] mg, p < 0.0001). Finally, regardless of patient-controlled analgesia (PCA) use, patients in the segmentectomy group still received lower total doses of opioids postoperatively compared to those in the lobectomy group (210 [180-230] vs. 216 [180-248.46], p < 0.0001). However, there were no differences between segmentectomy and lobectomy patients in the symptoms of pain, cough, fatigue, disturbed sleep, drowsiness and distress on postoperative days 1-5 (all p > 0.05).

Conclusions: Segmentectomy results in reduced intraoperative and postoperative opioid usage without exacerbating postoperative symptoms. It offers a more economical and effective opioid usage profile compared to lobectomy for suitable NSCLC patients, while maintaining effective postoperative symptom control.

Keywords: Segmentectomy, Opioid usage, Pain control

TABLE 1. Baseline patient characteristics and opioid (oral and parenteral opioids) administration in segmentectomy vs. lobectomy: before and after propensity score matching (PSM)

	Before PSM			After PSM		
	Segmentectomy group (n =489)	Lobectomy group (n =580)	P	Segmentectomy group (n =406)	Lobectomy group (n =406)	P
Sex, n (%)						
Male	132(26.99)	238(41.03)	<.0001	125(30.79)	147(36.21)	0.102
Female	357(73.01)	342(58.97)		281(69.21)	259(63.79)	
BMI (kg/m2), mean (SD)	22.6(3.01)	22.9(3.1)	0.015	22.59(3.03)	23.07(2.92)	0.906
Smoking status, n (%)						
Current	45(9.2)	101(17.41)	<.0001	41(10.84)	53(13.05)	0.338
Former	216(4.29)	44(7.59)		21(5.17)	28(6.9)	
Never	423(86.5)	435(75)		347(83.99)	325(80.05)	
ECOG PS, n (%)						
0	481(98.36)	568(98.1)	0.748	399(98.03)	399(98.28)	0.799
≥1	8(1.64)	11(1.9)		8(1.97)	7(1.72)	
ASA physical status classification, n (%)						
I	444(90.8)	536(92.41)	0.341	369(89.9)	374(92.12)	0.278
II	45(9.2)	44(7.59)		41(10.1)	32(7.88)	
Age-Adjusted Charlson Comorbidity Index , n (%)						
0-1	327(66.87)	318(54.83)	<.0001	252(62.07)	237(58.37)	0.535
2-3	142(29.04)	237(40.86)		135(33.25)	138(36.95)	
≥4	20(4.09)	25(4.31)		19(4.68)	19(4.68)	
Postoperative pathologic TNM stage, n (%)						
I-II	487(99.59)	531(91.55)	<.0001	404(99.51)	403(99.26)	1.000*
III-IV	2(0.41)	49(8.45)		2(0.49)	3(0.74)	
FEV1%, [%,M(IQR)]	94.65(84.65-105)	94.55(81.3-104.8)	0.999	95.25(84.3-105.6)	94.1(81.1-103.9)	0.343

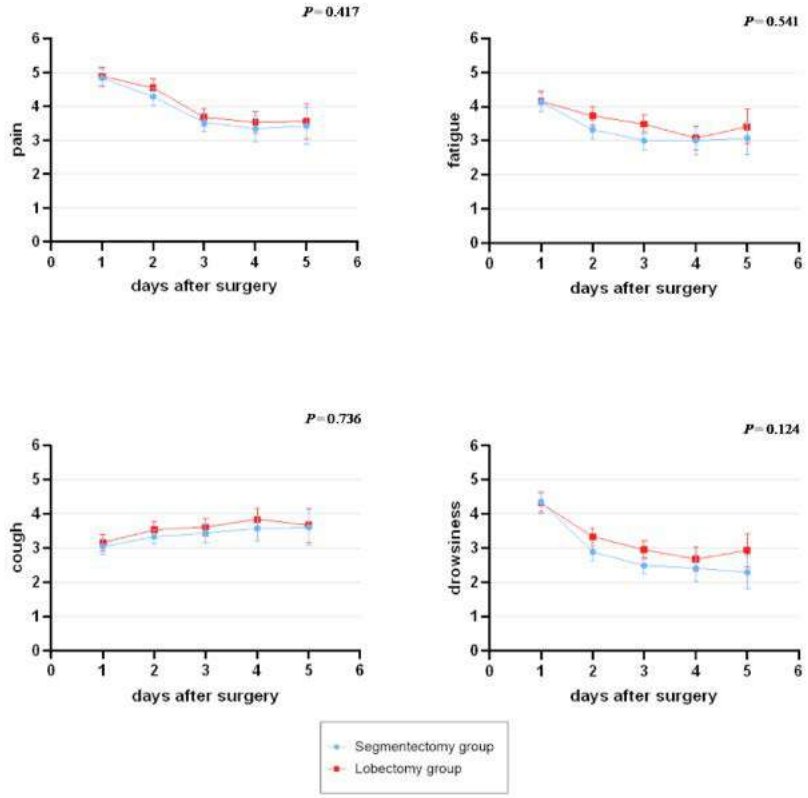
* refers to the use of Fisher's exact test. FEV1%: predicted value of exertional expiratory volume in the 1st second.

Table 2 Opioid (oral and parenteral opioids) administration in segmentectomy vs. lobectomy: before and after propensity score matching (PSM)

	Before PSM			After PSM		
	Segmentectomy group (n =489)	Lobectomy group (n=580)	P	Segmentectomy group (n =406)	Lobectomy group (n=406)	P
Intra-Operative						
Any opioid administration, n (%)	489(100)	580(100)	—	406(100)	406(100)	—
Total oral morphine equivalent dose [mg, M(IQR)]	83.2(65.60-116.68)	100.3(78.35-126.95)	<.0001	86.55(67.5-112.5)	100(77.55-126.9)	<.0001
Post-Operative patient Unit*						
Any opioid administration(oral and/or parenteral), n (%)	277(55.42)	423(72.93)	<.0001	225(55.67)	289(71.18)	<.0001
Total oral morphine equivalent dose [mg, M(IQR)]	18(0-48)	36.92(0-58.92)	<.0001	24(0-48)	36.92(0-74)	<.0001
NSAIDs, n (%)	331(67.69)	358(58.28)	0.002	269(66.01)	240(59.11)	0.042
PCA*						
Patient-controlled analgesia, n (%)	400(81.21)	509(86.21)	0.176	342(84.24)	377(85.75)	1.000
Total oral morphine equivalent dose [mg, M(IQR)]	180(180-210)	180(180-210)	0.9	180(180-210)	180(180-210)	0.216
Post-Operative patient Unit+PCA						
Any opioid administration(oral and/or parenteral), n(%)	454(92.84)	559(98.38)	0.01	379(93.35)	383(94.83)	0.332
Total oral morphine equivalent dose [mg, M(IQR)]	204(170-228)	216(180-257.44)	<.0001	210(180-229)	216(180-248.46)	0.008
NSAIDs, n (%)	331(67.69)	358(58.28)	0.002	269(66.01)	240(59.11)	0.042

*Post-Operative Patient Unit= ICU + General Ward *PCA=Patient-Controlled Analgesia

Figure 1. Comparison of postoperative days 1-5 symptom scores between segmentectomy and lobectomy



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EP.07A.08 Modified Periareolar Incision for Uniportal Segmentectomy

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Introduction: The periareolar approach is rarely used in previous reports of thoracoscopic surgery, and most of them directly destroy the breast into the thorax. Here, we modified this surgical approach by establishing a subcutaneous tunnel to avoid injury to the breastthat has certain advantages over conventional uniportal incision.

Methods: Fourteen patients were enrolled for segmentectomy. We avoided damaging the mammary gland into the thoracic cavity by creating a subcutaneous tunnel between the skin and the mammary gland that separated from the periphery of the areola outward to the fourth intercostal space of the anterior axillary line. A plastic wound protector was used to hold open the incision and stabilize its position. The incision was enlarged by fingers with the paraffin oil. In this way we have completed the Modified Periareolar incision. All the segmentectomy procedures were completed and specimens ware removed through the incision. The incision was sutured and the recovery effect was followed up.

Results: Among the 14 patients, the mean length of stay after surgery was 2.93 ± 1.03, and the postoperative pain score using VAS was 2.14 ± 1.40 and 1.57 ± 1.16 on the first and third day after surgery, respectively. In terms of short-term postoperative complications, 9 patients had no complications, 2 had pleural effusion, 1 had subcutaneous emphysema, and 1 had both pleural effusion and subcutaneous emphysema. Changes in nipple sensitivity were assessed on a five-point scale (1 is no effect and 5 is great effect), yielding a score of 2.29 ± 0.83. Patient scars were assessed using POSAS, with scores of 1.57 ± 0.76 and 1.71 ± 0.82 for observer and patient evaluations, respectively.

Conclusions: The periareolar approach has rarely been used in previous reports of thoracoscopic surgery. However, no article has reported the use of a periareolar approach in segmental resection. Most of the reported patients are male, but the demand for cosmetic effect in women is always higher than that in men. Previous studies have suggested that women have more developed breasts, so periareolar incisions are not suitable for women. However, our method of establishing a subcutaneous tunnel could maintains the integrity of the breast, so it can also be better applied to female patients, which is the innovation of our study.Our observations suggest that this approach has some benefit. Firstly, due to the elasticity of the chest skin, the retractor can bypass the mammary gland and create a good surgical field. Secondly, due to the pigmentation of the areola, the incision is more concealed and the aesthetic result is better. Third, according to the feedback of patients, the postoperative pain was mild and did not affect life. However, there are some technical difficulties with the incision we designed. Surgeons need time to adjust to new surgical methods. The establishment of the subcutaneous tunnel requires the surgeon to have a good anatomical basis. The occurrence of medium and long term complications needs to be further investigated.

Keywords: Minimally invasive, Modified periareolar incision, Uniportal segmentectomy

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EP.07A.09 A New Method to Detect Air Leaks in Video-assisted Thoracoscopic Surgery Using Indocyanine Green Inhalation Under Near-infrared Fluorescence

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Introduction: Postoperative air leaks are the most common complications after lung surgery, with an incidence of 8%-26%. The key principle in preventing postoperative air leaks is to accurately and comprehensively identify and repair the sites of air leakage during surgery. Currently, the gold standard method for identifying air leak sites in thoracoscopic surgery is the submersion sealing test. However, this method seriously affects the surgical field and may lead to the omission of air leak sites, and this method cannot continuously visualize air leak sites during repair. This case series aimed to demonstrate the feasibility of indocyanine green (ICG) inhalation for the detection of air leak sites.

Methods: We enrolled patients who underwent thoracoscopic lung surgery at our hospital between September 2023 and December 2023. After lung resection, indocyanine green (ICG, 3.75 mg/ml) was inhaled via a mesh nebulizer. The suspected air leak sites were then detected under near-infrared fluorescence. Subsequently, the submersion sealing test was used to validate the air leak sites identified through fluorescence. The detection efficiency of these two methods was evaluated.

Results: This case series included 5 patients. Intraoperatively, a total of 20 fluorescent air leak sites were identified under near-infrared fluorescence, among which 2 patients had extensive adhesion between the visceral pleura and parietal pleura, with 8 and 6 fluorescent air leak sites, respectively. After verification via the submersion sealing test, 17 (85%) fluorescent air leak sites were confirmed to be true air leak sites. The average time for detecting air leak sites under near-infrared fluorescence was 15.8 seconds, and fluorescence imaging could persist until the end of surgery. None of the patients experienced complications related to ICG inhalation. Two patients experienced postoperative air leak and were successfully treated by conservative treatment.

Conclusions: Intraoperative ICG inhalation provides a convenient, simple, and effective method for detecting air leak sites during thoracoscopic lung surgery. This method does not affect the surgical field and allows for continuous visualization of air leak sites. We demonstrated that ICG inhalation is a novel method for detecting air leak sites with great potential for clinical application.

Keywords: Intraoperative air leak detection, Indocyanine green inhalation, Near-infrared fluorescence

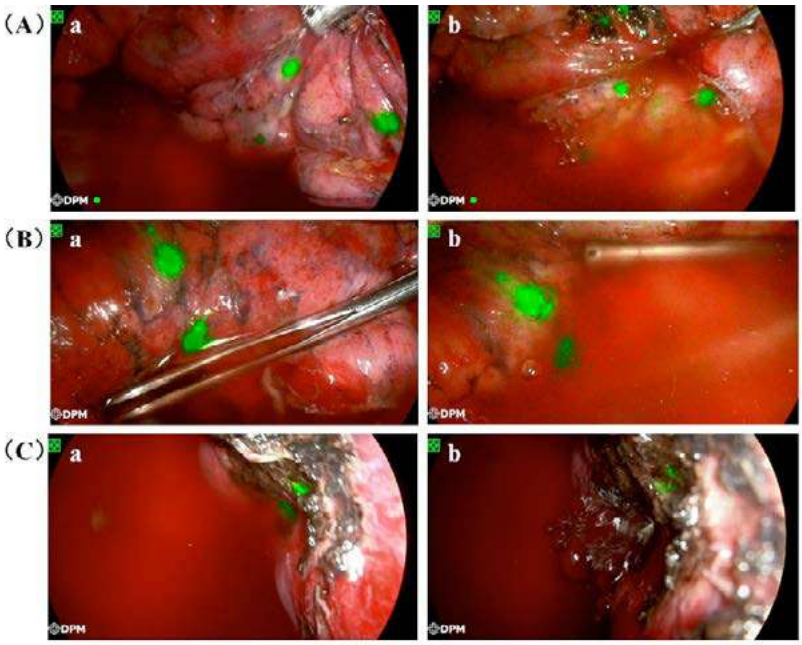

Figure 1. The fluorescence imaging of air leak sites. Subfigures a and b in each figure represent the detection results of air leak sites using near-infrared fluorescence and the submersion sealing test, respectively. In Figure (A), all three fluorescent imaging sites are all true air leak sites. In Figure (B), only the upper fluorescent imaging site is a true air leak site, while the lower fluorescent imaging site shows no bubbles in the submersion sealing test. In Figure (C), the fluorescent imaging site is a true air leak site, with a large number of bubbles generated in the submersion sealing test.

EP.07A.10 Concordance Between Lymph Node Station Examination Reported on a Checklist and the Final Pathology Report after Curative Lung Cancer Resection

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Introduction: Checklists improve communication between clinical teams. We previously reported discordance between lymphadenectomy claims in surgeons' notes and the final pathology report. We examined the concordance between station-specific lymph node examination reported by surgery teams on a checklist and the final pathology report.

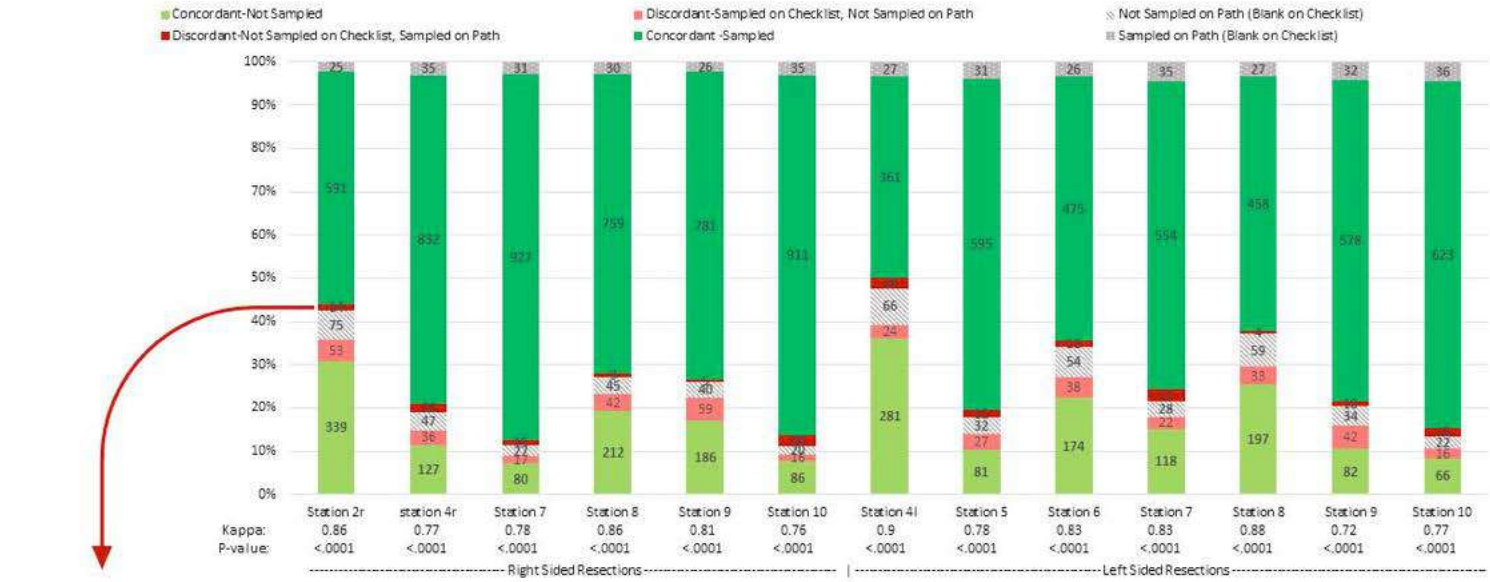
Methods: We examined curative-intent lung cancer resections in the Mid-South Quality of Surgical Resection cohort from 2009-2022, a population-based dataset involving implementation of a lymph node collection kit. The kit included a checklist requiring surgery teams to indicate whether or not they examined lymph nodes from specific stations (2R, 4R, 7, 8, 9, 10R for right-sided and 2L, 4L, 5, 6, 7, 8, 9 and 10L for left-sided resections). We examined frequency of nodal evaluation indicated by checklist and pathology report, further assessed with a kappa statistic, and the reasons attributed for non-examination of lymph nodes.

Results: Of 1875 resections with the kit, 1097 (59%) were right-sided; 778 (41%) left-sided. The checklist was used in 97% of right-sided, and 96% of left-sided resections. For right-sided resections, checklists indicated stations 7 (86%) and 10R (85%) were sampled most, stations 2R (32%) and 9 (17%) were sampled the least (Figure 1). Station 10R had the highest discordance rate with the pathology report (29 patients, 3% of 1097) while station 8 had the highest significant kappa statistic of 0.86 (Table 1.). The most common reason across stations for checklist non-examination was "no lymph nodes identified". In left-sided resections, stations 5 (80%), 9 (80%) and 10L (82%) were sampled the most, and 4L (39%), 6 (24%), and 8 (26%) the sampled the least. Stations 7 and 10 again had the highest rates of discordance, while station 4l had the greatest significant kappa statistic. Absence of identifiable lymph nodes was the most common reason attributed for non-examination. The reasons for lack of sampling across other stations were similar in that the overwhelming reasons were not nodes were identified or no reason was provided (blank or not specified).

Conclusions: Stations 2r, 4l and 8 had the largest kappa statistics while stations 7 and 10 had the greatest rates of discordance, while having the most prevalent sampling. The absence of nodes was the most common reason who not sampling a station, or the node was sampled during mediastinoscopy

Keywords: NSCLC, lymph nodes, surgical resection

Figure 1. Distribution of concordance between station-specific lymph node examination reported by surgery teams on a checklist and the final pathology report.



Checklist reasons for non-sampling													
No lymph nodes were identified	5 (35.7)	7 (35)	2 (14.3)	3 (33.3)		12 (41.4)	7 (36.8)	7 (58.3)	1 (9.1)	6 (28.6)	3 (75)		6 (40)
Other			5 (35.8)	1 (11.1)	1 (20)	6 (20.7)			1 (9.1)	2 (9.5)		1 (10)	3 (20)
Not specified	5 (35.7)	8 (40)	6 (42.9)	5 (55.6)	4 (80)	10 (34.5)	8 (42.1)	3 (25)	9 (81.8)	10 (47.6)	1 (25)	9 (90)	6 (40)
Exam was not possible due to patient			1 (7.2)			1 (3.4)							
Sampled at Mediastinoscopy	4 (28.6)	5 (25)					4 (21.1)	2 (16.7)		3 (14.3)			

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EP.07A.11 AI Models for Intraoperative Diagnosis Based on Surgical Resection Images in Stage IA LUAD: A Prospective, Multicentric Study

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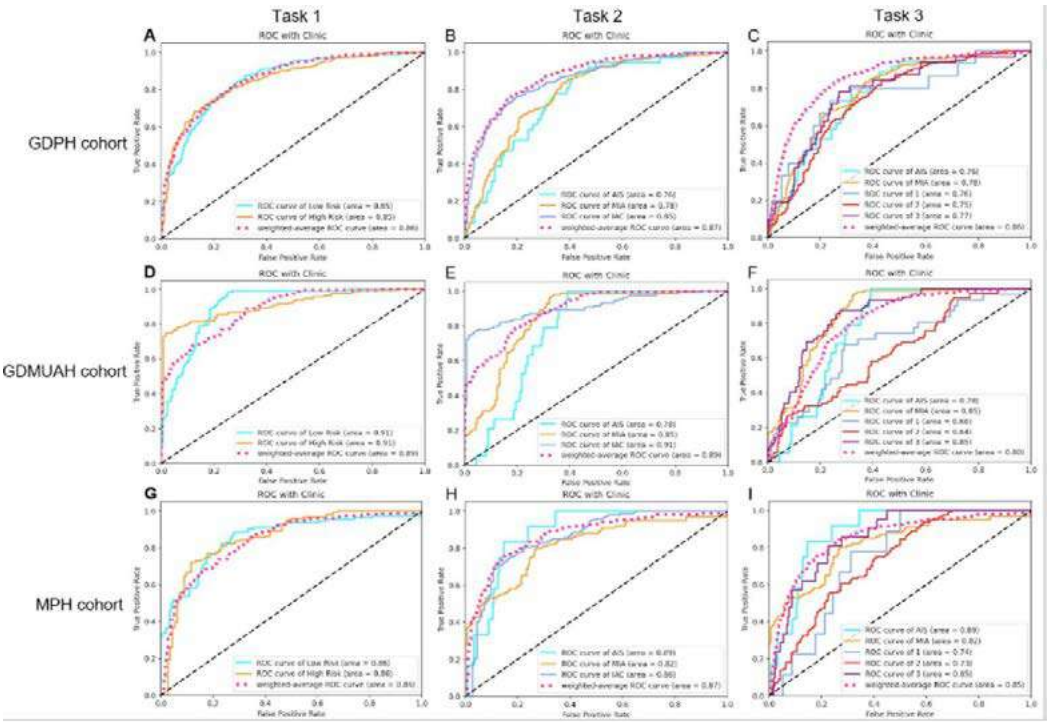
Introduction: Intraoperative pathological diagnosis is key for surgical strategies, including extensive lobectomy after diagnostic sublobar resection and extent of lymph node dissection. Frozen section requires sufficient time for sampling and high-level specialties in diagnosis based on the limited and sometimes poor-quality samples, which may lead to misdiagnosis or unidentifiability. We propose artificial intelligence models based on surgical resection images for intraoperative diagnosis and risk stratification of stage IA lung adenocarcinoma.

Methods: This study prospective enrolled patients with stage IA lung adenocarcinoma underwent complete resection between June 2020 and September 2023 in Guangdong Provincial People's Hospital (GDPH), Affiliated Hospital of Guangdong Medical University (GDMUAH), Meizhou People's Hospital (MPH). Surgical resection images of the LUAD were taken by smartphones in operating theaters under natural lighting condition (without flash or shadowless surgical lights). Artificial intelligence models based on surgical resection images and clinical characteristics were established for three tasks. Task1 tend to differentiate invasive lung adenocarcinoma (IAC) from non-IAC lesions. Task2 tend to classify pre-invasive lesion (PIL), minimally invasive adenocarcinoma (MIA) and IAC. Task3 tend to more specifically classify PIL, MIA, IAC Grade1, IAC Grade2 and IAC Grade3 according to 2021 IASLC Grading system in LUAD. Models were developed by combing clinical characteristics and coarse-fine fusion features from surgical resection images. Diagnostic performances were compared between thoracic surgeons, AI models and frozen section. The study was registered in Chinese Clinical Trial Registry (ChiCTR2300075999).

Results: We prospectively collected images of 1638 lung nodules in 1516 patients from GDPH, 122 lung nodules in 112 patients from GDMUAH and 89 lung nodules in 82 patients from MPH. For each tasks, we developed three models including coarse/fine models, coarse-fine fusion models and combined models with fusion features and clinical characteristics, with best diagnostic performance in combined models. In GDPH validation cohort, for task1 the diagnostic performances were 0.77 for coarse model, 0.79 for fusion model and 0.86 for combined model. In GDPH cohort, for task3 the diagnostic performances were 0.80 for fine model, 0.80 for fusion model and 0.86 for combined model. The proposed models have strong generalization ability in external validation cohort from GDMUAH and MPH for each task, and it could improve diagnostic performance of thoracic surgeons.

Conclusions: We developed intraoperative diagnostic models based on surgical resection images, which could comprehensively evaluate the whole section of nodules without the disturbance of sampling and reach a diagnosis rapidly to assist the decision of surgical strategies.

Keywords: Surgical resection images, Intraoperative diagnosis, Early-stage lung cancers



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EP.07A.12 Association Between Preoperative Diaphragm Thickness and Postoperative Complications in Elderly Patients with Lung Cancer

S. Kuriyama, K. Imai, S. Takashima, H. Iwai, H. Suzuki, R. Demura, Y. Harata, S. Shibano, Y. Minamiya, Akita University Graduate School of Medicine, Akita/JP

Introduction: With the increasing number of elderly patients with lung cancer, sarcopenia has been frequently reported as a prognostic factor. However, the perioperative impact of respiratory sarcopenia, defined by a decrease in respiratory muscle mass and a decline in respiratory muscle strength, remains unclear. In the present study, we focused on the diaphragm, the major respiratory muscle, and investigated the association between preoperative diaphragm thickness (DT) measured on computed tomography (CT) scans and perioperative complications and outcomes.

Methods: We enrolled 101 patients aged 75 years or older who underwent radical lobectomy or segmentectomy for primary lung cancer in our institution between January 2013 and March 2018. DT at the level of the origin of the celiac artery was measured on axial and coronal CT images, and the mean DT (MDT) was calculated from the four measurements. The outcome was defined as postoperative complications of Clavien-Dindo classification grade II or higher.

Results: The median age was 78 years (range 75-87), with 62 male and 39 female patients. The surgical procedures included 77 lobectomies and 24 segmentectomies. The measured DT values were as follows: right/left on axial images, 3.90±1.40 mm / 3.39±1.34 mm, respectively; and right/left on coronal images, 3.63±1.30 mm / 3.03±1.08 mm, respectively. The MDT was 3.49±1.03 mm. Postoperative complications occurred in 24 cases (23.8%). The group with postoperative complications had a significantly lower MDT ($p = 0.0005$), with a cutoff value for MDT determined as 3.4 mm by receiver operating characteristic curve analysis. Univariate and multivariate logistic regression analyses revealed that DT ≤ 3.4 mm was an independent factor associated with postoperative complications (odds ratio: 5.89).

Conclusions: Patients with MDT ≤ 3.4 mm on preoperative CT scans are at higher risk of postoperative complications and may have poorer outcomes. Therefore, careful perioperative management is required for high-risk cases.

Keywords: lung cancer, respiratory sarcopenia, diaphragm

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EP.07A.13 The Comparison of Early Surgical Outcomes and Lung Function Change after Complex Basal Segmentectomy and Lower Lobectomy

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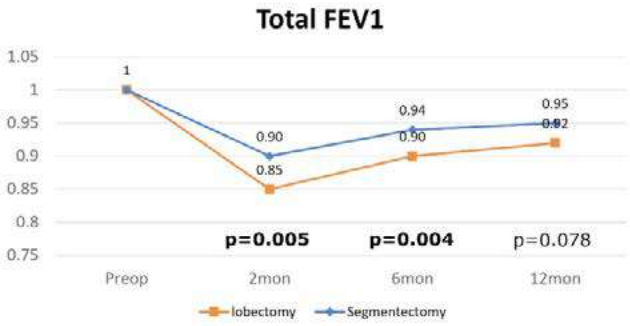
Introduction: Complex basal segmentectomies are often precluded due to the perceived augmented risk of failure and for augmented potential post-operative complications. Few studies have evaluated the post-operative pulmonary function change in complex basal segmentectomy compared to lower lobectomy. This study aimed to assess peri-operative outcomes and the course of lung function in two groups.

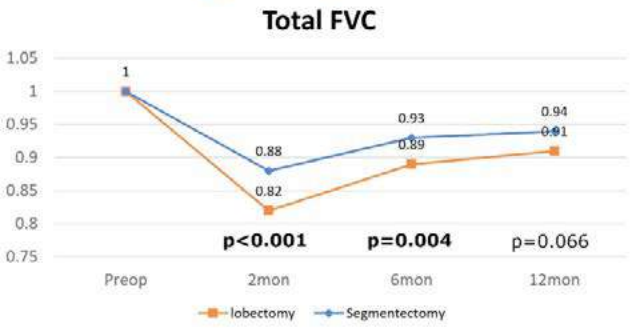
Methods: Patients who underwent lung surgery at one institution from August 2018 to December 2021 were included. Among them, 258 patients who underwent lower lobectomy and complex basal segment resection were divided into two groups. The complex basal segmentectomy was defined as the anatomical resection of at least one subsegment composing the basilar pyramid, excluding S6 and S7-10 segmentectomy. We investigated complications, early outcomes, remaining pleural space, and changes in lung function after surgery.

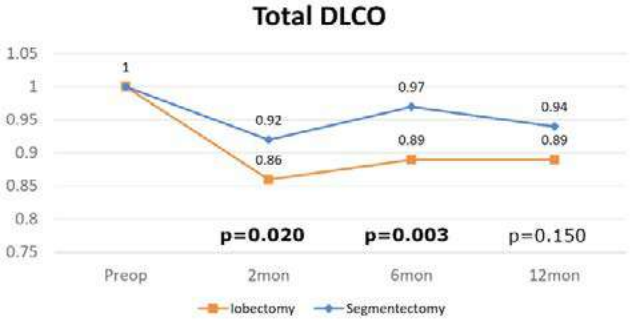
Results: There was no difference in the preoperative clinical profile in the two groups. There were 5 patients (9.6%) who achieved conservation with lobectomy, and there was no difference in operative time or blood loss between the two groups. Chest tube drain, chest tube duration, and postoperative hospital stay were shorter in the segmentectomy group than in the lobectomy group. (p<0.0001) Postoperative complications such as prolonged air leak, pneumonia, and pleural effusion occurred in lobectomy but did not occur in segmentectomy. (p=0.004). The pleural space remaining after surgery was also significantly smaller in the segmentectomy group. In terms of postoperative pulmonary function, there was a difference between the two groups at 2 months and 6 months after surgery, but there was no statistically significant difference at 12 months.

Conclusions: Although the rate of lobectomy conversion was relatively high, complex basal segmentectomy could achieve better early surgical outcomes than lower lobectomy and enough resection margin. Complex basal segmentectomy could preserve early pulmonary function and reduce space problems significantly compared with lower lobectomy.

Keywords: Complex basal segmentectomy, pulmonary function, early outcome







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EP.07A.14 The Postoperative Chest Tube Drainage Strategy of "Lesstube" Can Reduce Patient Pain and Shorten Hospital Stay

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Introduction: Lung cancer is a leading cause of cancer-related deaths worldwide. Surgical resection remains the most effective treatment for the majority of early-stage lung cancer patients. With the latest advancements in minimally invasive thoracic surgery, the efficacy of single-incision video-assisted thoracoscopic surgery (VATS) has been supported by accumulating evidence. According to multiple studies, single-incision VATS offers advantages over multi-port VATS, including less postoperative pain, greater satisfaction with surgical incisions, and shorter hospital stays. However, there is still controversy regarding the selection and placement of chest tubes after single-incision VATS.

Methods: A retrospective analysis was conducted on 425 patients who underwent single-incision VATS lung surgery (lobectomy, segmentectomy, wedge resection, or their combinations) in the Department of Thoracic Surgery at Fujian Medical University Union Hospital between May 2023 and November 2023. Based on different drainage strategies, the patients were divided into three groups: the Single group (SD) with one Abel drain, the Double group (DD) with two Abel drains, and the Traditional group (TD) with one Abel drain and one large-caliber chest tube. Pain and cough assessments were performed using the Numeric Rating Scale (NRS) three times a day (every 8 hours) during the first three postoperative days. Clinical data, including drainage volume and length of hospital stay, were collected. The SD and DD groups were categorized as the small tube group, while the TD group was classified as the large tube group. Chest X-rays or computed tomography (CT) scans were obtained on postoperative day 1 and 1 month after surgery to compare lung images. Adverse events such as pleural effusion, subcutaneous emphysema, lung infection, and inadequate lung reexpansion were documented.

Results: Our study found that patients in the SD group had the lowest VAS scores, while the TD group had the highest pain scores, with a p-value of < 0.0001, indicating that placing only an Abel drain significantly reduces postoperative pain. Additionally, the average length of hospital stay was 3.32 days in the SD group, 4.27 days in the DD group, and 4.25 days in the TD group, demonstrating faster recovery in the SD group with an average reduction of 1 day in postoperative hospital stay. In terms of chest radiography comparison, the small tube group also showed significant advantages. When comparing the occurrence of pleural effusion, subcutaneous emphysema, lung infection, and inadequate lung reexpansion on chest X-rays taken on the first postoperative day, the incidence rates of these events were slightly higher in the small tube group compared to the large tube group, but they did not reach statistical significance. Furthermore, the chest X-rays taken one month after surgery indicated that both the small tube and large tube groups showed improvement or even returned to normal in the aforementioned adverse events. Therefore, it can be concluded that there is no significant difference in long-term complications between these two groups.

Conclusions: Placement of only an Abel drainage tube postoperatively can significantly alleviate patients' postoperative pain scores, shorten hospital stay, and does not increase the risk of long-term complications.

Keywords: Lesstube, Chest tube drainage strategy, Lung cancer

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EP.07A.15 Prognosis after Surgical Treatment of Lung Cancer with Multifocal Ground-Glass Nodules: The Effect of Nodule Characteristics

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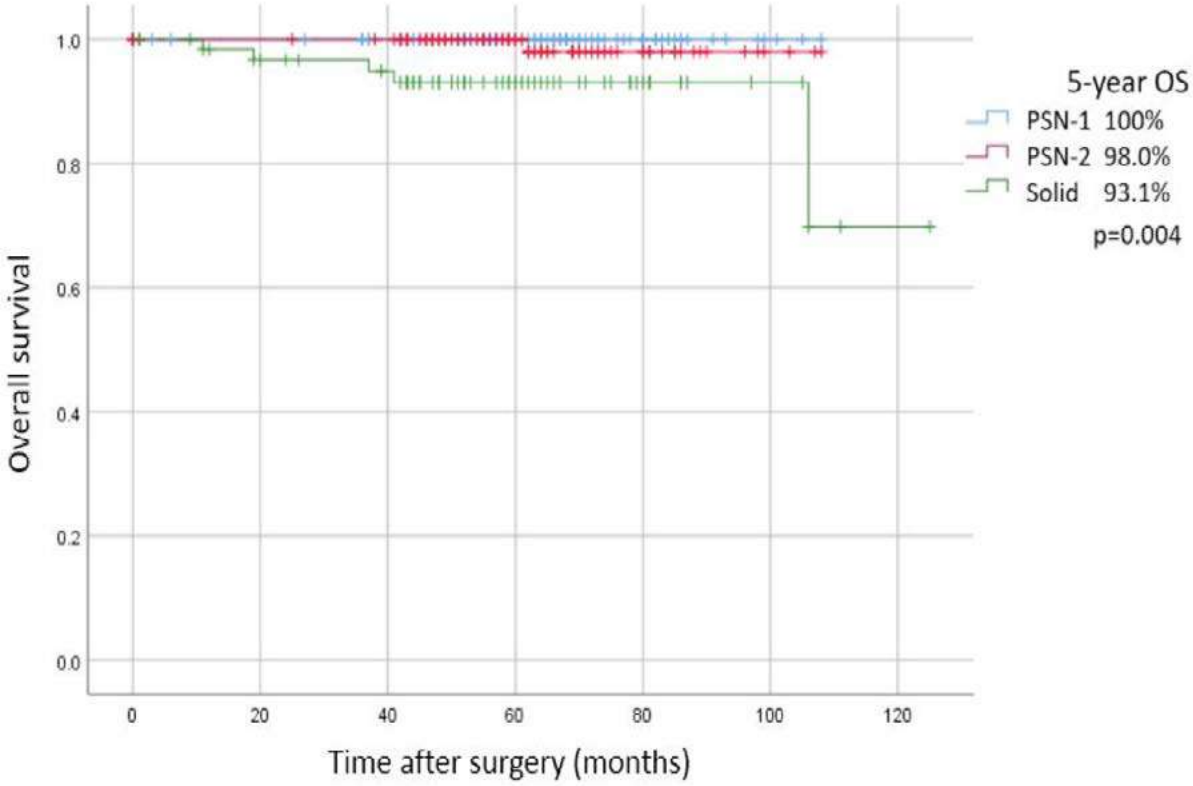
Introduction: Clinical decision for the management of lung cancer with synchronous multifocal ground glass nodules (GGN) is complicated because of extremely heterogeneous nodule characteristics and distribution and there is still no clear clinical guideline for this disease entity. Thus, we analyzed the effect of radiologic nodule characteristics on long-term prognosis after surgical treatment of lung cancer with multifocal GGNs.

Methods: Total of 284 patients who underwent pulmonary resection for the treatment of lung cancer with synchronous multifocal GGNs from 2013 to 2019 were reviewed retrospectively. The most invasive nodule based on radiologic features was defined as a dominant nodule, which was the primary target of initial surgery. Patients were divided into three group according to the radiologic consolidation-tumor ratio (CTR) of dominant nodule. [PSN-1 (0≤CTR<0.5), PSN-2 (0.5≤CTR<1), Solid (CTR=1)]. Long-term prognoses of three groups were compared.

Results: There were 114 (40.2%) patients in the PSN-1, 106 (37.3%) patients in the PSN-2 and 64 (22.5%) patients in the solid group. The mean number of nodule was 4.6 (range: 2 - 23). The mean number of resected nodules at the initial surgery was 2.4 (range: 1 - 13). In 32 (11.3%) patients, only the dominant nodule was resected. Dominant nodules of 9 (3.2%) patients were non-adenocarcinoma histology. Pathologic T stage of dominant nodules were T1a in 67, T1b in 88, T1c in 31, and T2a≤ in 98 patients. After initial surgery, 177 (62.3%) patients had residual GGN(s) and the mean number of residual GGN was 3.4 (range: 1 - 17). During median 60.7 months of follow-up period, residual GGNs in 43 (24.3%) patients had progressed and second intervention was conducted in 35 (19.8%) patients (surgery - 27, radiotherapy - 8). The 5-year disease-free survival rate were 100%, 94.8%, and 81.8% for PSN-1, PSN-2, and solid group (p<0.001) and overall survival rates were 100%, 98%, and 93.1% (p=0.004), respectively. The total number of nodule, presence of residual nodules, and progression of residual nodules did not affect survival.

Conclusions: The invasiveness of dominant tumor was the most important prognostic factor in the surgical treatment of lung cancer with multifocal GGNs. The residual non-dominant nodules did not jeopardize the survival. Secondary intervention was necessary in about 20% of patients due to the progression of residual GGN.

Keywords: multifocal lung cancer, lung cancer, ground-glass nodule



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EP.07A.16 The Prognostic Disparities Between the T3 Descriptors in Surgically Resected Primary Lung Cancer

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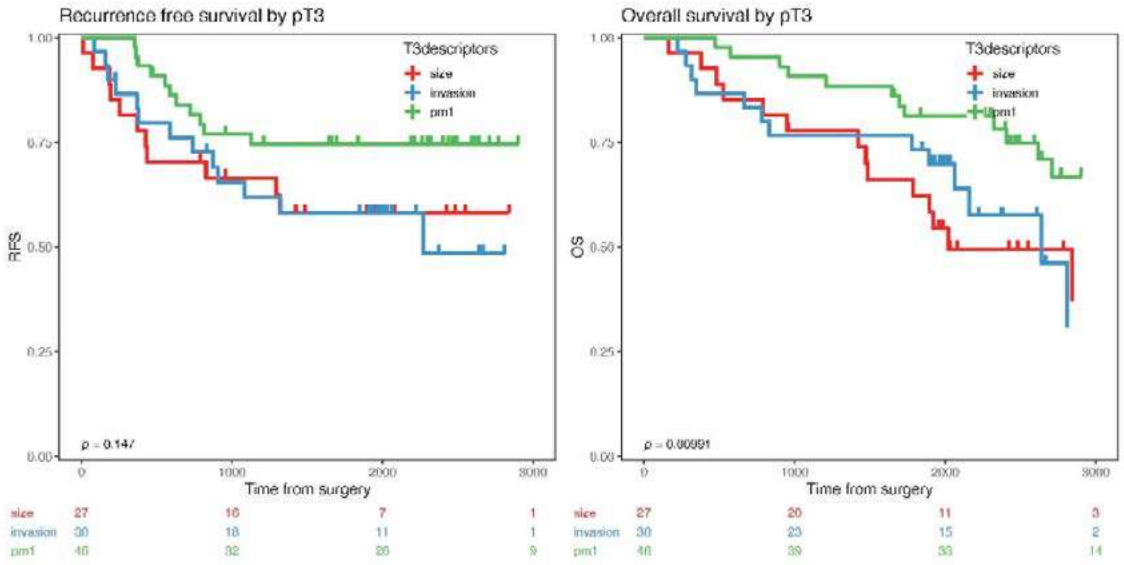
Introduction: Our aim was to study the disparities between the different T3 descriptors in surgically resected T3N0M0 primary lung cancer.

Methods: We retrieved data of completed resected primary lung cancer at our institute between 2010-2018. T3 lung cancer was divided into three groups, Size (S), Invasion (I), and Pulmonary metastasis within the same lobe (PM), according to the 8th TNM staging manual. Overall survival and recurrence free survival were compared using the Kaplan-Meier method with a log-rank test. A multivariable Cox regression model was performed to determine the prognostic factors.

Results: Among the 2488 cases of primary lung cancer with complete resection, 103 cases were pathologically diagnosed as T3N0M0. S, I, and PM included 30,46, and 27cases, respectively. Each group included 1 (3.7%), 2 (6.7%), and 18 (39.1%) cases with EGFR mutation. The RFS (Recurrence Free Survival) rate at 5 years for S, I, PM were 58.2%, 56.3%, and 72.7%, respectively (p=0.147). The OS (Overall Survival) rate at 5 years for S, I, PM were 62.2%, 71.0%, and 81.7%, respectively (p<0.01). The multivariable Cox regression test showed pT3 status (S vs PM, Hazard ration [HR]=0.31, 95% confidence interval [CI] 0.12-0.84, p=0.021) and mutation status (no mutation vs EGFR mutation, HR=2.81 95%CI:1.22-6.45, p=0.015) as statistically significant prognostic factors for RFS. Age (HR=1.08, 95%CI:1.04-1.13, p<0.01), surgical procedures (lobectomy vs wedge resection, HR=21.56, 95%CI:6.47-71.88, p<0.01) and pT3 status (S vs PM, HR=0.35, 95%CI:0.16-0.77, p<0.01) were statistically significant prognostic factors for OS.

Conclusions: Among the T3 descriptors, PM was a prognostic factor for both RFS and OS. EGFR mutation was a risk factor for recurrence, and considering the high rate of EGFR mutation in T3 cases with pulmonary metastasis, PM cases may have a better prognosis than the current study in the future, considering the results from the ADAURA trial. T3 descriptors should be validated in the future staging manual considering the disparities between the different T3 descriptors.

Keywords: pT3N0, prognosis



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EP.07A.17 One-Stage Versus Two-Stage Thoracoscopic Surgery for Synchronous Bilateral Pulmonary Nodules: A Propensity Score-Matched Analysis

Y. Han, F. Xiao, Q. Ma, Z. Zhang, D. Liu, C. Liang, China-Japan Friendship Hospital, Beijing/CN

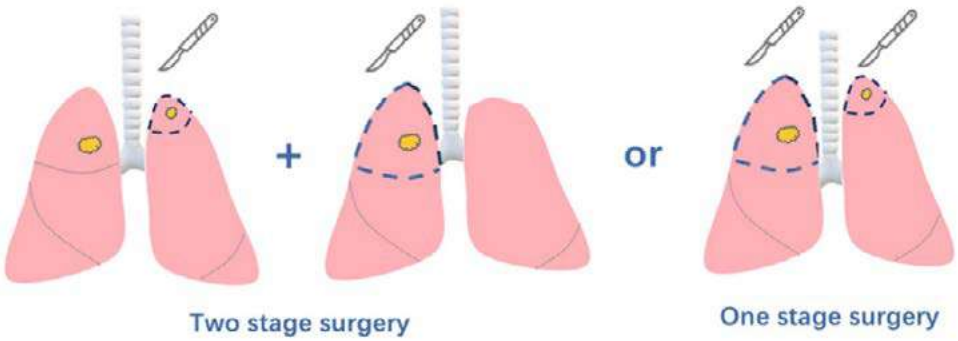
Introduction: The aim of this study was to compare the surgical efficacy of one-stage and two-stage video-assisted thoracoscopic surgery (VATS) for bilateral multiple pulmonary nodules (BMPNs).

Methods: A retrospective analysis was made of 156 patients, 84 who underwent one-stage and 72 who underwent two-stage VATS for BMPNs at our department between January 2019 and December 2022. Clinical features and perioperative outcomes were compared between the two groups using propensity score-matched (PSM) analysis.

Results: There were 48 patients in each group after PSM. No significant difference was observed in operation time, blood loss, and rates of overall complications (p>0.50) between one-stage and two-stage groups. One-stage procedure was associated with shorter overall duration of drainage (3 days [IQR 3-4 days] vs. 6 days [IQR 5-7 days]; p<0.001), shorter length of stay (5 days [IQR 4-5.75 days] vs. 9 days [IQR 7-10 days]; p<0.001), as well as lower total cost (14626.3±4149.4 vs. 18975.9±3720.8 USD, p<0.001) compared to two-stage procedure. Tumor progression of the contralateral lesions happened in 13 (18.1%) patients before second operation in two-stage group.

Conclusions: One-stage and two-stage VATS for BMPNs are both safe and feasible in selected patients. One-stage procedure possess potential advantages in reducing hospital stay and cost, as well as preventing tumor progression.

Keywords: multiple primary lung cancers, one-stage, two-stage



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EP.07A.18 Do Excessive Delays Affect Pathologic Upstaging for Early Lung Cancer?

J. Zhu, J. Zhang, R. Yip, C.I. Henschke, D.F. Yankelevitz, Mount Sinai Health System, New York/NY/USA

Introduction: Our past research into time-to-treatment for early-stage lung cancer found significant disparities, negatively affecting patients of Black or African American race, lower income, and those with vascular disease. Additionally, we found that patients who undergo radiotherapy for treatment of early-stage lung cancer face significant delays, compared to those who receive surgery. Despite these findings, we have yet to investigate the effects of excessive time delays on potentially worse lung cancer outcomes for clinical stage I lung cancers. The primary outcome of interest was pathologic upstaging, if the pathologic TNM stage was higher than the clinical TNM stage. The secondary outcome of interest was whether there were differences in lung cancer histology by each TTI quartile.

Methods: We reviewed all participants of the prospective cohort study, Initiative for Early Lung Cancer Research on Treatment (IELCART), from 2016-2024. Inclusion was limited to patients who received surgical resection for clinical stage I lung cancer (TNM 8th edition modified) with maximum diameter < 30mm (T1a-c). The median time from suspicious scan to surgery (TTI) was 84 days (IQR 57-124 days). Subsequently, the patients were split into four nearly equivalent quartiles from fastest to slowest TTI.

Conclusions: While the analyses did not yield statistically significant results, we found a trending increase in frequency of tumor size upstaging, with increasing TTI quartiles. This suggests a possible association with increasing time delays and increasing size. With complete data on recurrence and overall survival, we can better establish this connection. There were no notable differences in histology, besides more typical carcinoids in the third and fourth quartiles; this shows that providers are possibly treating all lung nodules < 30 mm equally, regardless of possible histology. Acting faster on more aggressive early-stage lung cancers needs to be a priority for future research.

Keywords: delays to treatment, lung cancer staging, early-stage lung cancer

Table 1: TNM upstaging and TTI categories (< 30 mm)

Characteristic	Overall, N = 854[1]	1st quartile (0-57 days), N = 219[1]	2nd quartile (57-84 days), N = 213[1]	3rd quartile (84-123 days), N = 210[1]	4th quartile (>123 days), N = 212[1]	p-value[2]
T upstaging	78 (9.1%)	15 (6.8%)	18 (8.5%)	20 (9.5%)	25 (12%)	0.3
N upstaging	48 (5.6%)	9 (4.1%)	15 (7.0%)	11 (5.2%)	13 (6.1%)	0.6
M upstaging	3 (0.4%)	0 (0%)	2 (0.9%)	1 (0.5%)	0 (0%)	0.2
[1]n (%)						
[2]Pearson's Chi-squared test; Fisher's exact test						

Table 2: Histology and TTI categories (< 30 mm)

Characteristic	Overall, N = 854[1]	1st quartile (0-57 days), N = 219[1]	2nd quartile (57-84 days), N = 213[1]	3rd quartile (84-123 days), N = 210[1]	4th quartile (>123 days), N = 212[1]	p-value[2]
Histology						0.091
Adenocarcinoma	656 (77%)	170 (78%)	161 (76%)	163 (78%)	162 (76%)	
Squamous Cell Carcinoma	90 (11%)	24 (11%)	29 (14%)	15 (7.1%)	22 (10%)	
Typical Carcinoid	79 (9.3%)	20 (9.1%)	11 (5.2%)	25 (12%)	23 (11%)	
Others	29 (3.4%)	5 (2.3%)	12 (5.6%)	7 (3.3%)	5 (2.4%)	
[1]n (%)						
[2]Pearson's Chi-squared test						

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EP.07A.19 Impact of Preoperative Pulmonary Function on Survival Following Lobectomy for Stage I and II Lung Cancer

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Introduction: Determining a patient's operability is pivotal for planning surgery in early-stage lung cancer. The aim of this study is to examine the impact of preoperative lung function values on survival following lobectomy for stage I and II lung cancer.

Methods: Retrospective data were collected from a single center on patients who underwent lobectomy for lung cancer in postoperative stages I and II. Our cohort was divided into three groups according to preoperative pulmonary function. Group A included patients with normal pulmonary function, with both FEV1 and DLCO >80% predicted. Group B included patients if at least one of these values was between 60-80% predicted. Group C included patients if at least one of these values was <60% predicted.

Results: A cohort of 977 patients was included in the study, with a median age of 67.7 years. The distribution of disease stages was as follows: 68.8% were classified as stage I, while 31.2% were categorized as stage II. Lung adenocarcinoma was diagnosed in 55.2% of patients, squamous cell carcinoma in 28.4%, and neuroendocrine carcinoma in 6.2%. The most common operation was right upper lobectomy (33.9%) followed by left upper lobectomy (25.5%) and right lower lobectomy (17.3%). Group A included 14.4% of the study patients, Group B 43.1%, and Group C 42.2%. Preoperative pulmonary function showed statistical significance for survival in the log-rank test (p=0.01). In Group C, patients were more likely to be current smokers (p<0.01), a higher frequency of BMI <30 kg/m2 (p=0.01), a history of liver failure (p<0.01), ECOG status >1 (p=0.01), and COPD (p<0.01). Moreover, they underwent open surgery with thoracotomy more frequently (p<0.01). However, no statistical significance was found between the three groups regarding cardiovascular comorbidities, kidney morbidity, or diabetes (p>0.05). The 5-year survival for Group A was 77.2%, for Group B 59.9%, and for Group C 55.3%. Independent factors influencing survival in the multivariate analysis were liver failure (HR: 2.219, 95% CI: 1.2-4.3, p=0.01), higher lung cancer stage (HR: 1.152, 95% CI: 1.04-1.27, p=0.01), neo-adjuvant therapy (HR: 1.697, 95% CI: 1.096-2.629), and the performance of an open operation (HR: 0.604, 95% CI: 0.41-0.87, p=0.01).

Conclusions: Despite advancements in major medical technology and surgical techniques, preoperative pulmonary function remains a factor influencing survival in lung cancer patients. However, patients with impaired pulmonary function showed similar survival rates to patients with reduced pulmonary function. Therefore, patients with impaired pulmonary function should be thoroughly investigated and discussed in a multidisciplinary tumor board, and not excluded from surgery, as it could prolong survival.

Keywords: lung cancer, surgery, lung function

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EP.07A.20 Intraoperative Near-infrared Fluorescence Visualization of the Pulmonary Bronchus with Indocyanine Green Inhalation

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Introduction: Intraoperative tracheobronchial injury is a rare but serious complication of lung surgery. With the increasing number of segmentectomies, surgeons need to locate finer and less easily identified segmental bronchi or even subsegmental bronchi. However, there is no simple or feasible method for visualizing the bronchus during surgery.

Methods: Herein, we report a case in which indocyanine green (ICG) inhalation was used to visualize the pulmonary bronchus during video-assisted thoracoscopic surgery. ICG (3.75 mg/ml) was inhaled into the lung of the operative side after single-lung ventilation for 5 minutes using a mesh nebulizer. Intraoperatively, fluorescence visualization of pulmonary bronchus was performed using near-infrared fluorescence (NIF) imaging system.

Results: The patient was a woman with a GGO located in the anterior segment of the right upper lobe, and thoracoscopic segmentectomy was scheduled. During surgery, the anterior segmental bronchus was difficult to locate accurately. ICG (3.75mg/ml) was inhaled into the lung of the operative side after single-lung ventilation for 5 minutes using a mesh nebulizer. Under the overlay imaging window of the NIF imaging system, the bronchus was shown in green, in sharp contrast to the surrounding lung tissue. We dissected the bronchi with the assistance of fluorescence imaging and were surprised to find that the bifurcation of the anterior and apical bronchi could be clearly identified by navigation via the inhaled ICG and NIF system. Segmentectomy was successfully performed, and no adverse events were recorded.

Conclusions: This case showed that ICG nebulization is feasible and safe for visualizing the pulmonary bronchus during thoracoscopic surgery. This method has great application potential for reducing intraoperative tracheobronchial injury.

Keywords: Pulmonary bronchus visualization, Near-infrared fluorescence, Thoracoscopic surgery

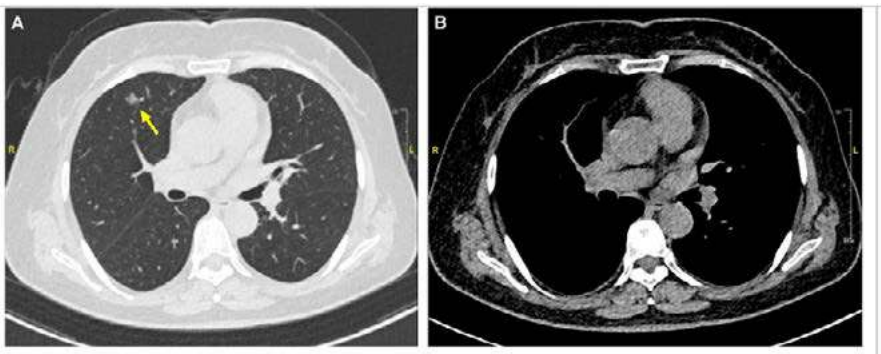

Figure 1. A chest CT revealed a GGO (yellow arrow) in the anterior segment of the right upper lobe (Subfigure A). The size of the GGO was approximately 11*9 mm in the lung window, and no visible solid component was observed in the mediastinal window (Subfigure B).

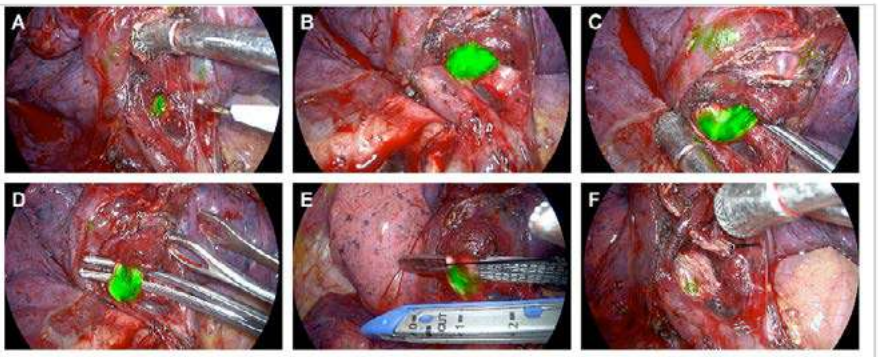

Figure 2. Under the overlay imaging window of the near-infrared fluorescence imaging system, the bronchi were shown in green, which contrasts with the surrounding lung tissue (Subfigures A and B). More importantly, the bifurcation of the anterior and apical bronchi could be clearly identified (Subfigures B and C). After the bronchus was fully dissected (Subfigure D), it was cut off with an endoscopic blue stapler (Subfigure E and F).

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EP.07A.21 Tubeless Strategy after Thoracoscopic Pulmonary Wedge Resection: A Better Choice for Specific Patients

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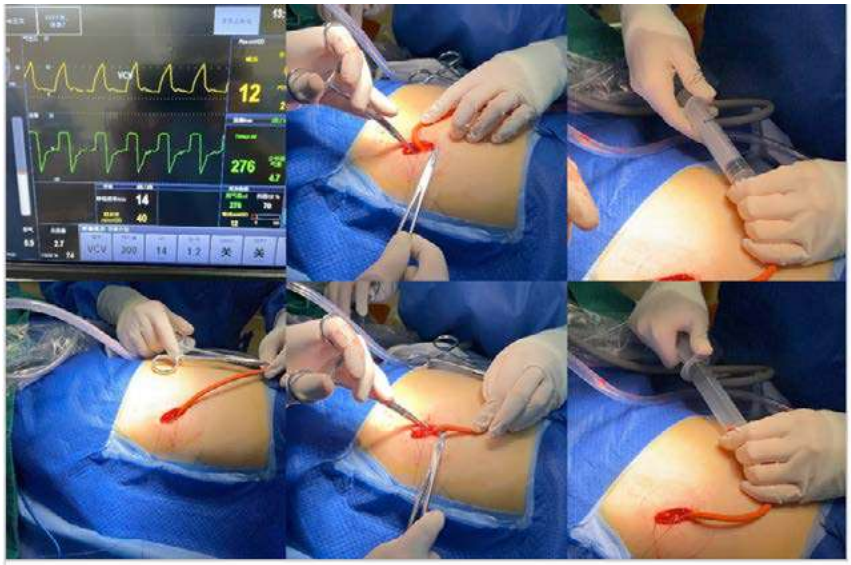
Introduction: The placement of a chest tube after pulmonary resection is generally considered necessary. However, discomfort of the drainage system impede the fast recovery of patients. Previously, we proved that catheter drainage was a safe alternative to chest tube for wedge resection and relieved postoperative pain. Here, we conducted this research to investigating the improvement of tubeless strategy compared to catheter drainage.

Methods: Patients who underwent pulmonary wedge resection under Video-assisted thoracoscopic surgery in our hospital between September 2020 and March 2024 were enrolled in this study. According to the presence or absence of postoperative thoracic drainage, the patients were divided into Catheter and No Intubation group. Propensity score matching method (PSM) was used and univariate analysis was performed to compare the clinical features and perioperative complications between the two groups.

Results: A total of 416 patients were included. PSM was used to identify 1:1 between the Catheter and No Intubation group. The matching factors were baseline characteristics, and 56 cases in each group were matched. The results showed that the operative time in the Catheter group was significantly longer than that in the No Intubation group (82.00 vs. 67.50 min, P <0.05). No significance was observed in postoperative complications, numerical rating scale score, reintubation rate and hospitalization stay.

Conclusions: It is feasible to omit thoracic drainage after surgery for some patients, resulting in a better experience, surgical satisfaction, and better wound recovery. This strategy should be extended to patients who undergo pulmonary wedge resection and are evaluated intraoperatively as having a low risk of complications.

Keywords: Pulmonary wedge resection, No intubation



Variate	Group: Catheter (*n*=56)	Group: No Intubation (*n*=56)	Statistics	*P*
Complication				
No	55(98.21)	56(100.00)	—	1.000*
Pulmonary complications	1(1.79)	0(0.00)		
Postoperative hospitalization, days [$M(P_{25},P_{75})$]	2.00(2.00,3.00)	2.00(2.00,2.00)	Z=-0.87	0.385#
Adhesion				
No	46(82.14)	50(89.29)	χ^2=1.17	0.280
Yes	10(17.86)	6(10.71)		
Bleeding, ml [$M(P_{25},P_{75})$]	5.00(5.00,5.00)	5.00(5.00,5.00)	Z=-0.49	0.624#
Surgery duration, min [$M(P_{25},P_{75})$]	82.00(65.00,110.00)	67.50(49.50,82.50)	Z=-3.95	**<0.001#**
NRS at the day after surgery [$M(P_{25},P_{75})$]	1.00(0.00,2.00)	1.00(0.00,1.00)	Z=-0.12	0.904#
Subcutaneous emphysema				
No	28(50.00)	31(55.36)	χ^2=0.32	0.570
Yes	28(50.00)	25(44.64)		
Chest radiation one month after surgery				
No	24(42.86)	19(34.55)	χ^2=0.81	0.369
Yes	32(57.14)	36(65.45)		
Reintubation				
No	56(100.00)	55(98.21)	—	1.000*
Yes	0(0.00)	1(1.79)		

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EP.07A.22 The Optimal Surgical Procedure Based on the Risk of Recurrence in Clinical Stage 0 or IA Lung Adenocarcinoma

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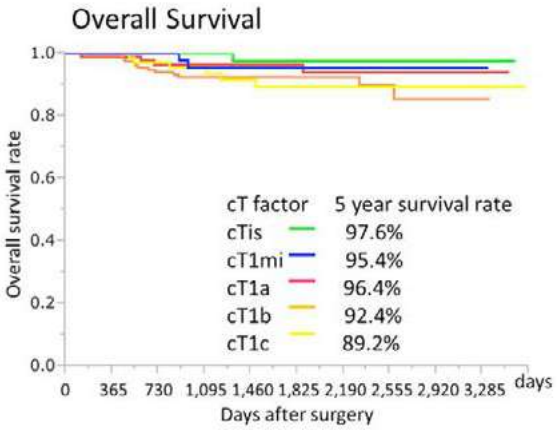
Introduction: Recently, two randomized controlled studies have proved noninferiority or superiority in survival after sublobar resection compared with lobectomy for peripheral lung cancers that are 2 cm or less. On the other hand, both trials defined inclusion criteria by maximum tumor diameter or consolidation tumor ratio (CTR), which diverges from the current tumor node metastasis (TNM) staging. In this study, we evaluated the optimal surgical procedures of clinical stage 0 or IA adenocarcinoma according to the TNM 8th edition and imaging features of tumors from the perspective of recurrence.

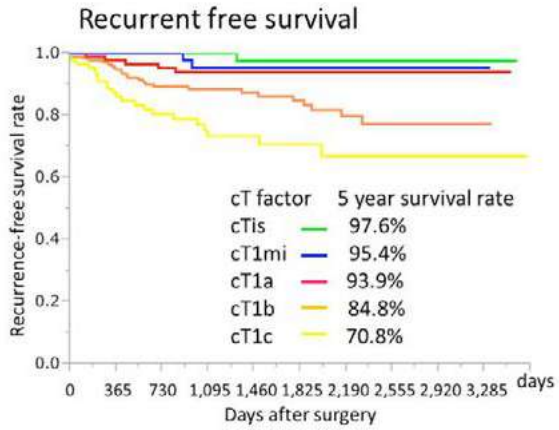
Methods: We retrospectively investigated 508 lung adenocarcinoma diagnosed as c-stage 0 or IA who underwent curative resection. Tumors were divided into pure GGO, part-solid tumors and solid tumors based on the CTR in thin-section CT: pure GGO, CTR=0; part-solid, 0<CTR<1; solid, CTR=1. A survival analysis was performed according to the clinical T descriptor, CT features and surgical procedures.

Results: The tumors were classified as follows: 74 with pure ground glass opacity (GGO), 237 part-solid tumors and 197 solid tumors. The types of surgical procedures were lobectomy (n=328), segmentectomy (n=73) and wedge resection (n=107). Clinical T descriptors were cTis in 74 patients, cT1mi in 68 patients, cT1a in 94 patients, cT1b in 181 patients and cT1c in 91 patients. For the entire cohort, the 5-year overall survival (OS) rate was 93.8%, and the 5-year disease-free survival (DFS) rate was 87.5%. The respective 5year OS and DFS rates by clinical descriptors were as follows: 97.6% and 97.6% in cTis, 95.4% and 95.4% in cT1mi, 96.4% and 93.9% in cT1a, 92.4% and 84.8% in cT1b and 89.2% and 70.8% in cT1c. Recurrence was observed 46 cases (9%), including 3 (3.1%) with cT1a, 23 (12.7%) with cT1b and 20 (22.0%) with cT1c. No recurrence was observed in cTis or cT1mi cases. Solid tumors with cT1b recurred more often than part-solid tumors among cT1b cases (16.8% vs. 6.8%) (p=0.046). There were no marked differences in the recurrence rate between part-solid and solid tumors in the cT1a and cT1c groups. The patients who received sublobar resection developed recurrence more often than the patients who received lobectomy among cT1b cases (21.4% vs. 10.1%) and cT1c cases (46.2% vs. 18.0%) (p=0.053 and p=0.023).

Conclusions: The cTis and cT1mi cases should be actively considered for sublobar resection, while cT1b (especially solid cT1b cases) and cT1c cases should be considered for lobectomy to prevent recurrence.

Keywords: Non-small cell lung cancer, Surgery, limited resection





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EP.07A.23 Initial Experience of Robotic Assisted Pulmonary Resection Using a Novel Surgical Robot with Haptic Feedback Function

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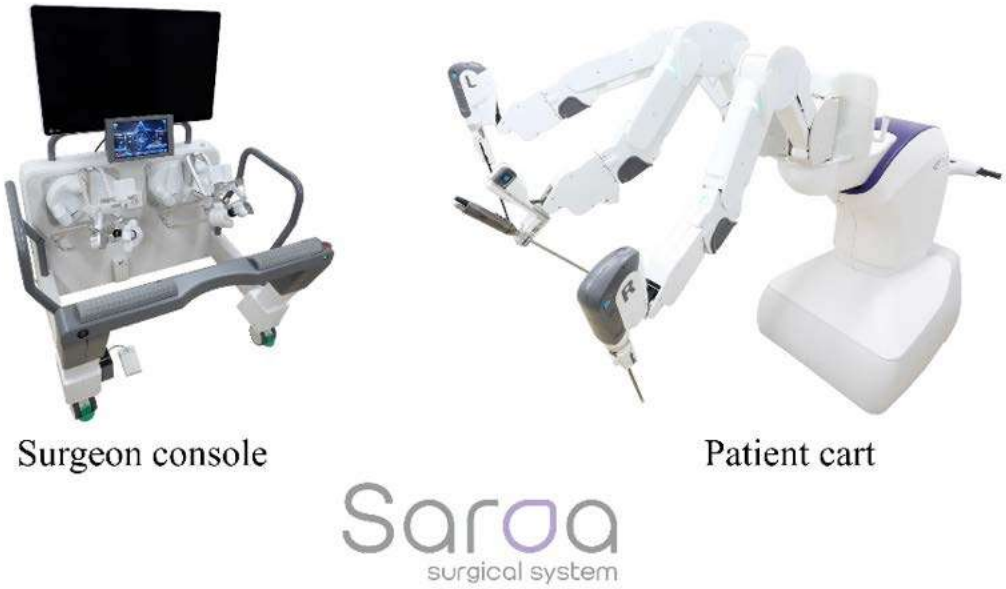
Introduction: Robotic-assisted thoracoscopic surgery (RATS) has the advantages of low patient burden and high precision without unsteady hand movements However, the lack of tactile sensations may result in unexpected iatrogenic organ damage.

Methods: The Saroa (Riverfield Inc., Tokyo, Japan) is a pneumatically driven robot that provides real-time haptic feedback to the surgeon. We performed the first thoracic surgery for lung cancer using the Saroa in the world in July 2023. A retrospective analysis was performed at our institution for patients who underwent lung resections using the da Vinci surgical system (Intuitive Surgical Inc. CA) and the Saroa from July 2023 to March 2024. The aim of this study is the evaluation of short-term outcomes, including intraoperative adverse events, operative time, blood loss, postoperative pain, and the feasibility and safety of thoracic surgery for lung cancer using the Saroa.

Results: Of 65 patients, 19 were performed using the Saroa. In terms of surgical procedure, six patients underwent segmentectomy and 13 underwent lobectomy in the Saroa group, and six patients underwent segmentectomy and 40 underwent lobectomy in the da Vinci group. We observed two patients and one converted to the thoracotomy due to pleural adhesion, respectively. No patient had postoperative complications of Clavien-Dindo classification IVa or higher, except two patients who died in the da Vinci group. The causes of death were cerebral infarction and acute exacerbation of interstitial pneumonia. Intraoperative adverse events didn't occur in both groups. No statistically significant difference was observed in terms of hospital stay:10 days for the Saroa group and 10 for the da Vinci group (p = 0.786). There was no significant difference in FEV 1.0% in the Saroa and the da Vinci group (68.68 % vs 68.86 %, p = 0.957), in operative time (213 min vs 237 min, p = 0.316), in blood loss (102 mL vs 249 mL, p = 0.428), in the Numerical Rating Scale (NRS) in the 1st p.o. day (2.95 vs 3.24, p = 0.617), but had a shorter console time (116 min vs 173 min, p= 0.00135) and a lower onset of prolonged air leakage (2/19 vs 6/46, p = 0.0371). Fifteen (78.9 %) patients in the Saroa group and 39 (84.8 %) in the da Vinci group had pathological stage I and II diseases.

Conclusions: This study found that robotic pulmonary resection for lung cancer using the Saroa can be safely performed.

Keywords: Robotic-assisted thoracoscopic surgery, Haptic force feedback function, Lung cancer



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EP.07A.24 European Experience of Early-Stage NSCLC Patients with Any Prior Cancer History Following Lobectomy or Segmentectomy

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Introduction: Patients with history of prior cancer are generally excluded from studies, however their incidence is increasing in clinical practice. They possess a genetically susceptible oncological profile that may influence both oncogenesis and treatment response. This study aimed to investigate whether history of prior cancer had different impact on oncologic outcomes of patients with peripheral early-stage non-small cell lung cancer (NSCLC) operated on by lobectomy or segmentectomy.

Methods: A retrospective multicenter study included patients with pathologically proven 2 cm or less N0M0 R0 NSCLC with or without history of prior cancer, operated on from 2015 to 2021 across nine European centers (one per country). Oncologic lung outcomes were assessed before and after propensity score matching (PSM) by cox regression (overall survival and recurrence-free survival) and competing regression analyses (lung cancer-specific survival) to adjust patients and tumor-related factors.

Results: 540 (28.2%) patients had history of prior cancer. Lobectomy and segmentectomy were performed in 1476 (77.3%) and 434 (22.7%) patients, respectively. Two matched sets of 408 patients each (operated on by lobectomy vs. segmentectomy) were formed using PSM. Following PSM: 1) 5-year overall survival was similar (p= 0.3) between patients who underwent lobectomy 86.5% (CI 95%: 82.8-90.4%) and segmentectomy 81.4% (CI 95%: 76.2-86.9%); 2) 5-year overall survival was statistically different (p= 0.02) between patients with history 80.5% (CI 95%: 74.3-86.5%) and without history of prior cancer 86.2% (CI 95%: 82.6-89.9%); 3) 5-year lung cancer specific survival was statistically different (p= 0.04) between patients who underwent lobectomy 95.2% (CI 95%: 92.8-97.6%) and segmentectomy 96.1% (CI 95%: 93.3-99%); 4) 5-year recurrence-free survival was similar (p= 0.1) between patients who underwent lobectomy 89.5% (CI 95%: 86-93.2%) and segmentectomy 89.1% (CI 95%: 84.9-93.4%); 5) 5-year lung cancer specific survival in patients with history of cancer was different (p= 0.01) between those who underwent lobectomy 88.9 % (CI 95%: 82.5-95.7%) and segmentectomy 94.9 % (CI 95%: 88.9-100%); 6) 5-year recurrence-free survival for patients with history of cancer was similar (p= 0.1) between patients who underwent lobectomy 85.3% (CI 95%: 77.6-93.6 %) and segmentectomy 89.5% (CI 95%: 82.3-97.3%); 7) 5-year recurrence-free survival for patients who underwent segmentectomy was similar (p= 0.9) between patients with history 89.5% (CI 95%: 82.3-97.3 %) and without history of cancer 88.6% (CI 95%: 83.5-94.1%). Locoregional recurrence (lobectomy 6.3% vs. segmentectomy 3.2%, p= 0.3) and distant recurrence (lobectomy 6.3% vs segmentectomy 6.4%, p=0.8) were the same in patients with history of prior cancer.Incidence of new primary lung cancer was similar (p= 0.7) in patients who underwent segmentectomy between those with (8.3%) and without history of prior cancer (10.2%). In cox-regression analysis segmentectomy did not influence survival, recurrence, it did not either impact lung cancer specific survival even in univariate analysis.

Conclusions: Compared to lobectomy, segmentectomy does not appear to be associated with inferior oncological outcomes in patients with peripheral pathologic early-stage NSCLC and with history of any prior cancer.

Keywords: segmentectomy, history of prior cancer, outcome

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EP.07A.25 Portable Cone Beam CT for Intraoperative Marking of Small Pulmonary Nodules; Anywhere, Anytime!

N. Mitsuoka, S. Yokoyama, M. Kashihara, Y. Terazaki, M. Mitsuoka, Kurume University, Fukuoka/JP

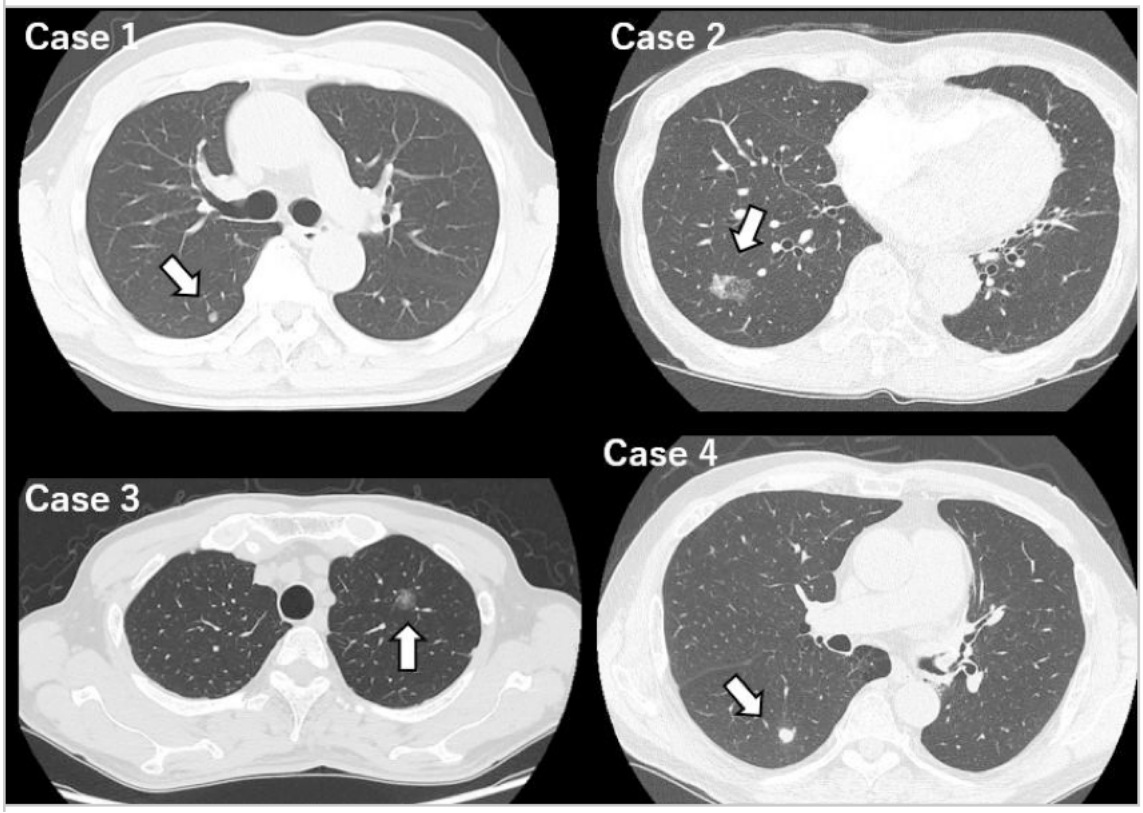
Introduction: Intraoperative lung field marking using Cone Beam Computed Tomography (CBCT) is extremely useful because it avoids air embolism, has a high identification rate of small lesions, and can be completed in the operating room. However, there have been drawbacks such as the need for an operating room equipped with a CBCT imaging machine, the inability to bend the bed, the unreasonable position, and the fact that it can be difficult for physique patients. Therefore, we have been proposing the need for the development of portable CBCT, but it has not yet been developed. In this study, CiosSpin, which is mainly used in areas other than pulmonary resection, was applied to the lung field.

Methods: A portable CBCT machine CiosSpin (SIEMENS Co., Ltd., Germany) and an operating table MOT-VS600 (MIZUHO Co., Ltd., Japan) were used for four patients with small peripheral pulmonary nodules predicted to be difficult to palpable. The location of the lesion was confirmed by CBCT before surgery (pre-scan) under general anesthesia and the portable C-arm position was noted. A surgical clip was attached to the surface of visceral pleura that was anticipated to be closest to the nodule. After the C-arm was repositioned, intraoperative scan was performed. Partial pulmonary resection was performed by identifying the tumor from the position of the clip and nodule.

Results: There were 3 males and 1 female with mean age of 68.3 years (range: 64-76). The preoperative diagnosis was AIS, MIA, invasive adenocarcinoma, and metastatic pulmonary tumor in one case each. Eventually, lobectomy was performed in one case, segmentectomy in two cases, and partial resection in one case. In all cases, the lesion could be depicted by CBCT, and in 3 of 4 cases, the bed was able to bend without adjusting the patient's position after pre-scan. There were no complications associated with this method.

Conclusions: If this technique is established, it will be possible to confirm the location of lesions by CBCT even if it is not a hybrid operation room, and it can be an extremely useful tool. The CiosSpin is designed with wider panel width than other models, making it easy to accommodate the lateral decubitus position, and has high-quality imaging. We report on this method including some areas that we would like to further improve.

Keywords: Cone Beam Computed Tomography, pulmonary nodule, pulmonary resection



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EP.07A.26 A Novel Four-Hook Puncture Needle for Accurate Localization of Small Pulmonary Nodules in VATS: A Single-Center Retrospective Study

B. liang, Q. Cai, The Fifth Affiliated Hospital, Southern Medical University, Guangzhou/CN

Introduction: Accurate localization of small pulmonary nodules is crucial for the success of video-assisted thoracoscopic surgery (VATS). Our center uses a Novel Four-Hook Puncture Needle for Accurate Localization (NFHPNAL), providing a minimally invasive and reliable method for precise localization. This retrospective study evaluated the accuracy and safety of pulmonary nodule resection guided by NFHPNAL.

Methods: This retrospective study describes a single-center study of NFHPNAL for preoperative localization of pulmonary nodules. Clinical, surgical, and pathological data were collected from patients undergoing pulmonary nodule localization from July 2023 to March 2024.

Results: The study reviewed 20 patients who underwent pulmonary nodule localization using NFHPNAL for guidance. A total of 20 pulmonary nodules were treated, with a median localization time of 12 minutes. Following localization, all patients underwent VATS with a median duration of 20 minutes. The median lesion size was 6.5 mm, and the distance between the lesion and the pleura or fissure ranged from 5 to 40 mm. No complications such as bleeding, chest infection, or dislodgement were observed. The overall malignancy rate was 75%. The use of NFHPNAL resulted in a 100% accuracy rate in localizing small pulmonary nodules, as confirmed by markers.

Conclusions: Pulmonary nodule resection guided by NFHPNAL is a safe and precise localization method, potentially minimizing the time spent searching for pulmonary nodules during surgery and simplifying the surgical process.

Keywords: Small pulmonary nodule localization, four-hook puncture needle, video-assisted thoracoscopic surgery

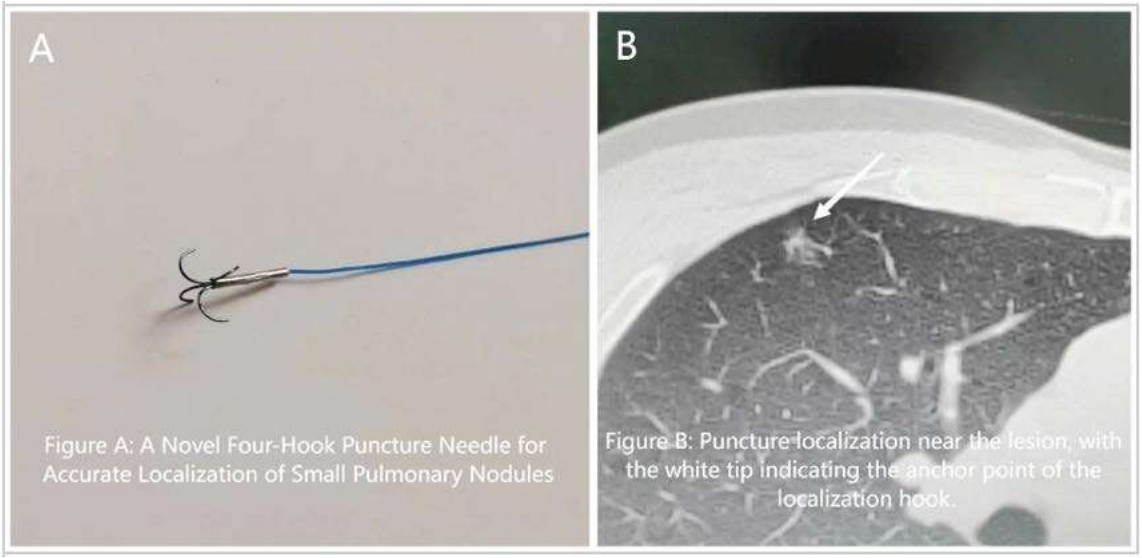

Figure A: A Novel Four-Hook Puncture Needle for Accurate Localization of Small Pulmonary Nodules

Figure B: Puncture localization near the lesion, with the white tip indicating the anchor point of the localization hook.

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EP.07B.01 Definitions of Local Control after Stereotactic Body Radiation Therapy for Early-Stage Lung Cancer Reported in the Literature

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Introduction: Definitions of local control after stereotactic body radiation therapy (SBRT) are not standardized and include determinations of relapse in the primary tumor, same lobe, ipsilateral lung, and/or regional nodes. Furthermore, radiologic and metabolic features used to distinguish primary tumor control from relapse are generally not validated and may contribute to varying determinations. We set out to systematically review criteria defining local control reported in peer-reviewed literature and evaluate these trends over time.

Methods: The Preferred Reporting Items for Systematic Reviews and Meta-Analyses guideline was used to identify, appraise, and synthesize articles published in PubMed reporting local control rates after lung SBRT from 2006-2023. Reviews, reports lacking disease-control determinations, and abstracts not written in English were excluded. Remaining articles were eligible for analysis and individually reviewed by three authors to categorize reported local control definitions by anatomic sites and criteria used to distinguish local control from relapse.

Results: Out of 155 peer-reviewed articles, 114 were eligible for analysis. Local control determinations were termed "local control," "local failure," "local recurrence," and "primary tumor control (or failure)" in 39%, 32%, 24%, and 4% of studies, respectively. Anatomic sites evaluated for local control relied upon primary tumor site, same lobe, ipsilateral lung, and regional nodes in 68%, 11%, 4%, and 2%, respectively; 15% did not specify an anatomic location in their local control definition. There was no change in the percentage of studies specifying local control as "primary tumor control" over time (p=0.45). Local control determinations were reported in 94% of studies and relied on 12 different criteria including specific imaging modalities (computed tomography [CT] or positron emission tomography [PET]), minimum growth (serial growth, Response Evaluation Criteria in Solid Tumors [RECIST], or 20-50% size increase), period of growth (2-36 months or serial growth), or histopathological confirmation in 28%, 31%, 18%, and 1%, respectively.

Conclusions: There is substantial variability in definitions used to report local control after lung SBRT in peer-reviewed literature. Many studies include same lobe, ipsilateral lung, and regional nodes in their assessments of local control, with some not specifying what anatomic sites of relapse were considered in addition to primary tumor control. We identified multiple studies that omitted any specific parameters for local control determinations. There is a need to standardize post-SBRT local control definitions for greater accuracy in reporting primary tumor control rates and to facilitate more robust comparisons between studies.

Keywords: stereotactic ablative radiotherapy, stereotactic body radiation therapy, response assessment

EP.07B EARLY-STAGE NON-SMALL CELL LUNG CANCER - RADIOTHERAPY OUTCOMES
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EP.07B.02 Comparative Outcomes of Surgery and SBRT for Stage I Lung Cancer in Koreans: A Propensity Matched Multidisciplinary Cohort Study

E. Lee[1], Y.J. Suh[2], J.W. Park[2], S.H. Kwak[1], H.E. Kim[2], C.Y. Lee[2], J. Cho[2], E.Y. Kim[2], [1]Yonsei University College of Medicine, Yongin Severance Hospital, Yongin/KR,[2]Yonsei University College of Medicine, Seoul/KR

Introduction: With increasing life expectancy and active chest CT surveillance in South Korea, there has been a rise in early-stage lung cancer cases among the elderly and those with comorbidities. Stereotactic Body Radiotherapy (SBRT) is emerging as a preferred treatment for patients unable to undergo surgery for stage I lung cancer. However, there is limited research comparing SBRT and surgery outcomes for stage I cancer. This study aims to identify criteria indicating that the outcomes of SBRT are not inferior to standard surgery for early-stage lung cancer.

Methods: Between 2012 and 2021, patients with stage I lung cancer who underwent SBRT and those who received surgical treatment at Severance Hospital, Yonsei University, were retrospectively analyzed. Tumor size, location, radiologic characteristics, and pleural attachment on computed tomography (CT) images were assessed using an AI-based CAD software (CT AI-CAD) (AVIEW LCS, Coreline Soft, Seoul, South Korea). Patient demographics and tumor characteristics were matched using Propensity Score Matching to evaluate recurrence outcomes in each group.

Results: This study compared a total of 2,055 surgical patients and 219 SBRT patients for stage I lung cancer, revealing notable demographic and clinical differences. The surgery group was significantly younger than those receiving SBRT (63.5 vs. 77.7 years, $p<0.001$), with a higher proportion of females (54.3% vs. 29.2%, $p<0.001$). Adenocarcinoma was more prevalent among surgical patients (90.6% vs. 66.6%), while SBRT patients had a higher frequency of ever-smokers (60.7% vs. 36.4%, $p<0.001$). Surgery patients also exhibited more sub-solid nodules compared to SBRT-treated individuals (65.5% vs. 44.3%, $p<0.001$). Despite both groups predominantly consisting of stage IA diagnoses and no differences in average tumor size, the SBRT group experienced a higher overall recurrence rate (12.3% vs. 7% in surgery, $p=0.02$). However, when comparing matched groups of 150 patients from each treatment, adjusted for age, sex, smoking status, and tumor characteristics using chest CT AI software, the recurrence rates showed no significant difference (SBRT 11.4% vs. surgery 10.7%, log-rank $p=0.9$).

Conclusions: After adjusting for key patient and tumor characteristics, this study demonstrates that SBRT is not inferior to surgery in terms of recurrence rates among stage I lung cancer patients. While current practice largely assesses treatment modality based on patient age, pulmonary function, and comorbidities, incorporating tumor characteristics itself into predicting recurrence risk could facilitate personalized recommendations for safe and effective treatments in stage I lung cancer patients.

Keywords: Stage I lung cancer, SBRT, Surgery

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EP.07B.03 Analysis of 30- And 90-day Mortality after Lung SBRT as an Indicator for Its Appropriateness

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Introduction: Surgeons analyze 30- and 90-day mortality rates after lung cancer resections as a quality metric. Although lung stereotactic body radiotherapy [SBRT] has minimal treatment-related toxicity, inoperable early-stage lung cancer [ES-LC] patients [pts] being considered for SBRT may have active competing co-morbidities at the time of decision making regarding SBRT. We therefore analyzed 30- and 90-day causes of death (CODs) after SBRT as a quality measure of appropriateness.

Methods: We surveyed our institutional review board-approved prospective lung SBRT data registry from 2003 to 2023 for medically inoperable ES-LC pts to study their CODs within 30 and 90 days following SBRT. Pts refusing surgical resection or deemed operable, with oligometastases, or treated for salvage were excluded. Selected pre-treatment pt and tumor factors were analyzed using logistic regression analysis to identify factors associated with 90-day mortality.

Results: For the 20-year interval, 1871 pts met study criteria, with 29.3% alive at analysis. Median follow up was 27.7 months. Patient characteristics included: female (52.5%), median age 74.1 years, median KPS 80. Among causes for pre-treatment inoperability, pulmonary [PULM] and cardiovascular [CV] disorders made up 57.5% and 14.5% of the total, respectively. Tumor characteristics included: median size 2.1 cm, median PET SUVmax 7.6, 67.5% with biopsy proven cancer, 26.0% central. The two most common SBRT schedules employed were 50 Gy/5 fractions (39.0%) and 34 Gy/1 fraction (27.5%). Fifty-seven (3.0%) pts died within 90 days of lung SBRT, of which 10 (0.5%) were within 30 days. No deaths were attributable to SBRT. When CODs were grouped by categories, CODs for 30-day and 90-day cohorts (in %) were CV (30.0; 38.6), PULM (10.0; 14.0), LUNG-CA (10.0; 12.2), infectious (20.0; 10.5) and other (30.0; 24.6), respectively. On multivariate analysis, male gender (p= 0.0399), lower body-mass index (p=0.0114), higher Charlson score (0.0008), and KPS <80 (p<0.0001) were associated with an increased risk of < 90-day mortality.

Conclusions: Early deaths after lung SBRT were rare. Although pre-treatment CV co-morbidities were the reason for inoperability in a minority of patients, the present analysis suggests CV diagnoses are the commonest causes of death within 90 days of lung SBRT. Notwithstanding the efficacy and long-term safety of lung SBRT with respect to cancer outcomes, these results suggest attention should be paid to competing CV risk factors when assessing pts for lung SBRT appropriateness.

Keywords: inoperable early stage lung cancer, SBRT, early causes of death

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EP.07B.04 Two-Stage Bilateral Video-Assisted Thoracic Surgery Combined with Gefitinib for Bilateral Primary Lung Cancer: A Case Report

B. liang, Q. Cai, T. Zhang, M. Shen, M. Kuang, The Fifth Affiliated Hospital, Southern Medical University, Guangzhou/CN

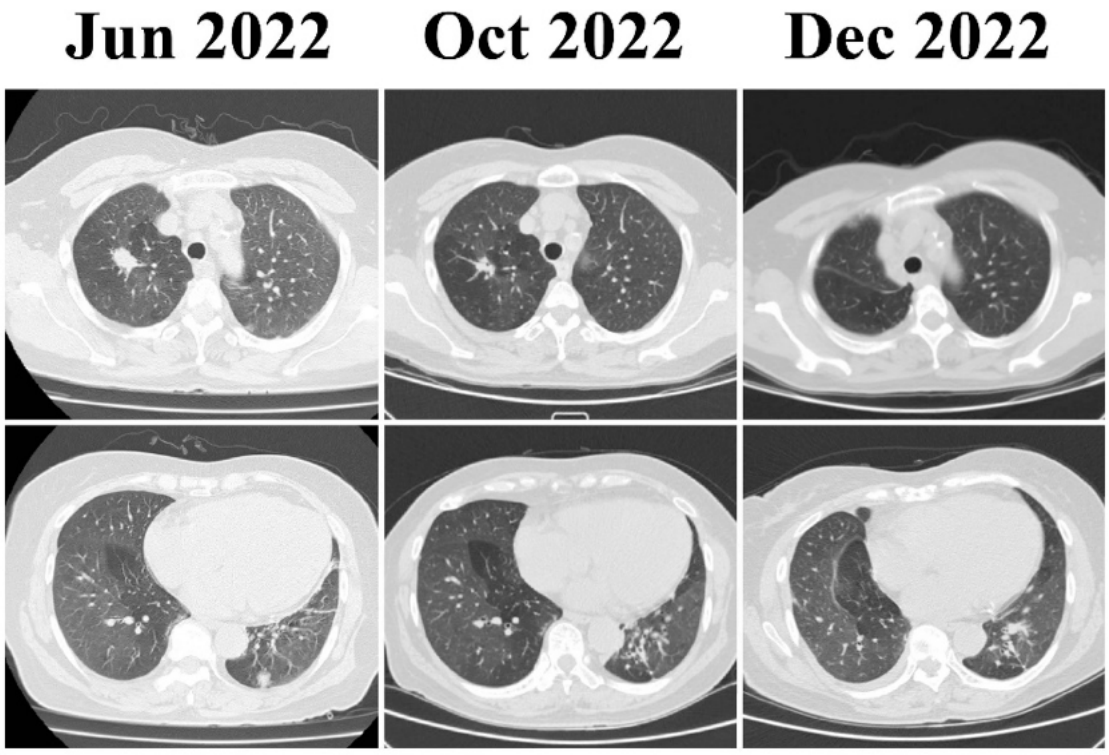
Introduction: Current guidelines advocate surgical intervention for early-stage bilateral primary lung cancer. This report presents a case located in the right upper and left lower lobes, addressed through a two-stage surgical approach after extensive multidisciplinary discussions. Adjuvant gefitinib therapy was provided during interim period between the surgeries, continuing after the second surgery.

Methods: Case report of two-stage bilateral video-assisted thoracoscopic surgery combined with gefitinib therapy in a patient with bilateral primary lung adenocarcinoma.

Results: A 70-year-old female with hypertension and coronary artery disease history experienced chest discomfort in June 2022. Chest CT identified a 3.0 cm lobulated mass in the right upper lobe and a 1.8 cm solid nodule in the left lower lobe, with no significant lymph node enlargement. Considering the patient's compromised cardiac function, a two-stage surgical approach was decided upon after comprehensive multidisciplinary discussion. The patient underwent video-assisted thoracoscopic surgery (VATS) for wedge resection of the left lower lobe in June 2022. Pathology reported adenocarcinoma, predominantly lepidic growth. High-throughput sequencing revealed EGFR Exon 21 L858R substitution mutation. Oral gefitinib 250 mg daily was initiated in July 2022. Three months post-treatment, an October 2022 chest CT revealed the right upper lobe lesion shrank to 1.8 cm. Following further multidisciplinary discussion, the patient underwent VATS for the resection of the right upper lobe and mediastinal lymph node dissection. Pathology confirmed adenocarcinoma with a predominantly lepidic growth pattern and interstitial fibrosis, and no evidence of lymph node metastasis. High-throughput sequencing revealed EGFR Exon 21 L858R substitution mutation and ALK Exon 24 R1231Q point mutation. Postoperatively, the original gefitinib regimen (250 mg daily) was maintained post-surgery, with no recurrence or metastasis observed at the 17-month follow-up.

Conclusions: In our case, adenocarcinomas were identified in distinct lobes of both lungs, posing a unique management challenge. Notably, the largest lesion in the right upper lobe significantly reduced in size after preoperative EGFR-TKI therapy, introducing uncertainty in accurate T staging. Through multidisciplinary discussions, we decided to base the patient's staging on the preoperative size of this lesion, designating it as T1N0M0, stage Ia, in line with guidelines that suggested no need for further adjuvant therapy post-surgery. However, given the positive response to gefitinib post-initial surgery, the team agreed to continue this treatment, anticipating further benefits for the patient. For oncologists managing similar rare cases, adopting a multidisciplinary discussion to determine the optimal treatment plan is recommended

Keywords: Bilateral Primary Lung Cancer, Two-Stage Bilateral Surger, Video-Assisted Thoracoscopic Surgery (VATS)



EP.07B EARLY-STAGE NON-SMALL CELL LUNG CANCER - RADIOTHERAPY OUTCOMES
SATURDAY, SEPTEMBER 7, 2024 - 11:58 - 11:59

EP.07B.05 Comparison of Image-Guided Thermal Ablation or Stereotactic Body Radiation Therapy for Primary Non-Small Cell Lung Cancer

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Introduction: Image-guided thermal ablation (IGTA) and stereotactic body radiation therapy (SBRT) are increasingly utilized for primary non-small cell lung cancer (NSCLC). Evidence comparing their relative efficacy and safety is limited, making treatment recommendations challenging when both modalities are options.

Methods: This was an IRB-approved, retrospective unmatched cohort study of patients with primary NSCLC treated at a tertiary academic medical center with either IGTA or SBRT for tumors measuring ≤30 mm in diameter. Treatment-site progression was assessed via clinical and radiographic reports. Acute (≤3 months from treatment) and late (>3 months from treatment) treatment-related adverse events (TRAEs) were identified from clinical notes and graded using the Common Terminology Criteria for Adverse Events, version 5. Rates of treatment-site progression and TRAEs following IGTA and SBRT were compared using Fisher's exact test.

Results: At the time of this analysis, 162 tumors were identified that were treated with IGTA (n=73, January 2011-December 2016) or SBRT (n=89, January 2009-December 2021). Patient and treatment characteristics are summarized in Table 1. Median follow-up time to last available imaging was 44.8 months for IGTA and 39.1 months for SBRT (p=0.32). Among the 134 tumors with follow-up time >12 months, treatment-site progression rates after IGTA and SBRT were 15.1% (8/53) and 0% (0/81) (p<0.001), respectively. For IGTA, treatment-site progression occurred in 0% (0/8), 25.8% (8/31), and 0% (0/14) of tumors ≤10 mm, >10-20 mm, and >20-30 mm, respectively; stratified by location, treatment-site progression occurred in 3.7% (1/27), 25.0% (4/16), and 30% (3/10) of tumors ≤2 cm, >2-4 cm, and >4 cm from the periphery, respectively. Grade ≥3 TRAE rates after IGTA and SBRT were 19.2% (14/73) and 3.4% (3/89) (p=0.001), respectively. Grade ≥3 TRAEs for IGTA included pneumothorax (n=11), pleural effusion (n=1), hemothorax (n=1), and acute respiratory failure leading to death (n=2); grade ≥3 TRAEs for SBRT included pneumonitis (n=2) and pneumothorax (n=1). Acute TRAE rates after IGTA and SBRT were 15.1% vs 0% for grade 3 (p<0.001), 2.7% vs 0% for grade 4 (p=0.20), and 1.4% vs 0% for grade 5 (p=0.45), respectively. Late TRAE rates after IGTA and SBRT were 0% vs 1.1% for grade 3 (p>0.99), 0% vs 2.3% for grade 4 (p=0.52), and 1.7% vs 0% for grade 5 (p=0.41), respectively.

Conclusions: These data represent over 13 years of experience delivering IGTA and SBRT for primary NSCLC. Our findings demonstrate significant differences in efficacy and TRAEs that can guide future research and clinical management decisions.

Table1: Patient and Treatment Characteristics. *Systemic therapy given 1 month prior to IGTA or SBRT

	IGTA (n=73)	SBRT (n=89)	p-value
Age Median | Interquartile Range	72 years | 66-78 years	77 years | 71-81 years	**<0.001**
Tumor Size Median | Interquartile Range	17.0 mm | 12.0-21.5 mm	14.0 mm | 11.5-19.0 mm	0.051
Tumor Size Category ≤10 mm | >10-20 mm | >20-30 mm	10 (13.7%) | 42 (57.5%) | 21 (28.8%)	17 (19.1%) | 59 (66.3%) | 13 (14.6%)	0.12
Prior Lung Cancer	44 (60.3%)	34 (38.2%)	**0.007**
History of COPD	30 (41.1%)	41 (46.1%)	0.63
Smoking History	60 (82.2%)	77 (86.5%)	0.51
Systemic Therapy*	8 (11.0%)	2 (2.2%)	**0.044**
IGTA Modality Radiofrequency Ablation | Microwave Ablation | Cryoablation	7 (9.6%) | 34 (46.6%) | 32 (43.8%)	-	-
SBRT Prescription 54 Gy in 3 Fx | 50 Gy in 4 Fx | 50 Gy in 5 Fx | 65 Gy in 10 Fx	-	74 (83.1%) | 8 (9.0%) | 6 (6.7%) | 1 (1.1%)	-
Follow-up Time Median | Interquartile range	44.8 mo. | 9.5-73.8 mo.	39.1 mo. | 26.8-66.6 mo.	0.32

Keywords: Non-small cell lung cancer, Image-guided thermal ablation, Stereotactic body radiation therapy

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EP.07B.06 Transplant Patients with Medically Inoperable Early-Stage Lung Cancer Have Worse Outcomes When Treated with SBRT

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Introduction: Lung stereotactic body radiotherapy [SBRT] is the standard of care for curative management of medically inoperable early-stage lung cancer [ES-LC] due to its excellent local control and minimal treatment-related toxicity. Patients (pts) with organ transplants are chronically immunosuppressed, with increased risk of developing cancer. We wished to characterize outcomes for transplant pts with inoperable ES-LC treated with SBRT.

Methods: We surveyed our institutional review board-approved prospective lung SBRT data registry from 2003 to 2023 for medically inoperable ES-LC solid organ transplant pts. Patterns of failure were assessed, as well as overall survival (OS) and disease-free survival (DFS). Univariable prognostic factors for OS and PFS were identified with Cox proportional hazards regression.

Results: For the 20-year interval, 28 of 1976 definitive pts (1.4%) met study criteria, with 17.9% alive at analysis. Median follow up was 12.4 months. Pt characteristics included: male (52.9%), median pack-years smoking 34; 7.1% smoking at SBRT; median age 70.0 years, median KPS 80. Organs transplanted were lung (57.1%), liver (21.4%), heart (21.4%). Median time from transplant to SBRT was 5.7 years. Tumor characteristics included: median size 2.4 cm, median PET SUVmax 7.8, 85.7% with biopsy proven cancer. The median SBRT schedule was 50 Gy/5 fractions (32.1%). Toxicity was reported in 9 (32.1%) pts: grade 1/2 in 8 pts (28.6%) and grade 5 (pneumonitis) in 1 pt (3.5%), with no differences in rates by organ transplanted. Failure patterns were: local 21.4%, lobar 7.1%, nodal 10.7% and distant 32.1%. First site of failure was distant [alone or in combination] in 50.1% pts. Median DFS and OS were 17.1 and 14.5 months, respectively. Metastatic cancer was the cause of death in 25% patients. Univariate analysis revealed increasing pack-years smoking was associated with increased disease failure [p=0.0016], but not with any other patient, tumor or transplant factors. Multivariate analysis revealed OS significantly associated with KPS [p=0.0075] and tumor size [p=0.0181].

Conclusions: Compared to historical SBRT results for ES-LC, transplanted pts had higher local failure, decreased cancer control and poorer overall survival. To explain these findings, we hypothesize that transplant-associated immunosuppression promotes understaging at diagnosis, enhanced metastatic progression despite treatment and a tumor biology resistant to SBRT.

Keywords: inoperable early stage lung cancer, SBRT outcomes, organ transplants

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EP.07B.07 The Impact of Radiation Therapy on Lung Cancer Patients with Interstitial Lung Disease

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Introduction: The purpose of this study was to evaluate the impact of radiation therapy (RT) on overall survival and pulmonary toxicity in lung cancer patients with interstitial lung disease (ILD).

Methods: We conducted an-IRB approved retrospective study of 38 consecutive patients with underlying ILD that were treated between 2001-2022 with RT for primary lung cancer. Because differentiating radiation pneumonitis from an ILD exacerbation is difficult, pulmonary complications were defined as new or increased use of steroids or supplementary oxygen. Survival rates were determined following completion of treatment by the Kaplan Meier method.

Results: Patients were predominantly male (61%) and were a median age of 73 years (range, 58-89 years). The KPS ranged from 50 to 90 with a median of 80. 34 (89%) patients had a smoking history (median pack years: 50). 19 (50%) patients had COPD in addition to ILD. The median FEV1 was 85% and DLCO was 43%. Prior to RT, 10 (26%) patients were on baseline prednisone and 17 (45%) were on oxygen (59% on 1-2L, 18% on 3-5L, 23% unknown). 19 patients had squamous cell carcinoma, 17 had adenocarcinoma, and 2 had SCLC. Patients were staged as I (n=17), II (n=2), III (n=16) and IV (n=3). 10 patients were treated with proton therapy. 12 patients were treated with SBRT (3-5 fractions to 24-50 Gy), 6 patients with definitive hypo-fractionated RT (60 Gy in 8 or 15 fractions), 3 patients with palliative RT (30 Gy in 10 fractions) and 17 patients with conventional fractionation to 54-80 Gy. The median follow-up time for survivors was 16.5 months (range: 8-42 months). The median overall survival from the end of RT was 12.1 months for all patients; 12.9 months for stage I-II patients and 8.4 months for stage III-IV patients. 71% patients required steroids or an increase in steroids after RT. 57% of patients developed a new requirement for oxygen or an increase in oxygen after RT.

Conclusions: ILD patients are at high risk for requiring an increased use of steroids and oxygen post-RT.

Keywords: ILD, radiation, fibrosis

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EP.07B.08 The Treatment Outcome of SBRT and Sublobar Resection for Vulnerable Elderly Patients with Stage IA Non-Small Cell Lung Cancer

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Introduction: In Japan, about 60% of patients who underwent resection for lung cancer were aged 70 years or older and 14% of patients were octogenarian. Lobectomy has long been the standard radical treatment for lung cancer. However, sublobar resection has become one of the standard treatments based on the results of recent two randomized controlled trials. In practice, we often face cases where we cannot perform standard resection for vulnerable elderly patients. Sublobar resection or stereotactic body radiotherapy (SBRT) are considered for these patients. There are no randomized controlled trials comparing sublobar resection and SBRT, so that the treatment for these patients remains controversial, especially for those with solid-predominant tumors. We aimed to compare the survival and incidence of complications of SBRT with those of sublobar resection for vulnerable elderly patients with clinical stage IA non-small cell lung cancer (NSCLC).

Methods: Using the radiology database and the thoracic surgical database of the Shizuoka Cancer Center, patients ≥ 75 years of age with performance status (PS) 0-2 who underwent SBRT or sublobar resection with curative intent for solid-predominant clinical stage IA NSCLC with ≤3cm in size from January 2010 to December 2017 were included in this study. All surgical patients were judged as ineligible for lobectomy with mediastinal lymph node dissection by surgeon in charge for reasons such as poor pulmonary function, comorbidities, and advanced age. Patients underwent sublobar resection without mediastinal lymph node dissection. A total of 119 patients were investigated in this study. To reduce selection bias, a propensity score matching method was used. The propensity score model was estimated using a logistic regression model that adjusted for preoperatively detectable patient characteristics, including age, sex, PS, smoking status, preoperative lung function (using vital capacity), comorbidities, solid tumor size on thin-slice CT (TSCT) and tumor appearance (pure-solid/part-solid) on TSCT. We compared the SBRT group to the surgery group on complications within 90 days after treatment and survival outcome.

Results: Of the 119 patients included, 86 underwent SBRT and 33 underwent sublobar resection. The median follow-up periods for surgery and SBRT were 5.1 and 4.2 years, respectively. The SBRT group included significantly older patients (median: 82 vs 79) and larger tumors (median: 18 vs 16 mm) than the surgery group. After matching, we analyzed 24 patients in each group. The incidence of ≥Grade 2 complications was not significantly different between the two groups (12.5% and 29.1%, p=0.286). Overall survival rate at 3 years was 77.1% in the SBRT group compared with 75% in the surgery group (p=0.343). Recurrence-free survival rate at 3 years was 69.4% in the SBRT group and 66.7% in the surgery group (p=0.336). There were no significant differences in survival between the two groups.

Conclusions: Our results suggest that SBRT might be relatively safer compared to surgery and post-treatment survival outcomes of SBRT may be comparable to those of surgery for vulnerable elderly patients. SBRT may be an effective treatment option for these patients. Randomized controlled trials are required to confirm these results.

Keywords: SBRT, sublobar resection, NSCLC

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EP.07B.09 Lymph Node Evaluation for Stage Cia Non-Small Cell Lung Cancer: Findings from a Single Institution

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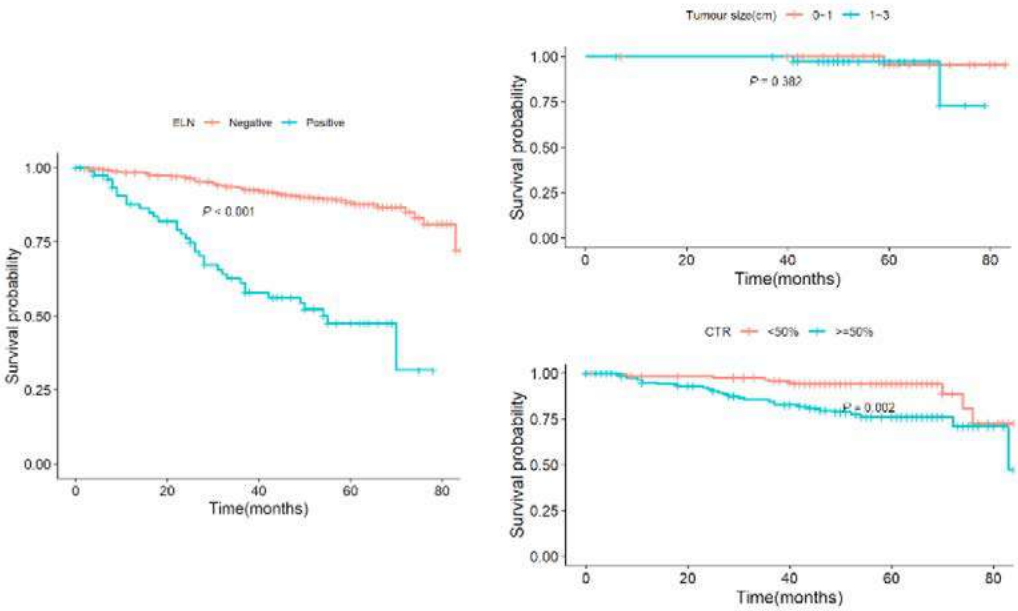
Introduction: Uncertainties persist regarding lymph node dissection protocols in individuals diagnosed with clinical stage IA non-small cell lung cancer.

Methods: We conducted a retrospective study on patients diagnosed with clinical stage IA non-small cell lung cancer between August 2014 and November 2018. Categorical variables were evaluated using the Chi-square test, while continuous variables were assessed using the T-test. Cox regression analysis was employed to investigate the relationship between lymph node characteristics and recurrence-free survival (RFS), accounting for potential confounding factors. Subgroup analysis was performed based on tumor size and the proportion of real tumor components. All statistical analyses were performed using R version 4.3.0.

Results: A total of 556 patients were included in the study, with a median age of 59 years (range: 26-83 years). Among them, 478 (86.0%) had adenocarcinoma, 43 (7.7%) had squamous cell carcinoma, and 245 (44.1%) were male. The median follow-up time for the entire study population was 57 months. ELN-positive patients exhibited a higher number of examined lymph nodes (ELNs) (p=0.001) and shorter disease-free survival (DFS) (p<0.001). Elevated consolidation tumor ratio (CTR) was significantly associated with reduced DFS in patients with comparable numbers and stations of ELNs. Lymph node dissection did not yield significant benefits for patients with a solid component comprising less than 50% of the tumor. However, in patients with a solid component exceeding 50%, there may be potential benefits when the number of ELNs ranges from 8 to 23 (HR < 1).

Conclusions: Sufficient lymph node assessment might not be necessary in stage cIA1 NSCLC, whilt it was required in stage cIA2-3 diseases. Proper lymph node examination might help to detect potential lymphatic metastasis in the malignancy with ≥1 in size and more solid componants, and prospective studies are required to indicate the compatible lymph node examination for survival and adverse events.

Keywords: examined lymph nodes, recurrence-free survival



EP.07C EARLY-STAGE NON-SMALL CELL LUNG CANCER - PERIOPERATIVE THERAPY
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EP.07C.01 Neoadjuvantimmunochemotherapy Versus Chemotherapy for Elderly Patients with IB-IIIB Non-Small-Cell Lung Cancerin Real-World Practice

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Introduction: The efficacy and safety of immunochemotherapy in elderly patients (≥ 65 years) have not been clarified. Therefore, we compare the safety and efficacy of neoadjuvant immunochemotherapy and chemotherapy in elderly patients (≥ 65 years) with stage IB-IIIB NSCLC.

Methods: This retrospective study consecutively included all IB-IIIB NSCLC elderly patients (≥ 65 years) who received 2-4 cycles preoperative immunochemotherapy or chemotherapy at the Department of Thoracic Surgery, the First Affiliated Hospital, Zhejiang University School of Medicine from 2016 to 2022. The primary endpoints were disease-free survival (DFS) and overall survival (OS). The secondary endpoints of this study were objective response rate (ORR), adverse events (AEs) and pathological response.

Results: A total of 140 patients were included in our study and were divided into two groups according to neoadjuvant treatment regimen: chemotherapy (n=47) and immunochemotherapy (n=93). The ORR in the immunochemotherapy group was significantly higher than in the chemotherapy group (73.1% vs 29.8%, P<0.001). The incidence of grade 3-4 AEs in the immunochemotherapy group was 19.4% and 8.5% in thechemotherapy (P=0.156). The rate of major pathologic response (MPR) in the immunochemotherapy group was significantly higher than in the chemotherapy group (64.4% vs 25.8%, P<0.001). The rate of pathologic complete response (pCR) in immunochemotherapy group was 32.2%, with 16.1% in the chemotherapy group (P=0.101). The median DFS in the chemotherapy group was 14.1 months (95% CI, 3.7 to 24.5) and not reached in the immunochemotherapy group (hazard ratio [HR], 0.243; 95% CI, 0.115 to 0.634; P<0.001). The median OS of the immunochemotherapy group was not achieved (HR,0.382; 95% CI, 0.162 to 0.896; P=0.027), with the chemotherapy group 33.9 months (95% CI, 25.4 to 42.4).

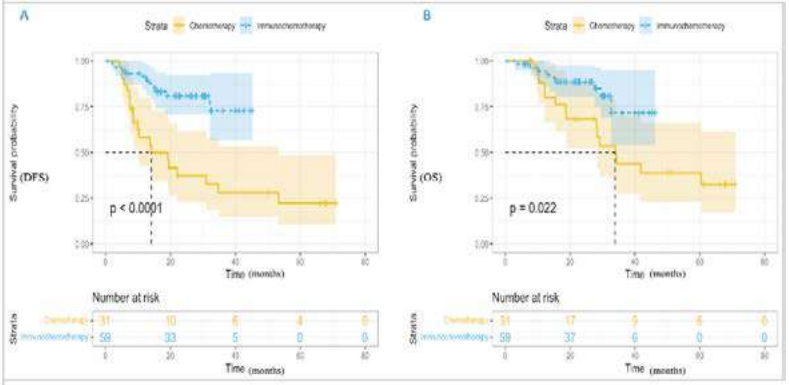
Conclusions: Neoadjuvant immunochemotherapy can produce longer survival, higher ORR and MPR rate than chemotherapy alone in elderly patients (≥ 65 years) with IB-IIIB NSCLC without increasing AEs.

Keywords: neoadjuvant treatment, non-small-cell lung cancer (NSCLC), elderly patients (≥ 65 years)

Table 2. Grade 3-4 AEs of neoadjuvant therapy in the ITT population (n = 140)

Event	Total, n=140	Chemotherapy, n=47	Immunochemotherapy, n=93	*P*-value
Any AEs	22 (15.7)	4 (8.5)	18 (19.4)	0.156
Hematologic				
Leukopenia	5 (3.6)	1 (2.1)	4 (4.3)	0.863
Agranulocytosis	3 (2.1)	0 (0.0)	3 (3.2)	0.551
Anemia	9 (6.4)	1 (2.1)	8 (8.6)	0.267
Thrombocytopenia	3 (2.1)	0 (0.0)	3 (3.2)	0.551
Gastrointestinal				
Nausea	0 (0.0)	0 (0.0)	0 (0.0)	NA
Emesis	0 (0.0)	0 (0.0)	0 (0.0)	NA
Diarrhea	1 (0.7)	0 (0.0)	1 (1.1)	1.000
Constipation	3 (2.1)	1 (2.1)	2 (2.2)	1.000
Hepatic injury	4 (2.9)	1 (2.1)	3 (3.2)	1.000
Renal injury	0 (0.0)	0 (0.0)	0 (0.0)	NA
Skin reaction	3 (2.1)	1 (2.1)	4 (4.3)	0.863
Hypothyroidism	0 (0.0)	0 (0.0)	0 (0.0)	NA
Coagulation disorders	0 (0.0)	0 (0.0)	0 (0.0)	NA
Esophageal fistula	0 (0.0)	0 (0.0)	0 (0.0)	NA

Abbreviations: ITT, intention-to-treat; AEs, adverse events.



EP.07C EARLY-STAGE NON-SMALL CELL LUNG CANCER - PERIOPERATIVE THERAPY
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EP.07C.02 Perioperative Cadonilimab and Chemotherapy in Stage II-IIIA Non-Small-Cell Lung Cancer: Preliminary Results from a Phase II Study

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Introduction: Neoadjuvant and adjuvant immunotherapy have improved clinical outcomes for patients with resectable non-small cell lung cancer (NSCLC). However, the optimal perioperative regimen remains unknown. Bispecific antibodies, which target immunomodulatory checkpoints, have demonstrated encouraging antitumor activity and safety profiles in advanced NSCLC. Cadonilimab is a bispecific antibody that simultaneously targets PD-1 and CTLA-4. We conduct a prospective, single-arm, phase 2 study to evaluate perioperative cadonilimab in patients with early-stage NSCLC.

Methods: Participants with resectable stage II to IIIA NSCLC received platinum-based chemotherapy (nanoparticle albumin-bound paclitaxel 260mg/m2, carboplatin AUC 5) plus cadonilimab (10 mg/kg) administered intravenously every 3 weeks for 3 cycles before surgery, followed by adjuvant cadonilimab intravenously every 3 weeks for 9 cycles. The primary endpoint was pathological complete response (pCR). Key secondary endpoints included major pathological response (MPR), objective response rate (ORR), event-free survival (EFS) and safety. Simon's two-stage design was applied, with 20 patients recruited in the first stage and 18 patients to be continued in the second stage.

Results: The first eight patients who have completed neoadjuvant treatment were included in this analysis (data as of 15 March 2024). Six patients underwent resection and all achieved R0 resection. Four patients in the intention-to-treat population achieved a MPR, including two patients who achieved a pCR. No patients had radiographic evidence of disease progression pre-surgery and seven patients achieved objective response. A surgical complication of grade 4 ketoacidosis was observed in one patient. No unexpected treatment-related toxic effects were identified. Treatment-related adverse events were predominantly of grade 1 or 2. Treatment-related grade 3 adverse events included one patient with hypothyroidism and one patient with third-degree atrioventricular block that resulted in surgical cancellation. No treatment-related grade 4 adverse events or deaths occurred.

Conclusions: This preliminary analysis indicates that incorporating cadonilimab into neoadjuvant chemotherapy led to a promising pathological response for patients with resectable stage II to IIIA NSCLC, alongside a well-tolerated safety profile. Enrollment is ongoing, and extended follow-up is required to assess event-free survival accurately. (ClinicalTrials.gov number: NCT05377658.)

Keywords: NSCLC, perioperative immunotherapy, bispecific antibody

EP.07C EARLY-STAGE NON-SMALL CELL LUNG CANCER - PERIOPERATIVE THERAPY
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EP.07C.03 Oncological Outcomes after Lobe-Specific Mediastinal Lymph Node Dissection in Thoracoscopic Right Upper Lobectomy for Clinical N0 NSCLC

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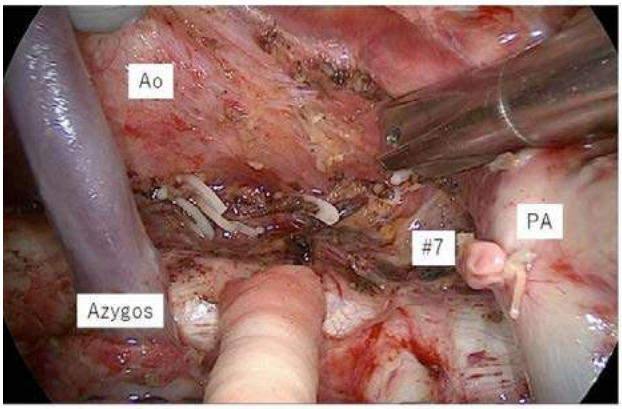
Introduction: Mediastinal lymph node dissection (MLND) during lung cancer treatment has significance for local control. In particular, station 4R LND in right upper lobectomy (RUL) is the most significant because it is closest to the tumor.

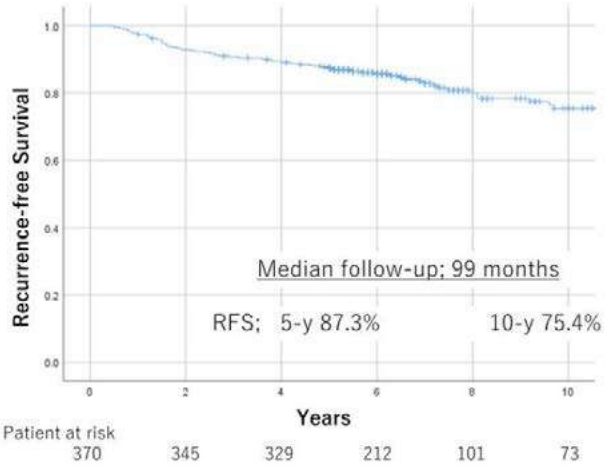
Methods: Between 2008 and 2018, 370 patients underwent thoracoscopic RUL with lobe-specific MLND for clinical N0 non-small cell lung cancer (NSCLC). Thoracoscopic lobectomy was performed by 3 or 4 port VATS. Regarding the lobe-specific MLND in RUL, subcarinal LND was omitted even in patient with hilar and upper zone mediastinal lymph node metastasis. To perform a precise dissection of lymph nodes (LNs) at station 4R, the pericardium is first exposed on the cranial side of the azygos vein. Then the pericardium is dissected towards the right main trunk of the pulmonary artery without breaking the station 4R LNs (RPE; retrograde pericardial exposure). We evaluated their oncological outcomes.

Results: The study patients comprised 176 men and 194 women (mean age, 65 years; range, 16-79 years). Clinical factor was T1mi in 44, T1a in 81, T1b in 155, T1c in 60, T2a in 21, T2b in 5, and T3 in 4. All cases were clinical N0 and performed complete surgical resection. The histological analysis showed adenocarcinoma in 337 (%), squamous cell carcinoma in 18, large cell neuroendocrine tumor in 7, adenosquamous cell carcinoma in 5, Pleomorphic carcinoma in 2, and large cell carcinoma in 1. Pathologic factor was Tis in 20, T1mi in 44, T1a in 93, T1b in 121, T1c in 36, T2a in 39, T2b in 4, T3 in 12, and T4 in 1. Pathologic stage was 0 in 20, IA1 in 135, IA2 in 109, IA3 in 32, IB in 32, IIA in 3, IIB in 19, IIIA in 16, and IIIB in 4. Nodal up-staging was seen in 30 patients (8.1%). Adjuvant therapy was performed in 32 (43%) out of 74 patients, including stage IB, II, and III. Median follow-up period for all 370 patients was 99 months. The actuarial 5-year and 10-year overall survival rates were 91.3% and 79.2%, respectively. The 5-year and 10-year recurrence-free survival rates were 87.3% and 75.4%, respectively. Thirty-five (9.5%) patients experienced recurrence during follow-up, including locoregional recurrence in 21 patients. Seven of 21 patients had recurrence in lymph node. Only one case had recurrence in the dissected area at the station 4R.

Conclusions: Precise dissection prevented recurrence at the pulmonary hilum and the dissected mediastinal zone.

Keywords: Thoracoscopic surgery, Lobe-specific mediastinal lymph node dissection, Oncological outcome





EP.07C EARLY-STAGE NON-SMALL CELL LUNG CANCER - PERIOPERATIVE THERAPY
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EP.07C.04 Adjuvant Aumolertinib in Resected Stage I EGFR-Mutated NSCLC: Prospectively Evaluating Efficacy in Residual GGN Lesions

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Introduction: The efficacy of postoperative EGFR-TKIs in treating unresected residual ground glass nodules (GGN) remains controversial, especially in pts with synchronous multiple primary lung cancer (sMPLC) who are at risk of disease progression.This study is a prospective, single-center, phase II clinical trial designed to assess the efficacy and safety of the third-generation EGFR TKI aumolertinib as adjuvant therapy. The main focus is to evaluate its performance in treating unresected residual GGN lesions. (ChiCTR2200066768).

Methods: Patients(Pts) with stage I EGFR-mutated NSCLC should have one or more residual GGN (<3 cm) whose malignancy were confirmed by both a radiologist and a thoracic surgeon after target lesions surgery. They received aumolertinib of 110 mg for 2 years. The primary endpoint is response rate of GGN lesions, while secondary endpoints include objective response rate, 3-year disease free survival, safety and tolerability.

Results: From June 2021 to July 2023, a total of 31 pts with EGFR positive mutation (19Del or L858R) were enrolled, and 45.2% (14/31) of them had co-mutations. Most were invasive adenocarcinoma (93.5%,29/31). At the data cutoff, all pts were alive with no tumor recurrence, 23(74.2%) pts had been followed up for over 1 year, 13 (41.9%) pts were followed up for at least 18 months. The 1-year DFS rate is 100%. In terms of lesions, the response rate (RR) was 69.4% (25/36). Lesions shrinkage were observed in 22 pts, the preliminary overall ORR was 71.0% (22/31). The ORR of residual GGN lesions ≥8mm (n=19) or <8mm (n=12) was 73.7% and 66.7% respectively. Notably, there were 7 pts with GGN completely disappeared including 2 pts with pure GGN (pGGN) and 5 pts with part-solid nodule (PSN), all of which were L858R mutation. Among the four pts with multiple GGNs, three achieved partial response (PR) remission, while the other maintained stable disease (SD).During aumolertinib therapy, rash (22.6%), pruritus (19.4%), diarrhea (9.7%), mouth ulcers (6.5%) and alopecia (3.2%) were common adverse events and no pts withdrew from therapy.

Conclusions: Our study provides evidence for the efficacy of aumolertinib in the treatment of stage I EGFR-mutated NSCLC with GGN lesions remaining after surgery. The potential benefits for pts with more remaining lesions, mixed component lesions, and L858R mutation deserve further exploration.

Keywords: Ground-glass nodule, Adjuvant, Aumolertinib

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EP.07C.05 Efficacy and Safety of Aumolertinib in Stage IB-IIIA NSCLC after R0 Resection and the Correlation Between Efficacy and Postoperative MRD Status

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Introduction: For patients with early-stage non-small cell lung cancer (NSCLC), surgical radical resection is an important treatment for the patients. However, patients are still at risk of tumor recurrence and metastasis after complete resection, and the risk increases with the increase of the stage according to the 9th edition TNM standard. ADAURA study has proved that stage IB-IIIA patients after R0 resection with or without standard chemotherapy could both benefit from Osimertinib. The primary endpoint DFS was significantly prolonged (NR vs 19.6 months, HR 0.17). However, the one-size-fits-all strategy and long-term treatment may cause unnecessary toxic side effects and psychological burden to patients. Minimal residual disease (MRD) status may be promising in personalized adjuvant therapy and it is recognized that patients with detectable MRD after resection have a worse prognosis than those undetectable. Therefore, whether MRD can play a guide role in adjuvant therapy urgently needs to be answered. Aumolertinib is a third-generation EGFR-TKI independently developed in China with high selectivity and low toxicity for EGFR mutations. Our study (ChiCTR2200059566) is designed to explore the efficacy of Aumolertinib for stage IB-IIIA NSCLC after R0 resection, and correlation between MRD status and efficacy. It may provide some hints for personalized postoperative treatment based on MRD.

Methods: A total of 120 patients with stage IB-IIIA NSCLC after R0 resection with EGFR mutations positive (19del and L858R) will be enrolled, and receive Aumolertinib (110 mg) once daily. The primary endpoint is disease free survival (DFS) rate at 2-year. Secondary endpoints included DFS rate at 2-year in patients with ctDNA status changes (positive to negative/negative to positive) and that for ctDNA continuously positive or negative patients.

Results: At date cut off March 25, 2024, we recruited 33 patient of stage I-IIIA NSCLC harboring EGFRm. In the total population, 27(81.8%) patients were female, 17(51.5%) patients harboring exon 19 deletion, 10 (30.3%) patients had 21L858R mutation, while 5(15.2%) patients had rare mutations. Additionally, 26 patients were stage I and 7 patients were stage II-IIIA. All the patients were administrated Aumolertinib (110 mg daily) after R0 surgical resection. At data cutoff, total 3 patients were dropped out because of adverse events or postoperative complications, and 16 patients received Aumolertinib adjuvant therapy and followed up more than 1 year, while 14 patients less 1 year. All patients are alive, and there is no patient presented with metastasis. The 1-year disease free survival (DFS) are 100% and 2-year DFS doesn't reach.

Conclusions: Our study demonstrates the primary efficacy and safety profile of Aumolertinib in the adjuvant treatment of NSCLC. Long term follow-up of our study is ongoing to investigate further survival outcomes.

Keywords: Adjuvant therapy, Minimal residual disease, aumolertinib

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EP.07C.07 Superiority of Modified-MPR in Prediction of Survival for Patients with Lung Cancer after Neoadjuvant Therapy

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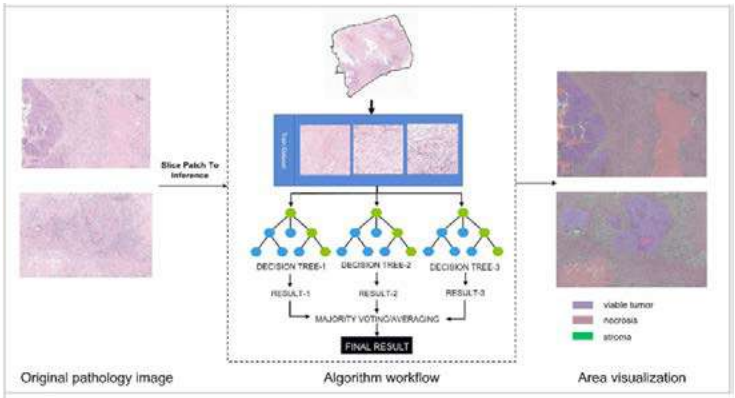
Introduction: Major pathologic response (MPR) after neoadjuvant therapy for lung cancer has the potential to serve as surrogate endpoint for survival. However, efficiency of MPR were moderate and unsatisfied, which may result from difficulty in determining tumor bed and residual tumor. In this study, we aimed to evaluate CT or PET-measured tumor bed and residual tumor based on artificial intelligence in pathologic response evaluation. And we explored the feasibility of modified-MPR as an alternative endpoint.

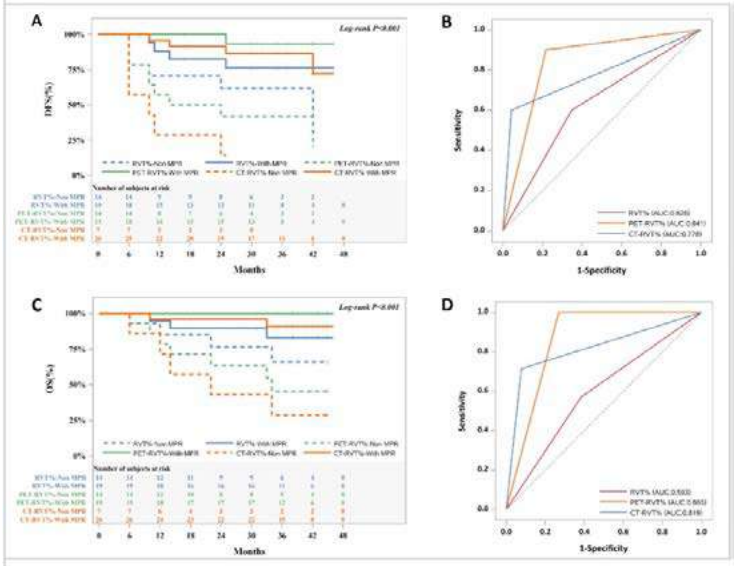
Methods: A total of 237 patients with lung cancer who received neoadjuvant therapy from Aug, 2019 to Oct, 2023 were retrospectively collected. The maximum tumor or metabolic area on baseline PET or CT were measured as tumor bed. Percentage of residual viable tumor (RVT%) was assess by deep learning model. CT or PET-based residual viable tumor% (CT-RVT%, PET-RVT%) represented RVT area divided by tumor bed assessed by CT or PET, respectively. Disease-free survival (DFS) and overall survival (OS) were analyzed by Kaplan-Meier approach and compared with log-rank test. The efficacy of CT-RVT%, PET-RVT%, and RVT% was compared by receiver operating characteristic (ROC) curve.

Results: Here, we reported preliminary result of 33 patients (median age: 58-year-old, range: 29-67 years; 28 men) from Aug, 2019 to Sep, 2020. There were 10, 17, and 10 patients achieved MPR in RVT%, CT-RVT%, and PET-RVT% groups respectively. In RVT% group, no survival difference (DFS or OS) was found between MRP and non-MPR patients. While grouping by CT-RVT% and PET-RVT%, patients who achieved MPR had superior DFS (P<0.001) and OS. Moreover, PET-RVT% and CT-RVT% show higher area under ROC curve (AUC) when compared to RVT% in DFS (0.841 vs 0.778 vs 0.626, p<0.001) and OS (0.865 vs 0.819 vs 0.593, p<0.001).

Conclusions: Our modified-MPR combining PET-CT and deep learning model showed better efficacy as predictor of DFS and OS.

Keywords: major pathologic response, lung cancer, neoadjuvant therapy





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EP.07C.08 Surgical Factors and Adjuvant Therapy Use after Neoadjuvant Therapy for Patients with Resected Stage II-IIIB(N2) NSCLC

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Introduction: The current standard of care for resectable NSCLC includes immune checkpoint inhibitors (ICIs) administered in combination with platinum-based chemotherapy as neoadjuvant or perioperative regimens. In the US, neoadjuvant nivolumab plus chemotherapy was approved in 2022 and neoadjuvant pembrolizumab plus chemotherapy followed by adjuvant pembrolizumab in 2023. This retrospective study aimed to understand surgical approach and subsequent use of adjuvant therapy among real-world patients receiving neoadjuvant therapy with or without ICI.

Methods: We drew on data originating from ~280 cancer clinics included in the US nationwide Flatiron Health electronic health record-derived, deidentified database. Patients with diagnosis from 1/1/2019 to 3/31/2023 of clinical stage II, IIIA, or IIIB(N2) NSCLC, who received neoadjuvant therapy and underwent tumor resection by 9/30/2023 (excluding clinical trial participants) were eligible. Data cutoff was 12/31/2023.

Results: Among 1550 patients with cII-IIIB NSCLC undergoing resection, only 159 (10%) received neoadjuvant therapy, including 76 (48%) with an ICI-based and 83 (52%) with non-ICI neoadjuvant. Patients receiving ICI-based neoadjuvant were older, with a later diagnosis year (Table). Oncology practice type and insurance coverage were similar in the two cohorts. Tumor characteristics that differed numerically included lower percentages of patients with stage cIIIA and greater percentages with stage cII and with squamous NSCLC who received ICI-based (vs. non-ICI) neoadjuvant (Table). Similar percentages underwent lobectomy, and pneumonectomy rates were low. Numerically greater percentages underwent a minimally invasive resection after ICI-based neoadjuvant, including >70% with robotic-assisted surgery (Figure). Adjuvant systemic therapy was administered to 43% in ICI-based and 53% in non-ICI neoadjuvant cohorts, respectively.

Conclusions: This study illustrates changing approaches to surgical resection and neoadjuvant/perioperative therapy for stages cII-IIIB(N2) NSCLC. Uptake of ICI-based neoadjuvant therapy remains low, but its use does not compromise ability to perform minimally invasive resection. Factors influencing use of adjuvant therapy after neoadjuvant therapy should be more closely examined.

Keywords: neoadjuvant therapy, adjuvant therapy, surgical resection

Figure. Surgical approach to NSCLC resection for all patients and the type of minimally invasive initial approach (MIIA) for 43 and 49 patients in non-ICI and ICI-based neoadjuvant cohorts, respectively.
ICI, immune checkpoint inhibitor; RATS, robotic-assisted surgery; VATS, video-assisted surgery.

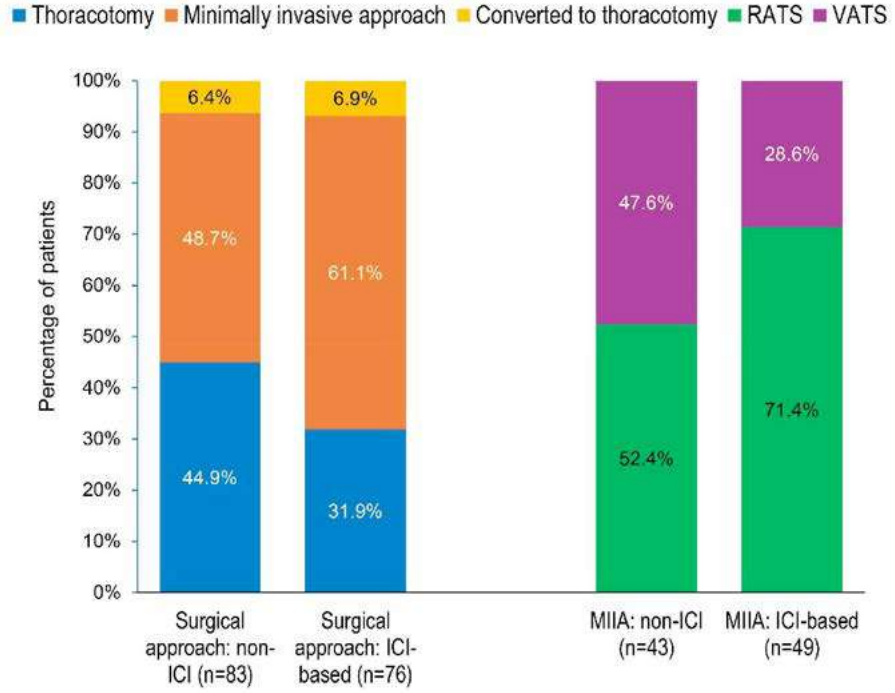

Table. Patient baseline and NSCLC tumor characteristics and resection

Variable	Non-ICI neoadjuvant (n=83)	ICI-based neoadjuvant (n=76)
Male sex, n (%)	43 (52)	44 (58)
Age, median (range), years	65 (35–84)	68 (40–84)
≥75 years, n (%)	12 (14)	18 (24)
Community (non-academic) practice	63 (76)	60 (79)
ECOG performance status, n (%)[a]		
0–1	68 (94)	68 (99)
≥2	4 (6)	1 (1)
Not documented/unknown	11	7
Diagnosis year, n (%)		
2019–2021	60 (72)	7 (9)
2022–2023	23 (28)	69 (91)
NSCLC histologic type, n (%)		
Nonsquamous	53 (64)	38 (50)
Squamous cell carcinoma	28 (34)	37 (49)
Not otherwise specified (NOS)	2 (2)	1 (1)
Clinical NSCLC stage, n (%)[a]		
II	17 (20)	32 (42)
III	49 (80)	42 (58)
NOS[b]	17	2
Clinical T category, n (%)[a]		
T0	1 (1)	0
T1	17 (25)	12 (17)
T2	15 (22)	20 (29)
T3	24 (35)	21 (30)
T4	11 (16)	17 (24)
Not documented/unknown/TX	15	6
Clinical N category, n (%)[a]		
cN0	24 (37)	32 (45)
cN1	12 (18)	17 (24)
cN2	28 (43)	22 (31)
cN3	1 (2)	0
Not documented/unknown/NX	18	5
Last neoadjuvant dose to surgery, median (range), days	41 (1–395)	42 (0–154)
Resection type, n (%)		
Lobectomy	71 (86)	67 (88)
Pneumonectomy	4 (5)	5 (7)
Segmentectomy, wedge resection, other	8 (10)	4 (5)

Percentages may not add up to 100 because of rounding.
NOS, not otherwise specified.
[a]Percentages for ECOG, NSCLC stage, and clinical T and N category represent the percentage of patients with available data.
[b]Includes not documented or unclassified clinical stage.

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EP.07C.09 Neoadjuvant Chemoimmunotherapy (CIT) In Resectable Non-Small Cell Lung Cancer (NSCLC): Real-World Treatment Patterns and Surgical Outcomes

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Introduction: Surgical resection continues to be the standard of care for early-stage resectable NSCLC, but post-surgical recurrence rates are as high as 50%. Improved event-free and overall survival have been demonstrated in clinical trials exploring neoadjuvant and peri-operative CIT; as such, use of neoadjuvant CIT (platinum doublet + nivolumab) has become part of the current treatment paradigm. Treatment patterns, response, toxicity and surgical outcomes in routine clinical practice from this evolving treatment approach is a current knowledge gap. We aim to characterize the characteristics, treatment response and surgical outcomes of a real-world neoadjuvant CIT-treated NSCLC cohort.

Methods: Demographic, clinical, treatment and outcome details were extracted from a province-wide, real-world outcomes registry of patients treated in routine practice. A population-level cohort of patients receiving neoadjuvant CIT were analyzed. Our primary endpoint was major pathological response (MPR) rate, with secondary endpoints including pathological complete response rate (pCR), objective response rate (ORR), surgical outcomes and adverse events (AE).

Results: Fifty-five patients received neoadjuvant CIT (Table 1). 87% received the recommended 3 cycles, eliciting an objective complete response in 8% and ORR of 67% (63% in PD-L1 >=50%). 29% had serious treatment related AEs requiring treatment delay/discontinuation; primarily nausea/vomiting. 7% experienced immune-related AE (n=1: colitis; n=3: rash; n=1: pneumonitis).To date, n=40 had surgical resection; surgery pending for 13%. 15% were ineligible for surgery post-CIT (n=3: residual N2 or progression; n=1: non-oncology related death; n=1: complete response, n=3: unfit for surgery). 98% of resections had R0 surgical margins. 13% received adjuvant platinum-pemetrexed/paclitaxel post CIT. Downstaging to from cN2 to yN0 occurred in 46% of patients. 43% MPR (53% in PD-L1 >=50%), 25% pCR (32% in PD-L1 >=50%; 35% in Stage III patients). Surgical complications occurred in 15 (37%), most commonly air leaks with spontaneous resolution (10%). Serious complications included sepsis (n=1) & hypoxemic respiratory failure with NSTEMI and immune pneumonitis (n=1). Combined, surgical complications resulted in a median 6-day hospitalization (range 2 - 180). The median follow-up time was 4 months, recurrence was noted ≤12 months post-surgery in n=3 (8%) of resected patients (n=2: local/regional, n=1: distant).

Conclusions: Surgical resection post-neoadjuvant CIT is a pragmatic management approach for resectable NSCLC. Treatment protocol completion, surgical outcomes and adverse event rates were similar to pivotal studies. Neoadjuvant CIT delivers meaningful pathological response in a real-world unselected clinical population, with Stage III disease deriving substantial benefit in this context.

Keywords: neoadjuvant immune checkpoint inhibitors, early-stage resectable NSCLC, real-world treatment outcomes

Table 1: Baseline Characteristics at Diagnosis

Characteristic	Cohort (n=34)
Median Age; range	67 yrs; 63 - 72
Sex	
Male	53%
Female	47%
ECOG at CIT Initiation	
≤ 1	95%
≥2	5%
Tobacco Exposure	
Yes	93%
No	7%
Histology	
Adenocarcinoma	58%
Squamous	42%
Tier I Mutation Status (n=27 with molecular testing):	
Tier I	
BRAF	4%
ERBB2	7%
KRAS (n=11) [G12C (n=6); Non-G12C (G12A, G12F, G12V) (n=5)]	41%
Nodal Involvement at Diagnosis	
N0	33%
N1	38%
N2	29%
T Stage	
T1	21%
T2	22%
T3	36%
T4	21%
Stage at Diagnosis (AJCC 8th edition)	
IIA	4%
IIB	38%
IIIA	47%
IIIB	11%
PD-L1 %	
Insufficient Sample	5%
< 1	17%
1-49	35%
> 50	43%

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EP.07C.10 Real-World Outcomes of Patients Treated with Neoadjuvant Immunotherapy for Resectable Non-Small Cell Lung Cancer

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Introduction: Neoadjuvant immunotherapy + chemotherapy (NAIO) has shown significant benefit over platinum-based chemotherapy (CT) alone in multiple clinical trials. However, the efficacy in real-world patient populations remains understudied.

Methods: Patients with stage IB-IIIA NSCLC who underwent NAIO or CT followed by surgical resection at YNHH from October 2015 - August 2023 were included. Demographics, stage, treatment data, surgical details, pathologic information including pathologic complete response (pCR), and survival outcomes between NAIO vs CT were compared by Chi-square or Fisher's exact test, and Kaplan-Meier survival curves using SAS 9.4.

Results: Among 53 consecutive patents (30 neoadjuvant CT, 23 neoadjuvant IO+CT), demographics did not differ significantly between groups and resembled CheckMate 816 participants (age, smoking status, clinical stage) but included more females (38%) and adenocarcinoma histology (60.4%). Similar to CheckMate816, the majority of patients in both groups received cisplatin as their chemotherapeutic agent (53.3% and 56.5%). The NAIO group more often had a known and high pre-op PD-L1 status (p=0.06); 6 patients (26.1%) received IO with PD-L1<1%. Patients who received NAIO were less likely to receive adjuvant treatment (17.4%, vs 46.7% p=0.03). IO was not significantly associated with differences in extent of surgical resection, sleeve rates, conversion rates, or operative time. Patients who received NAIO had a numerically higher pCR (21.7% vs 6.7%, p=0.22) and lower recurrence rate compared with those who received CT (17.4% vs 36.7%, p=0.14). Overall and disease-free survival curves diverged, favoring NAIO, but did not reach statistical significance (p=0.39 and 0.43).

Conclusions: In a real-world patient population, NAIO is well tolerated without impact on surgical outcomes compared to CT. In alignment with randomized trials, patients who received NAIO had a trend towards higher rates of pCR and appeared less likely to experience recurrence or death following surgery. Further updated data will be presented at IASLC 2024 WCLC.

Keywords: NSCLC, neoadjuvant, immunotherapy

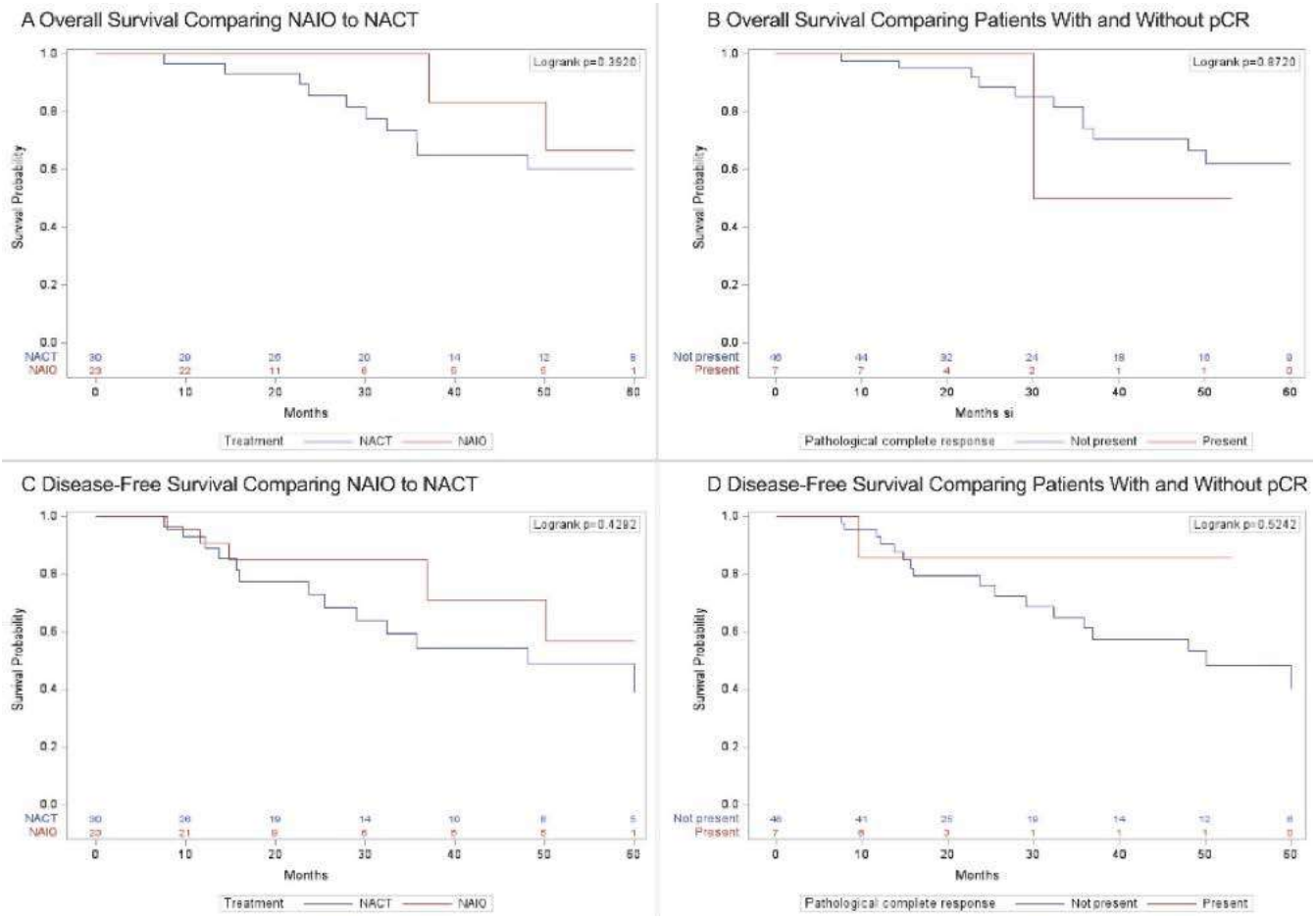

Table 1. Characteristics of Included Patients

Variables	Neoadjuvant chemotherapy (n=30)	Neoadjuvant immunotherapy +/- chemotherapy (n=23)	Total	Chi-square or Fisher's exact test
	n (column %)	n (column %)	n	*p*-value
BASELINE CHARACTERISTICS				
Age				
Median (range) / yrs	66.5 (50-80)	69 (46-79)		0.98
<65 yr	15 (50.0)	11 (47.8)	26	
>=65 yr	15 (50.0)	12 (52.2)	26	1.00
Gender				
Male	18 (60.0)	15 (65.2)	33	
Female	12 (40.0)	8 (34.8)	20	0.70
ECOG				
0	11 (36.7)	12 (52.2)	23	
1	15 (50.0)	11 (47.8)	26	
2	4 (13.3)	0 (0.0)	4	0.17
Smoking status				
Never	3 (10.0)	0 (0.0)	3	
Former	23 (76.7)	20 (87.0)	43	
Current	4 (13.3)	3 (13.0)	7	0.41
Pack years				
Median (range) / yrs	30 (0-80)	30 (8-75)		0.95
Clinical stage				
IB	0 (0.0)	2 (8.7)	2	
IIA	2 (6.7)	1 (4.4)	3	
IIB	7 (23.3)	4 (17.4)	11	
IIIA	21 (70.0)	16 (69.6)	37	0.48
Histology				
ACA	20 (66.7)	12 (52.2)	32	
SCC	10 (33.3)	11 (47.8)	21	0.29
Pre-op PD-L1 status				
Negative (<1%)	4 (13.3)	6 (26.1)	10	
Low/intermediate (1-49%)	11 (36.7)	10 (43.5)	21	
High (>=50%)	5 (16.7)	6 (26.1)	11	
Unknown	10 (33.3)	1 (4.4)	11	0.06
Platinum-based chemotherapy				
Carboplatin	11 (36.7)	8 (34.8)	19	
Cisplatin	16 (53.3)	13 (56.5)	29	
Both	3 (10.0)	2 (8.7)	5	1.00
OUTCOMES				
Pathological complete response				
No	28 (93.3)	18 (78.3)	46	
Yes	2 (6.7)	5 (21.7)	7	0.22
Extent of resection[1]				
Lobectomy or less	21 (70.0)	16 (69.6)	37	
Bilobectomy	5 (16.7)	2 (8.7)	7	
Pneumonectomy	4 (13.3)	5 (21.7)	9	0.57
Sleeve resection[2]				
No	25 (83.3)	20 (87.0)	45	
Yes	5 (16.7)	3 (13.0)	8	1.00
Surgical approach[3]				
VATS	7 (23.3)	2 (8.7)	9	
RATS	5 (16.7)	5 (21.7)	10	
Open	18 (60.0)	16 (69.6)	34	0.40
Conversion minimally invasive to open[4]				
No	24 (80.0)	22 (95.7)	46	
Yes	6 (20.0)	1 (4.4)	7	0.12
Operative time				
Median (range) / min	308.5 (145-687)	349 (175-999)		0.44
Any adjuvant treatment				
No	15 (50.0)	19 (82.6)	34	
Yes	14 (46.7)	4 (17.4)	18	
Unknown	1 (3.3)	0 (0.0)	1	0.03

1 Lobectomy or less = any type of sublobar lung resection (e.g., wedge, segment) or lobectomy, bilobectomy = either two complete lobes or one complete lobe + sublobar lung resection of an additional lobe

2 Sleeve resection means a more complex lung resection with circumferential excision of involved lung tissue around a bronchus or pulmonary artery branch

3 VATS= video-assisted thoracoscopic surgery, RATS = robotic-assisted thoracoscopic surgery

4 Conversion means that a surgery that was initially started minimally invasively (i.e., VATS or RATS) was converted to an open thoracotomy intraoperatively for any reason. Common reasons include lack of exposure due to scars, or uncontrollable bleeding.

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EP.07C.11 Adjuvant Immunotherapy for Patients with Resectable NSCLC after Pathologic Complete Response

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Introduction: Neoadjuvant therapy combining immune checkpoint inhibitors with chemotherapy has significantly improved pathologic response and survival in patients with resectable NSCLC. However, it remains controversial whether adjuvant immunotherapy should be given for patients who achieve pathologic complete response (pCR).

Methods: A real-world prospective cohort study was performed in a single-center setting from April 2020 to March 2024. Patients who were diagnosed with resectable stage IB-IIIB NSCLC and achieved pCR after three cycles of neoadjuvant immunochemotherapy were enrolled. Patients receiving adjuvant immunotherapy for one year were assigned to adjuvant immunotherapy group (N=36), while others were assigned to no adjuvant immunotherapy group (N=27). The primary outcome of this study was disease-free survival (DFS). Treatment-related adverse events were evaluated during adjuvant immunotherapy.

Results: The age, gender, proportions of smokers and squamous cell carcinoma were generally similar between the two groups. Compared to the adjuvant immunotherapy group, the proportion of patients in stage IIIA was higher (70.4% vs. 52.8%) and the proportion in stage IIIB was lower (14.8% vs. 30.6%) among those who did not receive adjuvant immunotherapy, but no statistical difference was observed. The median follow-up time for the two groups of patients was 24.0 and 25.5 months (P=0.856), respectively. Only two patients (5.6%) experienced lung cancer recurrence in the adjuvant immunotherapy group, while only one patient (3.7%) who did not receive adjuvant immunotherapy experienced recurrence. The DFS survival curves for the two groups largely overlap (P=0.6325), and the median DFS has not been identified yet. During adjuvant immunotherapy for one year, there is no severe (≥grade 3) treatment-related adverse events reported in the adjuvant immunotherapy group.

Conclusions: After a follow-up period of 24 months, postoperative adjuvant immunotherapy has not led to a tendency of DFS benefit in these patients. Longer follow-up time is required to compare DFS between the two groups.

Keywords: Non-small cell lung cancer (NSCLC), Pathologic complete response, Adjuvant immunotherapy

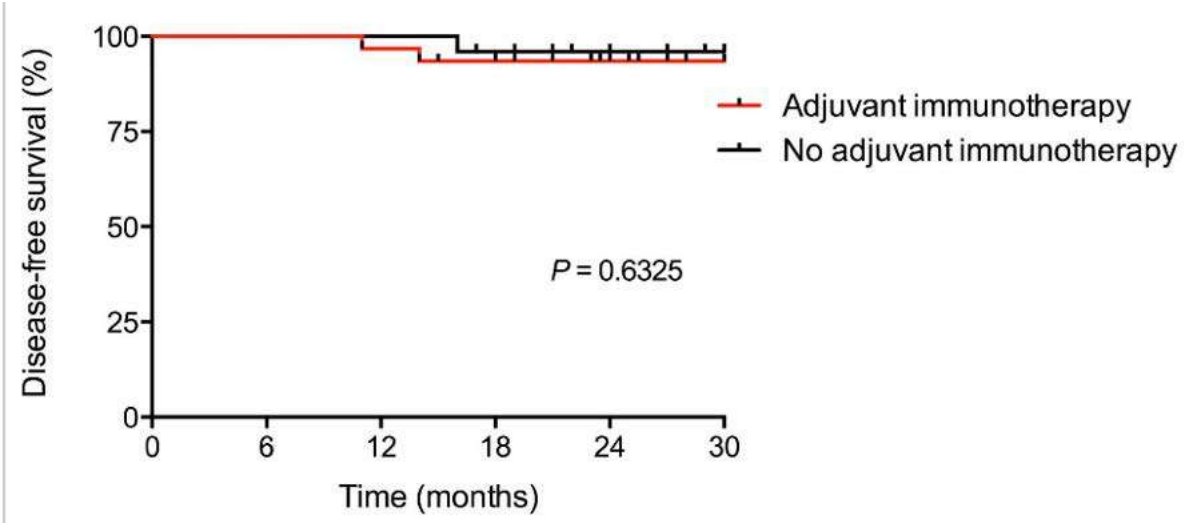

Table 1. Clinical features of patients

Variables	Adjuvant immunotherapy group	No adjuvant immunotherapy group	P value
Gender			
Male	34 (94.4)	24 (88.9)	0.643
Female	2 (5.6)	3 (11.1)	
Age (yrs)	59 (56-66)	62 (56-66)	0.722
Smoking history			
Non-smoker	5 (13.9)	5 (18.5)	0.733
Former or current smoker	31 (86.1)	22 (81.5)	
Clinical TNM stage			
IB	0	1 (3.7)	0.198
IIA-B	6 (16.7)	3 (11.1)	
IIIA	19 (52.8)	19 (70.4)	
IIIB	11 (30.6)	4 (14.8)	
Histological subtypes			
Squamouse cell carcinoma	29 (80.6)	22 (81.5)	0.926
Non-squamouse cell carcinoma	7 (19.4)	5 (18.5)	
Immune checkpoint inhibitors			
Nivolumab	23 (63.9)	15 (55.6)	0.911
Other ICIs	13 (36.1)	12 (44.4)	
Median follow-up (month)	24.0 (19.0-30.0)	25.5 (19.0-34.0)	0.856
Recurrence event	2 (5.6)	1 (3.7)	1.000

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EP.07C.13 Aumolertinib as Adjuvant Therapy in Postoperative EGFR-Mutated Stage I NSCLC with Multiple High-Risk Factors

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Introduction: Surgery is the standard treatment regimen for early NSCLC. However, there are still about 20% of stage I patients(pts) who are at risk of early recurrence or metastasis, even after complete surgical resection. The high-risk factors for lung cancer are important factors affecting the survival of stage I pts, including imaging, pathology, surgical methods, gene mutation types, and MRD ctDNA positivity. Stage I postoperative NSLCL patients combined with risk factors had worse prognosis, and the more risk factors combined, the worse prognosis will be.

Methods: A total of 26 pts with stage I EGFR-mutated lung adenocarcinoma who underwent radical surgery from Apr 2021 to Jan 2024 were enrolled, including 5 pts with stage IA and 21 pts with stage IB. Up to 17 pts (65%) had high-risk factors, and 13 pts (50%) were combined with ≥ 2 high-risk factors. The risk factors that threaten survival identified from the basic variables of enrolled pts include the presence of solid, micropapillary, or complex gland components, poorly differentiated carcinoma, visceral pleural invasion (VPI), non-EGFR co-mutations, surgical approach, smoking history, etc. All patients received adjuvant treatment with the third-generation EGFR-TKI aumolertinib (110mg, orally QD).

Results: At data cut-off, all patients have no symptoms of tumor recurrence and continued to administrate aumolertinib. 13 pts (57%) have been followed up for over 1 year, and 100% pts were alive and disease-free at 12 months, the 1-year DFS was 100%. During aumolertinib therapy, only 1 pts suffered a mild rash.

Conclusions: Our study first time demonstrate that the third-generation EGFR-TKI aumolertinib has efficacy and tolerable safety profile in pts with completely resected stage I EGFR-mutated NSCLC with multiple high-risk factors. This study is still progress and further analyses are undergoing to determine longer-term outcomes.

Keywords: Aumolertinib, Multiple High-risk factors, NSCLC

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EP.07C.14 Clinical Outcomes of Neoadjuvant Immunotherapy in Stage I-II Non-Small Cell Lung Cancer: A Real-World Study and Meta-Analysis

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Introduction: Neoadjuvant immunotherapy (neoIO) brought an evolution for resectable early-stage non-small cell lung cancer (NSCLC). Although the multimodality management with immunotherapy prior surgery for stage III diseases were fully reported in several phase 3 clinical trials, few studies investigated the role of neoIO in the management for stage IB and II patients (pts). To address this knowledge gap, we aimed to evaluate the efficacy of neoIO for stage IB and II NSCLC from a real-world study and further confirm through a meta-analysis on prospective clinical trials.

Methods: Stage I-II (AJCC 8th edition) NSCLC pts receiving neoIO followed by radical surgery between May 2019 and April 2023 in our institution were retrospectively collected. The clinical characteristics and oncological outcomes were reviewed and analyzed. Besides, a meta-analysis study registered at the PROSPERO database (No. CRD42023411932) was conducted. To identify relevant clinical trials investigating neoIO for stage I-II resectable NSCLC, a comprehensive search was performed across multiple literature databases and oncology conferences up to March 10th, 2024. The primary outcomes were major pathologic response (MPR) and pathologic complete response (pCR).

Results: In retrospective cohort, 49 pts with a mean age of 61.9±8.5 years were included, and 87.8% being males. 34 pts (69.4%) had squamous subtype. All pts were administrated with PD-1 inhibitors, among which 93.9% (n=46) with chemotherapy, and the other 3 with monotherapy. The ORR rate (RECIST 1.1) was 71.0% (95% CI: 56.6 to 82.2). 47 pts (95.9%) underwent minimal invasive surgery with R0 resection rate of 98.0% (95% CI: 89.3 to 99.9). The MPR rate and pCR rate were 59.2% (n=29, 95% CI: 45.2 to 71.8) and 44.9% (n=23, 95% CI: 31.9 to 58.7), respectively (Figure 1A). Moreover, a meta-analysis including 1398 pts from 6 randomized control trials and 18 prospective studies revealed a pooled MPR rate of 35.9% (95% CI: 28.3 to 43.8) (Figure 1B) and pooled pCR rate of 19.3% (95% CI: 11.4 to 28.3) (Figure 1C). As for subgroup analysis of treatment regimens, promising pathological response rates in neoadjuvant immunochemotherapy (MPR, 41.6%; 95% CI: 33.2 to 50.2; pCR, 27.1%; 95% CI: 20.5 to 34.1) were reported. Interestingly, a high pathologic regression but with significant heterogeneity in neoIO combined with other agents was observed.

Conclusions: This retrospective real-world study and meta-analysis on stage I-II NSCLC suggested perioperative oncological benefits of neoIO. More evidence of long-term outcomes and optimal regimens is guaranteed for the use of neoIO in earlier-stage NSCLC.

Keywords: Neoadjuvant immunotherapy, Early-stage NSCLC, Meta-analysis

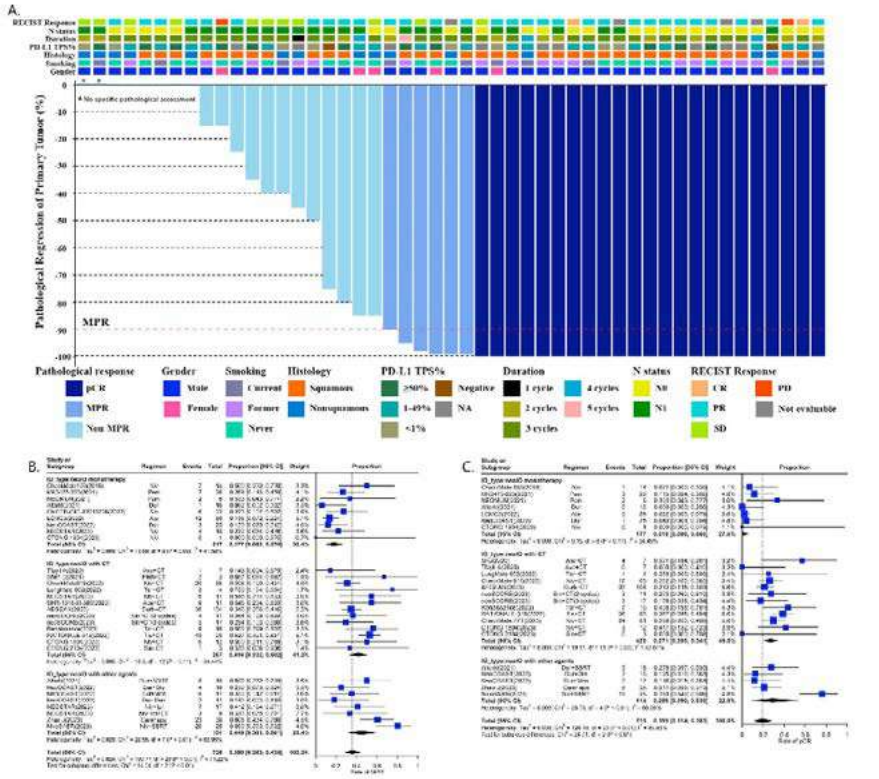

FIGURE 1. Pathological response of stage I-II NSCLC received neoadjuvant immunotherapy. A, Clinicopathological characteristics and clinical outcome of retrospective cohort (n = 49). B, Pooled analyses of MPR rate. C,Pooled analyses of pCR rate . (neoIO, neoadjuvant immunotherapy; CT, chemotherapy; Sin sintilimab; Ate, atezolizumab; Pem, pembrolizumab; Niv, nivolumab; Dur, durvalumab; Ade, adebrelimab; Tor, toripalimab;Tis,tislelizumab ;Ipi, Ipilimumab SBRT, stereotactic body radiotherapy; Ole, olecluma b; Mon, monalizumab; Dan, danvatirsen; MPR, major pathologic response; pCR, complete pathologic response; CI, confidence interval; PD, progressive disease; SD, stable disease; PR, partial response; CR, complete response; RECIST, Response Evaluation Criteria In Solid Tumors.)

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EP.07C.15 Neoadjuvant Immuno-Chemotherapy in Resectable Non-Small Cell Lung Cancer - A Retrospective Cohort Study

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Introduction: Neoadjuvant (NA) nivolumab-chemotherapy (nivo-chemo) has shown an improved survival and pathological complete response (pCR) rate, vs chemo alone, in early-stage, resectable non-small cell lung cancer (NSCLC). Nevertheless, there is a paucity of real-world data.

Methods: We performed a real-world, retrospective analysis of outcomes and toxicities in patients with resectable NSCLC (stage IB-IIIA; EGFR/ALK alterations excluded) treated with three cycles of NA nivo-chemo followed by surgery at a single, tertiary-level Canadian cancer centre from September 2022 to March 2024.

Results: Eighteen consecutive patients were treated with NA nivo-chemo. The median age was 69.5 years (range, 58 to 79) and 66% were males. 39% (n-7/18) and 11% (n-2/18) had N1 and N2 nodes, respectively. All patients completed three cycles of NA nivo-chemo. Objective response rate was 77% (n-14/18), as per RECIST1.1 (including two complete responses). Progression was noted in two patients (the CT predated initiation of treatment by more than 8 weeks in these patients). The median time to surgery was 10.6 weeks (range, 6-17.6). 83% patients (n-15/18) had a surgery (2 pneumonectomy, 13 lobectomies); and of these, 86% (n-13/15) are on surveillance while two patients had an event (death or progression). All (n-14/15) had R0 resection except one. 33% patients (n-6/18) had a pCR, including two with stage IIIA disease (PD-L1 TPS < 1% in four patients, PD-L1 TPS ≥ 50% in two patients). 61% (n-11/18) patients were started at a reduced chemo dose in cycle 1. 44% patients required further dose reduction in cycle 2. Grade 3 or 4 toxicities were seen in 22% patients (n-4/18), (neutropenia (n-2), febrile neutropenia (n-1) and pneumonitis (n-1, unresolved, grade 3 and resulting in decreased pulmonary reserve precluding surgery; patient is on close surveillance). Peri-operative (within 7 days) complications unrelated to systemic treatment were seen in 66% patients (n-10/15). One patient died on post-operative day 2 due to postoperative intra-thoracic bleed from pulmonary artery stump.

Conclusions: NA nivo-chemo in resectable NSCLC is safe and associated with improved pCR rate. A few patients may progress on NA treatment or have a grade 3-5 toxicity precluding curative surgery. Hence, individualized informed decisions should be made. There is an unmet need of biomarkers/models that can predict pCR/toxicity for better patient selection.

Keywords: NSCLC, resectable, immunotherapy

Table. Disease and treatment characteristics

Variable	*N (%)*
Chemotherapy backbone	
Carboplatin-paclitaxel	11 (61)
Carboplatin-pemetrexed	4 (22)
Cisplatin-pemetrexed	2 (11)
Cisplatin-gemcitabine	1 (6)
Stage	
IB	3 (17)
IIA	2 (11)
IIB	7 (39)
IIIA	6 (33)
Histology	
Squamous	8 (44)
Adenocarcinoma	7 (38)
Adeno-squamous	1 (6)
Carcinosarcoma	1 (6)
NSCLC-NOS	1 (6)
PD-L1 (Tumor proportion score)	
< 1%	8 (44)
1 to 49%	6 (34)
≥ 50%	4 (22)

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EP.07C.16 Real-World Outcomes of Patients with Resectable Early-Stage Non-Small Cell Lung Cancer Treated with Neoadjuvant Chemoimmunotherapy

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Introduction: Chemoimmunotherapy has emerged as a promising treatment for resectable stage IB-IIIA non-small cell lung cancer (NSCLC). Neoadjuvant nivolumab in combination with chemotherapy, according to the Checkmate-816 study, is associated with improved pathological complete response (pCR), major pathological response (mPR), and event-free survival (EFS) as compared to neoadjuvant chemotherapy. We aim to evaluate the real-world outcomes of this regimen.

Methods: We conducted a retrospective analysis of patients with stage IB-IIIA NSCLC treated at Mayo Clinic with neoadjuvant nivolumab plus chemotherapy between March 2022 and December 2023. pCR was defined as no evidence of residual invasive cancer in the resected primary tumor and lymph nodes. mPR was defined as ≤10% viable tumor cells in the resected primary tumor and lymph nodes. EFS was defined as the time from initiation of neoadjuvant systemic therapy to any progression, recurrence, or death. Descriptive statistical analyses were performed with BlueSkyStatistics 7.40.

Results: Twenty-six patients (median age 67) were included and 12 (48%) were male. Ten (38%) had stage IIB, 15 (58%) stage IIIA, and 1 (4%) stage IVB. Seventeen (65%) had N0, 4 (16%) N1, and 5 (19%) N2. Of the N2, one had multinodal station involvement and one had bulky nodal disease (≥ 3 cm). Eighteen (69%) were adenocarcinoma, 6 (23%) squamous, and 2 (8%) adenosquamous. Two (8%) had EGFR exon 19 deletion, 2 (8%) MET exon 14 skipping mutation, 1 (4%) EGFR exon 18 mutation, and 1 (4%) EML4-ALK translocation. Two with PD-L1 expression of 0%, 7 with 1-49%, and 8 with > 50%. All patients received neoadjuvant nivolumab. Eighteen (69%) received carboplatin/pemetrexed, 6 (23%) carboplatin/paclitaxel, and 2 (8%) carboplatin/gemcitabine for a median of 3 cycles (range 2-4). Seven (27%) developed immunotherapy-related toxicity; 2 required hospitalization for grade 3/4 toxicity (one patient with hepatitis and one patient with colitis). All patients underwent surgical resection via lobectomy. Two (8%) developed life-threatening post-operative complications resulting in death: one cardiac arrest, and one post-operative chyle leak and multiorgan failure. Twelve (46%) achieved pCR and 2 (8%) achieved mPR. Five (19%) received adjuvant therapy; 3 (12%) nivolumab and 2 (8%) targeted therapies (one osimertinib and one alectinib). Twenty-four (92%) were alive at the end of this study's analysis. The median EFS for the entire cohort was not reached.

Conclusions: In this small retrospective analysis of patients with stage IB-IIIA NSCLC treated with neoadjuvant nivolumab plus chemotherapy, 54% achieved a mPR or cPR. All patients were able to undergo surgical resection via lobectomy suggesting room for outcome improvement. Results from this study corroborate the use of neoadjuvant chemoimmunotherapy in the real-world setting.

Keywords: chemoimmunotherapy, neoadjuvant, non-small cell lung cancer

EP.07C EARLY-STAGE NON-SMALL CELL LUNG CANCER - PERIOPERATIVE THERAPY
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EP.07C.17 A Nomogram Prediction Model for Assessing the Risk of Recurrence in NSCLC Patients Underwent Neoadjuvant Immunotherapy: A Retrospective Study

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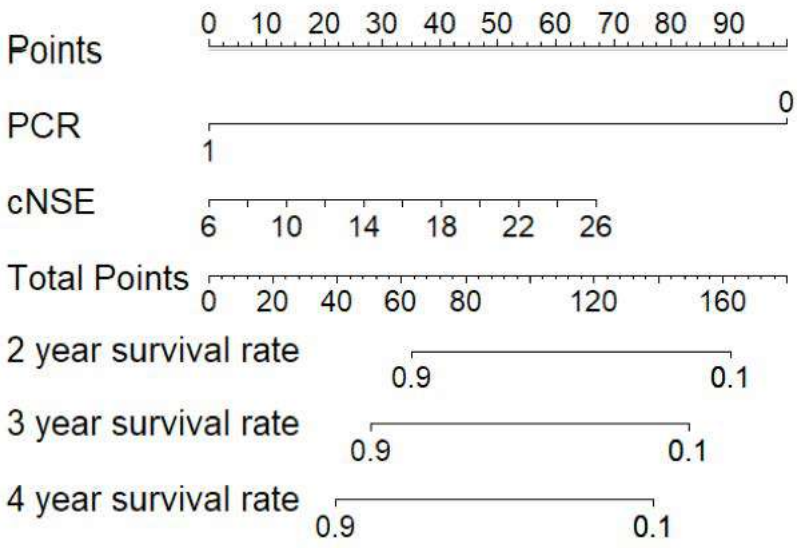
Introduction: Neoadjuvant immunotherapy notably enhances the prognosis of NSCLC patients by regulating the tumor microenvironment. However, some patients still suffer from recurrence after a radical operation with neoadjuvant treatment. This study aimed to estimate the blood markers at the beginning of treatment and before surgery, as well as other clinical characteristics and their relationship with recurrence.

Methods: IB-IIIB NSCLC patients undergoing surgery after neoadjuvant immunotherapy and at least one blood test were included.70% of patients were randomized to the training group and others to the validation group. A least absolute shrinkage and selection operator (LASSO)-derived Cox regression was used to figure out the risk factor to build a nomogram model. And evaluate the model through analysis of area under the curve (AUC), C-index, calibration plot, and decision curve analysis.

Results: 296 patients at Guangdong Provincial People's Hospital from 2019-2023 were enrolled, including 207 for the training group. Retrospectively collected patient profiles, treatment information, and blood examination findings. After filtering, NSE and PCR were selected for the nomogram. The model showed well in the calibration plot for both the training group and the testing group. The area under the curve (AUC) was 0.87 in the 3-year group, but only 0.525 in the validation group. The C-index was 0.757 in the training group and 0.55 in the test group.

Conclusions: In our study, we develop a nomogram model in order to identify recurrence.

Keywords: neoadjuvant, immunotherapy, nomogram



EP.07D EARLY-STAGE NON-SMALL CELL LUNG CANCER - QUALITY OF CARE
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EP.07D.01 Regional Longitudinal Evaluation of Treatment Patterns in Early-Stage Non-Small Cell Lung Cancer (ELEVATE)

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Introduction: Given the evolving treatment landscape in non-small cell lung cancer (NSCLC), varying management approaches and disparate factors affecting treatment decision across territories, understanding these differences is key to support more effective clinical practice. This study aimed to describe early-stage NSCLC treatment patterns and factors behind treatment choice in the Asia-Pacific (APAC) region.

Methods: Lung cancer specialists were recruited between June 2022 and July 2023. A cross-sectional survey was administered to eligible specialists. Responses related to treatment choice and considerations in early-stage NSC

Results: 212 specialists were recruited from Australia (n = 32), Hong Kong (n = 27), Singapore (n = 27), South Korea (n = 42), Taiwan (n = 42) and Vietnam (n = 42). Surgery followed by adjuvant chemotherapy was most commonly selected by respondents for Group A (62.6%-77.7%) and Group B (47.2%-63.5%) patients across territories. However, definitive chemoradiation was more commonly chosen for Group C. For adjuvant therapy, more respondents selected regimens with targeted therapy and immunotherapy for patients with oncogenic mutation (OM) and without OM, respectively. Overall, the proportion of respondents who selected regimens with targeted therapy (for patients with OM) or immunotherapy (for those without OM) was lower in Australia, compared with Hong Kong and Taiwan. Tumor size, Eastern Cooperative Oncology Group performance status (ECOG PS), nodal stage and lymphovascular invasion were some of the top factors considered by respondents when choosing neoadjuvant or adjuvant systemic treatments for patients with early-stage NSCLC. For Group A, there was a wide discrepancy in neoadjuvant treatment considerations between territories (e.g., 21.1% of Australian respondents selected presence of targetable biomarker, compared with 71.4% of Hong Kong respondents). Furthermore, when considering adjuvant therapy in Group C, 37.5% and 80.8% of respondents in Vietnam and Hong Kong selected ECOG PS of 0, respectively.

Conclusions: This study showed that treatment choice and considerations in early-stage NSCLC management differ widely across APAC territories. These may be due to drug reimbursement, local practices and patient factors (e.g. presence of OM). Our findings provide useful insights on whether real-world practice aligns with clinical guidelines, and enable clinicians to make more informed decisions.

Patient disease staging based on TNM descriptors (AJCC 8th edition)

Group A	Group B	Group C
1B, periphearl (T2a,N0)1, central (T1abc-T1a,N0)IIA (T2b, N0)IIB (T3 non-invasive, N0)	IIB (T3 invasive, N0)II (T1abc-T2ab, N1)IIIA (T3N1)IIIA (T4 no extension, N0-1)	IIIA (T1-2,N2)IIIA (T4 extension, N0-1)IIIB (T3,N2)

Keywords: Early stage non-small cell lung cancer, treatment pattern, regional

EP.07D EARLY-STAGE NON-SMALL CELL LUNG CANCER - QUALITY OF CARE
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EP.07D.02 Comprehensive Treatment Availability is Associated with Improved Outcomes Among Veterans with Early-Stage Lung Cancer Treated at VA Hospitals

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Introduction: Comprehensive, multidisciplinary care is essential for the management of early-stage lung cancer, for which the predominant treatment is either lung resection or stereotactic body radiotherapy (SBRT). The Veterans Health Administration (VHA) - the nation's largest integrated healthcare network - performs lung resections at approximately 100 different VHA medical centers; however, in-house SBRT is available in fewer than half of these centers. Therefore, comprehensive lung cancer care (i.e., availability of both surgery and SBRT) remains highly variable across VA sites. We sought to evaluate the association between variable access to SBRT and outcomes among Veterans with early-stage lung cancer receiving care within the VHA.

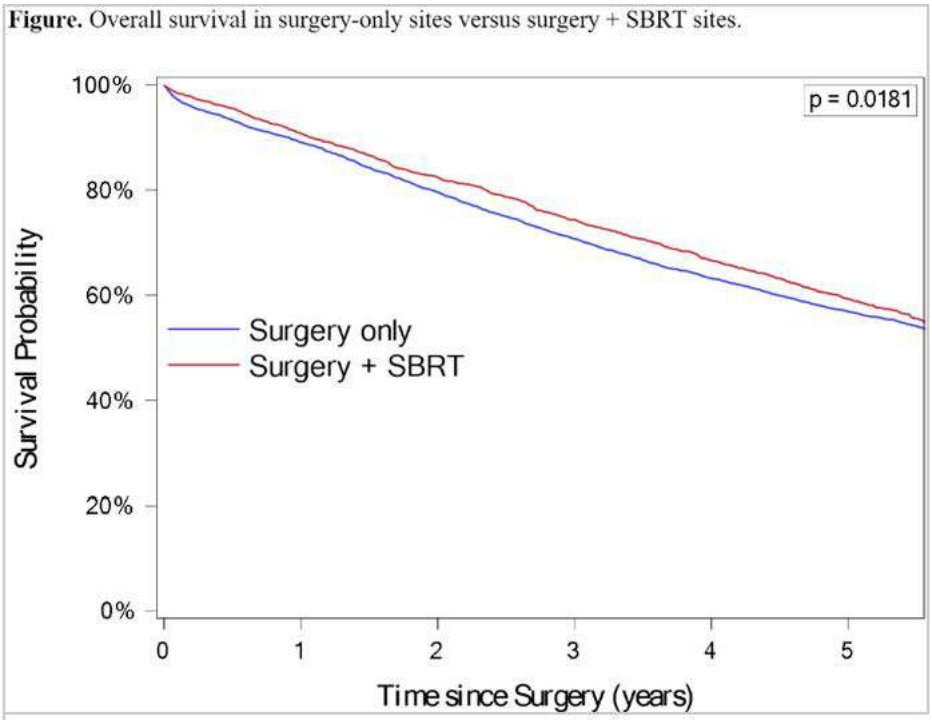
Methods: We performed a retrospective cohort study analyzing patients with clinical early-stage (≤5cm, N0) NSCLC treated with lung resection at a VHA medical center. Of the facilities performing lung cancer surgery, we further queried whether these centers had SBRT capabilities and, if so, confirmed when these capabilities were established. Patients were grouped by whether they underwent lung resection at a site with surgery-only versus a site with surgery + SBRT on the date of surgery. We compared short-term and long-term outcomes between surgery-only versus surgery + SBRT sites, including metrics related to quality of care (i.e., VALCAN-O operative quality score), patient selection (i.e., VALCAN-M mortality risk score), and overall survival.

Results: We identified 6,289 patients undergoing lung resection from 2006 to 2016, with 4,673 (74.3%) and 1,616 (26.7%) patients receiving care at a surgery-only versus a surgery + SBRT site, respectively. Sociodemographic factors were similar between the two cohorts. Patients undergoing lung resection at surgery + SBRT sites had significantly higher operative quality scores (point estimate 0.569, 95% CI 0.458-0.679, p<0.001) and lower operative mortality risk scores (point estimate -1.362, 95% CI -1.675--1.049, p<0.001). Short-term outcomes were better at surgery + SBRT sites with lower rates of 30-day major complication (OR 0.830, 95% CI 0.700-0.985), 30-day mortality (OR 0.552, 95% CI 0.348-0.874), and 90-day mortality (OR 0.588, 95% CI 0.424-0.815). With a median (IQR) follow-up of 6.3 (2.6-11.6) years, 5-year overall survival was higher at surgery + SBRT sites (59.4% vs 56.9%, p=0.02, Figure).

Conclusions: The short-term and long-term outcomes for Veterans with early-stage NSCLC undergoing lung resection were better at VA facilities with both thoracic surgery and SBRT capabilities. These findings support recommendations to increase the availability of SBRT at all VA medical centers offering lung cancer care.

Keywords: Lung Cancer, Comprehensive Care, VA Hospitals

Figure. Overall survival in surgery-only sites versus surgery + SBRT sites.



EP.07D EARLY-STAGE NON-SMALL CELL LUNG CANCER - QUALITY OF CARE
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EP.07D.03 A Quality Improvement Initiative to Address Biomarker Testing and Quality of Care Delivery for Early-Stage NSCLC at 3 Cancer Centers in the US

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Introduction: Despite advances in therapeutic options for non-small cell lung cancer (NSCLC), overall survival remains lower than other common malignancies. Those with early-stage NSCLC have the best opportunity for long-term survival, but suboptimal implementation of evidence-based diagnostics and therapies may negatively influence outcomes. In the US, cancer care in the community setting, where >80% of individuals with lung cancer receive care, is particularly susceptible to gaps in quality-of-care delivery. To address this, the Association of Cancer Care Centers (ACCC) has launched a two-phase quality improvement initiative to improve care for early-stage NSCLC in community and academic cancer centers.

Methods: Phase I included a national survey of providers to identify barriers to and facilitators of optimal care for early-stage NSCLC. In Phase II, survey results are used to guide selection of target areas (or key areas) for quality improvement projects at 3 cancer centers. The process included evaluating baseline data at each site to assess current patterns of care followed by a facilitated, multidisciplinary workshop, a 1-month follow-up, and 3-6-month interval QI project. Baseline data collection included patient demographics, biomarker testing rates, multidisciplinary tumor board (MTB) use, and patterns of adjuvant and neoadjuvant therapy delivery. Process-level data and descriptive statistics are reported as frequencies or percentages.

Results: Baseline data were evaluated on individuals with stage IB-IIIA lung cancers from 2020-2021 at 3 sites. Respectively, sites 1/2/3 had 20/40/10 lung cancers diagnosed; average ages of patients were 69/71/67 years; were 65%/50%/50% female; with histology that was 65%/52%/70% adenocarcinoma, 30%/40%/30% squamous cell, 5%/5%/0% other. Overall, 65%/62%/90% of these cases were discussed at MTB. EGFR testing was performed in 55%/45%/80% of cases, while PDL1 was performed in 55%/95%/80%. During each workshop, potential quality improvement solutions around key areas included biomarker testing, improving MTB reach, survivorship planning, and nurse navigation, shown in Table 1.

Conclusions: Biomarker testing proportions showed room for improvement, as did MTB use at two sites. Updated guidelines for biomarker testing are not sufficient to drive process change in cancer centers. A concentrated, multidisciplinary team effort is critical to ensuring equitable, efficient testing and optimized comprehensive care delivery.

Keywords: Biomarker, Quality, Multidisciplinary

Table 1.

	Problem Statements	Root Causes	Potential Solutions
Site 1	55% of patients with early-stage (IB to IIIA) NSCLC are not receiving actionable biomarker testing (*EGFR* and PD-L1), information critical to informing neoadjuvant and/or adjuvant treatment plans. On average, tests are ordered 13 days post-surgery (range of 0-56 days post- surgery). **Recommendation:** Order *EGFR, ALK*, and PD-L1 for all patients with early-stage (IB to IIIA) NSCLC at time of diagnosis.	Variations in what is ordered (PD-L1 vs *EGFR* vs both), when tests are ordered, and which reference labs perform testing. Lack of an automatic (pathology-driven reflex) testing protocol for early-stage NSCLC.	Develop and implement a pathology-driven reflex biomarker testing protocol for new patients diagnosed with early-stage NSCLC.
Site 2	45% of patients (n=40) with early-stage NSCLC were tested for EGFR. Among 22 patients with an adenocarcinoma component, 59% were tested for EGFR. **Recommendation:** Order *EGFR, ALK*, and PD-L1 for all patients with early-stage (IB to IIIA) NSCLC at time of diagnosis to guide treatment decisions regarding neoadjuvant and/or adjuvant treatment.	Lack of a standardized automatic (pathology-driven reflex) testing protocol for early-stage NSCLC. When tissue quantity is not sufficient (QNS), testing is not performed. Liquid biopsy (plasma testing) is not ordered.	Implementing a pathology-driven reflex biomarker testing protocol for new patients diagnosed with early-stage NSCLC. Issues to consider: Who will order the test? When will the test get ordered (at time of diagnosis vs at time of surgical resection)? If tissue is QNS, then who will order the liquid biopsy?
Site 3	Among patients with early-stage NSCLC, 90% of patients received biomarker testing at the time of surgical resection or later. Only 10% received biomarker testing at the time of initial diagnosis. **Recommendation:** Order *EGFR, ALK*, and PD-L1 at time of initial diagnosis to guide neoadjuvant treatment decisions.	Lack of biomarker testing protocol at the time of initial diagnosis. Test order may be delayed if patient is hospitalized (inpatient Medicare 14-day rule).	Implementing a pathology-driven reflex biomarker testing protocol for new patients diagnosed with early-stage NSCLC.

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EP.07D.04 Outcomes with Evolving Patterns of Neoadjuvant Therapy: A Population-Based Analysis

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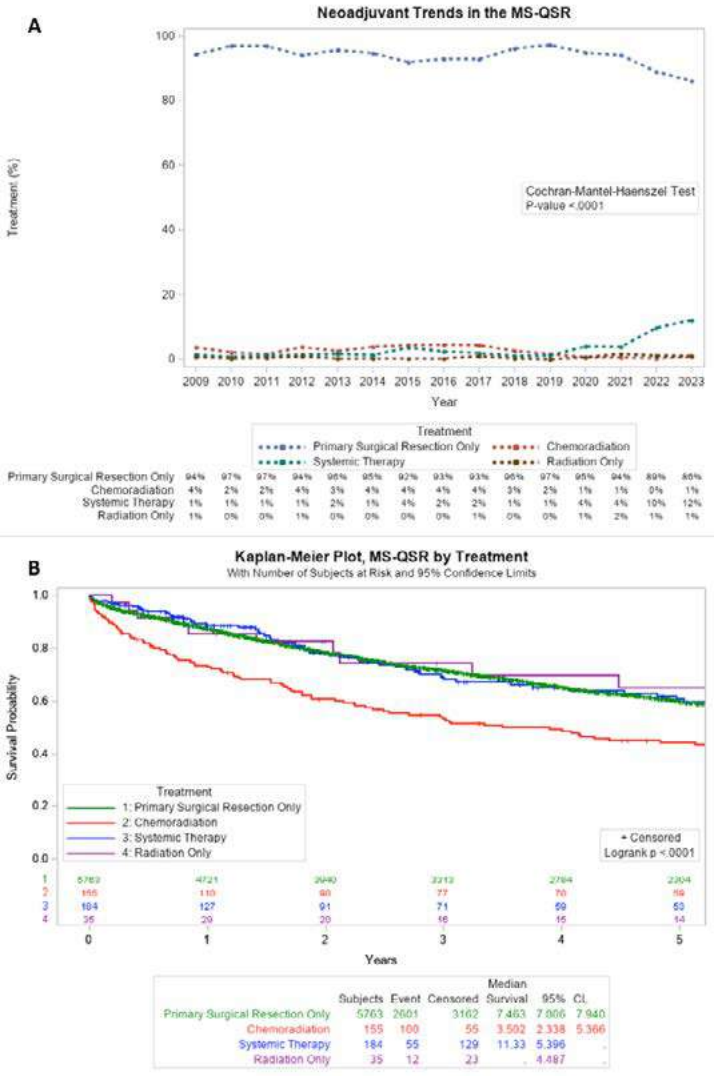
Introduction: Neoadjuvant chemo-immunotherapy is expanding surgical treatment options for patients with locally-advanced non-small cell lung cancer (NSCLC). We evaluated emerging trends in use of neoadjuvant therapy for resected NSCLC in a regional population-based cohort.

Methods: We categorized the Mid-South Quality of Surgical Resection cohort into patients with primary resection and neoadjuvant therapy. Neoadjuvant therapy was classified as: systemic therapy (chemotherapy and/or immunotherapy), radiation therapy only, and chemoradiation. We assessed treatment trends within the neoadjuvant categories using the Cochran-Mantel-Haenszel test and overall survival (OS) across treatment groups using standard statistical methods. With the primary surgery only cohort as reference, we constructed a Cox proportional hazards model including age, sex, race, aggregate clinical stage, and extent of resection.

Results: Of 6137 patients, 6.1% received neoadjuvant therapy: 3% received systemic therapy, 0.6% radiation therapy alone, and 2.5% chemoradiation. The use of neoadjuvant systemic therapy increased sharply in 2021, rising from 4% to 12% in 2023. Neoadjuvant chemoradiation decreased from 4% in 2009 to 1% in 2023 (p<0.0001; Figure Panel A). Survival of the neoadjuvant radiation therapy cohort was worse than others (Figure Panel B). In the Cox model, chemoradiation (aHR: 1.503, 95% CI: 1.222-1.848, p=0.0001) was associated with greater hazard than primary surgical resection (Table). Systemic therapy (aHR: 0.762, 95% CI: 0.583-0.998, p=0.0479) was associated with a lower risk of death, while neoadjuvant radiation only did not differ significantly (aHR: 0.707, 95% CI: 0.4-1.251, p=0.2335).

Conclusions: The use of neoadjuvant systemic therapy has rapidly risen since 2021, likely due to the increasing use of chemo-immunotherapy combinations. Neoadjuvant systemic therapy was associated with improved survival rates compared to chemoradiation and may also be associated with improved survival over primary surgical resection.

Keywords: Lymph Nodes, Neoadjuvant Therapy, Surgical outcomes



EP.07D.05 Molecular Testing Care Gap Analysis of EGFR Mutation for Early-Stage NSCLC Patients in Community Practices

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Introduction: Approvals of targeted therapies have rapidly increased over the past decade, leading to complex and frequently updated clinical guidelines. This trend has contributed to pervasive gaps in NCCN guideline-directed care. Here we report a care pathway analysis to characterize NCCN-recommended molecular testing rates in early stage NSCLC (eNSCLC).

Methods: The study analyzed de-identified data from Tempus' nationwide longitudinal electronic health records database, focusing on 18-89 year-old patients newly diagnosed with lung cancer in 2022. Patients were randomly sampled for abstraction of >120 data elements from their unstructured clinical documents, including progress notes, pathology reports, discharge summaries, and genomic testing results. 913 patients (289,317 unstructured clinical documents) across 4 community practices in the US were included. Curated data were independently reviewed by an oncologist and clinical data director and cross checked against ML/AI predictions to ensure data quality.

Results: 39 non-squamous, resected NSCLC patients with pathologic stage IB-IIIB [T3, N2] (n=39) were identified as qualifying for EGFR testing according to 2022 NCCN NSCLC Guidelines. 13/39 (33%) of these patients did not receive molecular testing for EGFR mutation. 10/13 (77%) untested patients had an actionable biomarker testing care gap (e.g. negative nodes or margins after surgery, no specified reason). 3/13 untested patients had no actionable biomarker testing care gap (e.g. unresectable via surgical attempt, patient refused treatment).

Of 26 EGFR tested patients, 22 (85%) patients received testing prior to adjuvant treatment to inform therapy selection. 4/26 (15%) of these patients harbored an actionable EGFR mutation. Patient demographics and insurance type were analyzed as possible explanations for care gaps.

Conclusions: This analysis revealed a significant care gap in eNSCLC patients receiving EGFR molecular testing, which is necessary for adjuvant TKI therapy eligibility per NCCN guidelines. Addressing this gap through healthcare interventions, such as care pathway automation tools, could improve adherence to guidelines, ultimately enhancing patient outcomes.

Keywords: Early NSCLC, NGS, EGFR

Table 1: Site level eNSCLC cohort attrition & EGFR testing rate

	Site 1 N	Site 1 % of previous	Site 2 N	Site 2 % of previous	Site 3 N	Site 3 % of previous	Site 4 N	Site 4 % of previous	Total N	Total % of previous
Total new lung diagnoses in 2022	403		810		342		128		**1,683**	
Sampled for analysis	354	(88)	270	(33)	197	(58)	92	(72)	**913**	**(54)**
Primary NSCLC diagnosis	230	(65)	125	(46)	140	(71)	55	(60)	**550**	**(60)**
No evidence of being in clinical trial	230	(100)	124	(99)	140	(100)	55	(100)	**549**	**(100)**
Available staging data	206	(88)	92	(74)	89	(64)	53	(96)	**440**	**(80)**
Early stage [Stage IB-IIIB]	61	(30)	21	(23)	25	(28)	18	(34)	**125**	**(28)**
Non-squamous	40	(66)	11	(52)	19	(76)	8	(44)	**78**	**(62)**
Resected	22	(66)	4	(36)	11	(53)	2	(25)	**39**	**(50)**
EGFR tested	15	(68)	3	(75)	8	(73)	0	(0)	**26**	**(67)**

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EP.07D.06 Characteristics of and Long-Term Outcomes of Non-Small-Cell Lung Cancer Diagnosed Among Young Adults in the United States

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Introduction: Recent studies have shown that overall survival among patients with resected stage I non-small-cell lung cancer (NSCLC) remains suboptimal, with only 70% of patients surviving 5 years after surgery. However, given that >95% of lung cancers are diagnosed among individuals aged >50 years, most analyses evaluating survival after lung cancer resection reflect outcomes among older adults and not younger adults. We evaluated the characteristics of and long-term outcomes of NSCLC diagnosed among young adults in the U.S.

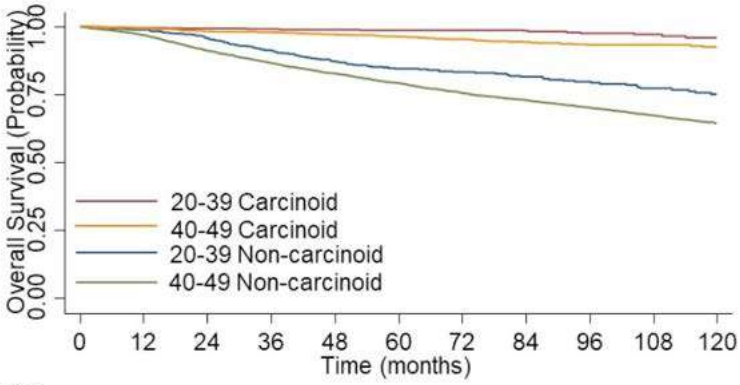
Methods: Patients aged 20-49 years diagnosed with NSCLC from 2004-2020 in the National Cancer Database were identified. Patients were grouped by age (i.e., 20-39, 40-49). We evaluated the tumor characteristics (e.g., stage at diagnosis, histology) within each age group. Among patients diagnosed with stage I NSCLC, we evaluated patterns in the receipt of surgery. Lastly, among patients undergoing surgery for stage I NSCLC, we evaluated 10-year overall survival stratified by age group and histologic subtype.

Results: A total of 60,647 patients met study inclusion criteria, of which 8,685 (14.3%) were aged 20-39 and 51,962 (85.7%) were aged 40-49. The proportion of patients aged 20-39 and 40-49 diagnosed with stage I lung cancer (as opposed to other stages) was 22.6% (n=1,962) and 15.0% (n=7,778), respectively. Over 20% (n=1,182) of lung cancers diagnosed among patients aged 20-39 were carcinoid tumors, compared to 5.6% (n=2,894) of lung cancers diagnosed among patients aged 40-49. Among patients with stage I disease, 93.4% and 91.3% underwent surgery, respectively. Ten-year survival for patients with resected stage I carcinoid tumors was very high, ranging from 93.5-96.1% (Figure 1). In contrast, 10-year survival among patients with resected stage I non-carcinoid tumors was only 78.0% (95% CI: 72.7-82.4) for patients aged 20-39 and 66.6% (95% CI: 64.9-68.2) for patients aged 40-49 (Figure 1).

Conclusions: In this national analysis of young adults diagnosed with NSCLC, only 15-22% of patients aged 20-49 were diagnosed with stage I NSCLC. Carcinoid histology comprised a considerable proportion of lung cancers in this age group, especially among patients aged 20-39. While 10-year survival among patients with resected stage I carcinoid tumors was excellent—ranging from 93-96%--long-term survival among young adults with resected stage I non-carcinoid tumors was notably worse, ranging from 67-78%.

Keywords: Non-small cell Lung cancer, Carcinoid, NCDB

Figure 1: Ten-year Overall Survival Among Young Adults Aged 20-39 and 40-49 With Resected Stage I Carcinoid vs. Non-carcinoid NSCLC in the National Cancer Database.



Number at risk											
20-39 Non-carcinoid	763	722	659	561	465	382	310	257	211	169	126
20-39 Carcinoid	1209	1142	1037	906	754	621	491	391	284	197	118
40-49 Non-carcinoid	6791	6426	5792	5053	4405	3744	3151	2658	2185	1737	1332
40-49 Carcinoid	1673	1598	1489	1311	1099	900	718	550	418	311	219

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EP.07D.07 Assessing the Adoption of Combined Immunotherapy and Chemotherapy in Eligible Patients with Non-Small Cell Lung Cancer

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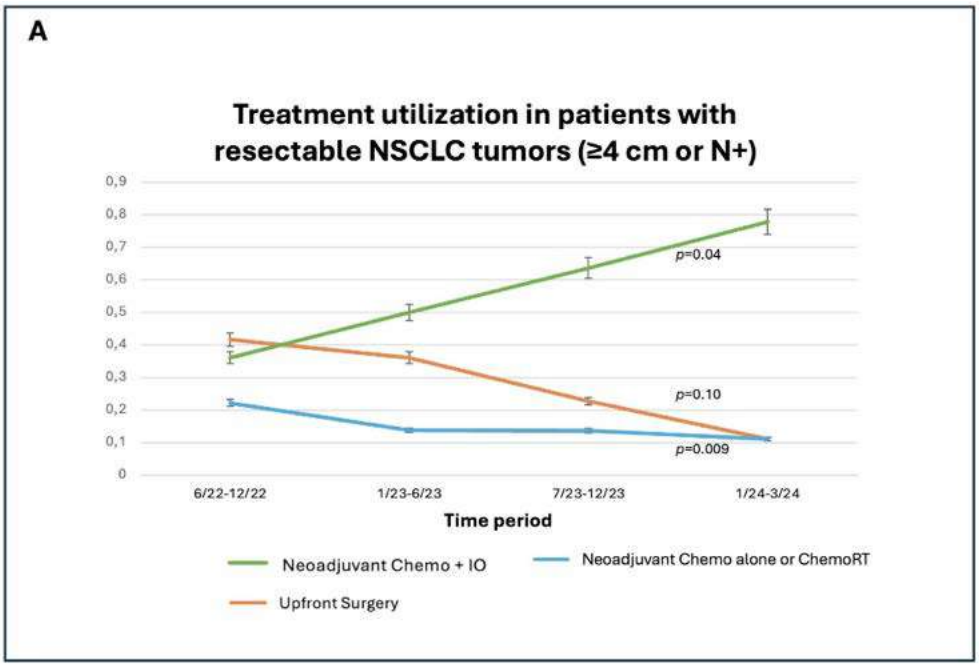
Introduction: Phase III trials of neoadjuvant chemoimmunotherapy utilizing immune checkpoint inhibitors followed by surgery have demonstrated favorable oncological outcomes in patients with resectable NSCLC. As a result, international guidelines now recommend neoadjuvant chemoimmunotherapy followed by surgery as standard of care. We assessed the adoption of neoadjuvant chemoimmunotherapy at our center after FDA approval in March 2022.

Methods: Patients who underwent surgery for NSCLC with tumors ≥4 cm or positive nodal disease from June 2022 through March 2024 were identified using an institutional database. Patients with N3 or oligometastatic disease were excluded. Demographics and preoperative workup were compared between patients who received neoadjuvant therapy (chemotherapy+/-radiation or chemoimmunotherapy) and patients with upfront surgery. Linear and logistic regression analyses were used to assess temporal trends in treatment.

Results: Of 103 patients who underwent resection of clinical stage IB-IIIB NSCLC during the study period, 69 (67%) received neoadjuvant therapy (52 chemoimmunotherapy, 17 chemotherapy+/-radiation). The patients who received neoadjuvant therapy were younger than patients with upfront surgery (66 vs. 72 years, p<0.001). Primary tumor size did not differ between groups, however, patients with cN1-2 disease received neoadjuvant treatment more frequently than patients with lesions ≥4 cm and negative lymph nodes (p<0.001). Significantly more patients who received neoadjuvant therapy underwent invasive mediastinal staging as compared with patients with upfront surgery (94% vs. 65%, p<0.001). Mutational testing was also more common among patients who received neoadjuvant therapy (PDL1 80% vs. 35%, p<0.001; EGFR 44% vs. 12%, p=0.003; ALK 45% vs. 12%, p=0.002). The use of neoadjuvant chemoimmunotherapy increased 6% per quarter (p=0.04) during the study period, while use of neoadjuvant chemotherapy+/-radiation and upfront surgery declined (p=0.009, p=0.10). (Figure 1A) Increasing age (OR=0.89, 95%CI 0.81-0.96), tumor size (OR=1.60, 95%CI 1.09-2.52), nodal involvement (OR=34.0, 95%CI 6.43-281.1), and time (OR=1.31, 95%CI 0.96-1.82) were associated with neoadjuvant treatment. Multinomial regression adjusting for these clinical factors demonstrated that patients were less likely to undergo chemotherapy+/-radiation (OR=0.71, 95%CI 0.50-1.02) or upfront surgery (OR=0.68, 95%CI 0.48-0.96), as compared with chemoimmunotherapy, as the study period progressed.

Conclusions: At our institution, the use of neoadjuvant chemoimmunotherapy in eligible patients with resectable NSCLC has increased significantly since June 2022, especially in patients with lymph node metastasis and large tumors. Multidisciplinary efforts are needed to ensure guideline-concordant care. Further real-world data showing trends in care and outcomes for patients with resectable NSCLC are needed to improve our decision-making as new treatment paradigms skyrocket.

Keywords: Non-Small Cell Lung Cancer, Neoadjuvant Therapy, Immunotherapy



Rate of adoption of chemoimmunotherapy over the time. (A) Time series plot showing the use of different treatment pathways over time for patients with tumors ≥4 cm or N+. Linear modeling of treatment rates indicated use of neoadjuvant chemoimmunotherapy increased 6% per quarter (p=0.04) while use of neoadjuvant chemotherapy+/-radiation and upfront surgery declined (p=0.009, p=0.10). Chemo, chemotherapy; IO, immunotherapy with immune checkpoint inhibitors; NSCLC, non-small cell lung cancer; RT, radiotherapy.

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EP.07D.09 A Global Study to Evaluate Access and Dynamics of Multidisciplinary Teams Care and Biomarker Testing in Early-Stage NSCLC

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Introduction: The treatment landscape in early-stage non-small cell lung cancer (NSCLC) has evolved significantly with approvals of perioperative treatment options. Multidisciplinary team (MDT) care is increasingly important given the multitude of treatment options and higher complexity in the decision making process. This ongoing study aims to understand access and dynamics of MDT care (including biomarker testing) in early-stage NSCLC and its impact on treatment selection across global geographies. To date, literature review has been completed with results presented in this abstract.

Methods: Our study employs a mixed-methods approach with three phases: 1) targeted literature review, 2) qualitative interview, and 3) quantitative online survey and patient chart review, in US, UK, Germany, Spain, Italy, Japan, Brazil, Turkey, Switzerland, Canada, and Mexico. Literature review was performed to identify existing evidence and clinical guidelines related to MDT care and biomarker testing in early-stage NSCLC. Pubmed was searched from inception to December 2023 using a combination of search terms related to MDT, NSCLC, and countries.

Results: Overall, 195 papers and 14 guidelines were identified, of which 90 papers and all 14 guidelines were included in the final review. Six of the 11 countries had guidelines recommending MDT care in early-stage NSCLC (Table 1). Furthermore, nation-specific guidelines from five countries mentioned biomarker testing for early-stage NSCLC. The most frequent topics reported in literature included time from diagnosis and staging to MDT care, patient outcomes associated with MDT, adherence to MDT and national treatment recommendations, and MDT member composition, logistics, and economic impact. Management of NSCLC by MDT was found to be associated with better survival outcomes. Key knowledge gaps in MDT literature include identifying ideal patient candidates for MDT care, and access to and outcomes from MDT care by patient characteristics such as disease stage. In addition, most published literature was generated from retrospective cohort analyses and primarily based on regional or single-clinic evaluation of MDT care. Regarding biomarker testing, timing of which could affect treatment decisions, most national guidelines did not reference early stage, and differences in access to and type of testing were identified.

Conclusions: While there are clinical guidelines recommending MDT care and biomarker testing in early-stage NSCLC, there is a lack of studies evaluating MDT and biomarker practices in NSCLC across global geographies, and the impact these practices have on treatment selection. Subsequent phases of this study aim to address the evidence gap through physician interview and survey across global geographies.

Keywords: Multidisciplinary care, Lung cancer, NSCLC

Table 1. Overview of national early-stage NSCLC treatment guidelines on MDT care and biomarker testing

Country	National NSCLC Treatment Guidelines on MDT	National NSCLC Treatment Guidelines on Biomarker Testing
United States	Guidelines: NCCN Guidelines V.1.2024 Recommending MDT care for early-stage NSCLC	Guidelines: NCCN Guidelines V.1.2024 Recommending biomarker testing for early-stage NSCLC (EGFR, ALK, PD-L1 for stage IB-IIIB)
Switzerland	Follows German guidelines, Onkopedia NSCLC Guidelines 2022 Recommends MDT care for minimum locally advanced or more advanced stage NSCLC	Follows German guidelines, Onkopedia NSCLC Guidelines 2022 Recommending biomarker testing for early-stage NSCLC (EGFR, ALK, PD-L1 for stage II-III resectable)
Japan	Guidelines: JLCS 2022, PAGA 2020 Recommending MDT care for minimum locally advanced or more advanced stage NSCLC	Guidelines: JLCS 2022 Not specified for early stage
United Kingdom	Guidelines: NICE 2024, NOLCP 2022 Recommending MDT care for early-stage NSCLC	Guidelines: NICE 2024, NOLCP 2022 Not specified for early stage
Germany	Guidelines: Onkopedia NSCLC Guidelines 2022 Recommends MDT care for minimum locally advanced or more advanced stage NSCLC	Guidelines: Onkopedia NSCLC Guidelines 2022 Recommending biomarker testing for early-stage NSCLC (EGFR, ALK, PD-L1 for stage II-III resectable)
Spain	Guidelines: SEOM 2022 Recommending MDT care for early-stage NSCLC	Guidelines: SEOM 2022 & SEAP 2022 Not specified for early stage (acknowledged to be useful in early stages)
Italy	Guidelines: AIOM 2021 Guidelines Recommending MDT care for early-stage NSCLC	Guidelines: AIOM 2021 Guidelines Recommending biomarker testing for early-stage NSCLC (EGFR and PD-L1 for stage II-IIIA)
Canada	No country-specific guidelines identified (provincial guidelines available)	Guidelines: Lung Cancer Canada 2014 Not specified for early stage (acknowledged to be useful in early stages)
Brazil	Guidelines: SBOC 2023 Recommending MDT care for early-stage NSCLC and for stage IIA-IIIB potentially resectable	Guidelines: BSP 2023 Recommending biomarker testing for early-stage NSCLC (EGFR, ALK, PD-L1 for stage I-III)
Mexico	Guidelines: IMSS 2019 Guidelines Recommending MDT care for early-stage NSCLC	Guidelines: IMSS 2019 Guidelines Not specified for early stage
Turkey	No country-specific guidelines identified	Guidelines: Federation of Turkish Pathology Societies 2021 Not specified for early stage

Abbreviations: AIOM, Italian Association of Medical Oncology; BSP, Brazil Society of Pathology; CAP, College of American Pathologists; IMSS, Mexican Social Security Institute; JLCS, Japan Lung Cancer Society; JSMO, Japanese Society for Medical Oncology; MDT, multidisciplinary team; NCCN, National Comprehensive Cancer Network; NICE, National Institute for Health and Care Excellence; NOLCP, National Optimal Lung Cancer Pathway; NSCLC, non-small cell lung cancer; PAGA, Pan-Asian Guidelines Adaptation; SBOC, Brazilian Society of Clinical Oncology; SEOM, Spanish Society of Medical Oncology.

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EP.07D.10 Deciphering Destiny: Is Curation of NSCLC Limited to Stage IA?

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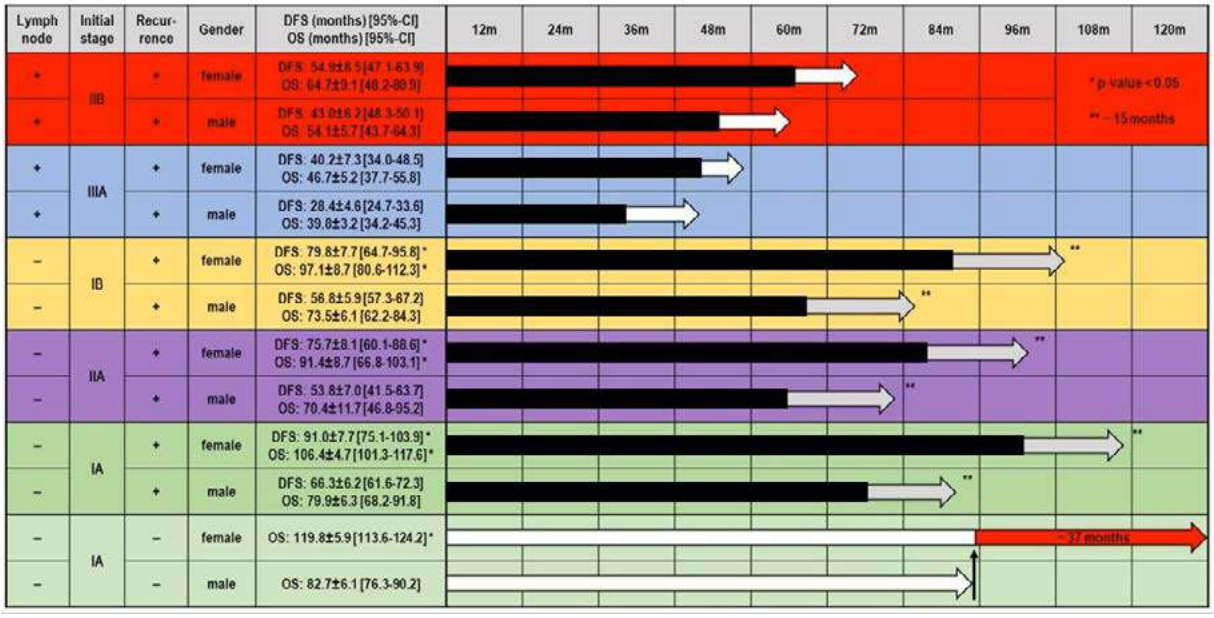
Introduction: 'Curative treatment' is offered to the majority of patients with localized NSCLC. According to the WHO, healthy women in industrialized countries have an approximately 39 months longer life expectancy than healthy men. Against this background, we analyzed gender-specific long-term survival in NSCLC patients and evaluated if cure with unrestricted life expectancy is achieved.

Methods: After applying the exclusion criteria (stage >IIIA, neoadjuvant therapy, positive resection margin, survival <90 days, non-adenocarcinoma or non-squamous cell carcinoma) we analyzed all consecutive patients who were anatomically resected for NSCLC at our institution between 2010 and 2022. Patients received adjuvant treatment in accordance with current guidelines. We compared female to male patients according to NSCLC stage and calculated overall survival (OS; months) and disease-free survival (DFS; months) defined as freedom from locoregional and distant metastasis. In early stage NSCLC we performed a propensity score matching (PSM) to avoid external factors influencing survival.

Results: A total of 4,052 resected patients were included. The patients' mean age was 66.2±8.9 years. We analyzed 1791 (44.2%) female and 2261 (55.8%) male patients. Metastatic lymph node involvement was a strong negative prognosticator affecting DFS (stage IIB: 54.9 vs. 43.0. p=0.177; stage IIIA: 40.2 vs. 28.4. p=0.303) and OS (stage IIB: 64.7 vs. 54.1. p=0.236; stage IIIA: 46.7 vs. 39.8. p=0.081) equally in all patients. Lymph node negative females had significant longer DFS (stage IB: 79.8 vs. 56.8. p=0.024; stage IIA: 75.7 vs. 53.8. p=0.029) and OS (stage IB: 97.1 vs. 73.5. p=0.036; stage IIA: 91.4 vs. 70.4. p=0.041) than male patients. In recurrence, patients with initial stage IB and IIA had a median OS of 15 months. In stage IA with PSM (p>0.05) for age, comorbidities, surgical access, smoking history and patients' fitness DFS and OS of female (n=457) patients were significantly longer than for males (n=457) (DFS: 91.0 vs. 66.3. p=0.008; OS: 106.4 vs. 79.9. p<0.0001). Interestingly, in a subgroup analysis of recurrence-free patients we found an approximately 37-month OS benefit for females over males in stage IA (119.8 vs. 82.7. p<0.0001). The hazard ratio was 2.39 [95%-CI: 1.24-5.06] for male versus female gender.

Conclusions: Due to earlier recurrence, male gender seems to have a negative impact on long-term survival after resection for NSCLC. Recurrence-free long-term survival in female patients is almost identical to the longer life expectancy of women in the healthy population. Consequently, one might argue that NSCLC can only be considered 'cured' at stage IA.

Keywords: gender-specific long-term survival, localized NSCLC, anatomic resection



EP.07E EARLY-STAGE NON-SMALL CELL LUNG CANCER- DEVELOPMENTS IN EGFR MUTATED EARLY STAGE NSCLC, SATURDAY, SEPTEMBER 7, 2024 - 11:58 - 11:59

EP.07E.01 Intrinsic Impacts of the Expression of PD-L1 On Postoperative Recurrence in EGFR-Mutated Lung Adenocarcinoma

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Introduction: The emergence of molecular-targeted agents and immune checkpoint inhibitors (ICIs) has resulted in a substantial paradigm shift in the perioperative treatment of early-stage non-small cell lung cancer (NSCLC). Therefore, information on EGFR mutations and the expression of PD-L1 is extremely important for the development of postoperative therapeutic strategies. However, the intrinsic impact of the PD-L1 expression status on postoperative recurrence in EGFR-mutated lung adenocarcinoma remains unknown. In this study, we explored the intrinsic impacts of the PD-L1 expression status on postoperative recurrence in patients with surgically resected EGFR-mutated lung adenocarcinoma.

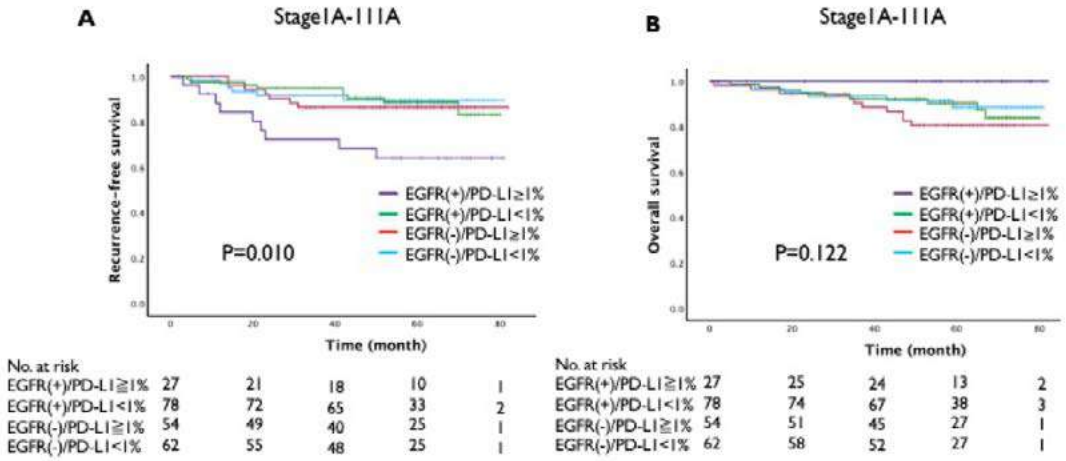
Methods: Data from 221 surgically resected pathological stage IA-IIIA lung adenocarcinomas, collected between January 1st, 2017, and December 31st, 2019, were analyzed. This included measurements of EGFR mutations and the PD-L1 expression. Recurrence-free survival (RFS) and overall survival (OS) were estimated using a Kaplan-Meier analysis and log-rank test. The independent risk factors for RFS were assessed using univariate and multivariate analyses.

Results: Among the patients, 140 were PD-L1-negative (<1%), while 81 were PD-L1-positive (≥1%). PD-L1 positivity was significantly associated with male sex (p=0.038), smoking habit (p=0.005), ND2 lymph node dissection (p=0.013), higher malignant subtype (p=0.003), higher histological grade (p=0.001), and advanced pathological stage (p=0.004). Conversely, EGFR mutations were more common in the PD-L1-negative group than in the PD-L1-positive group (p=0.006). Patients were categorized into four groups based on their EGFR mutation status and PD-L1 expression status: PD-L1-positive (≥1%) with or without EGFR mutations (EGFR(+)/PD-L1≥1% or EGFR(-)/PD-L1≥1%), and PD-L1-negative (<1%) with or without EGFR mutations (EGFR(+)/PD-L1<1% or EGFR(-)/PD-L1<1%). Among these groups, EGFR(+)/PD-L1≥1% cases exhibited the worst 5-year RFS (log-rank, p=0.010)(FigureA), while there was no significant difference in 5-year OS (log-rank, p=0.122) (FigureB). Furthermore, a multivariate analysis revealed that PD-L1 positivity was an independent significant factor for RFS in EGFR-mutated lung adenocarcinoma (p=0.013).

Conclusions: PD-L1 positivity emerged as an independent risk factor for RFS in patients with EGFR-mutant resected lung adenocarcinoma. These findings may provide valuable insights into the prognostic impact of PD-L1 expression and guide the implementation of postoperative adjuvant therapy in this patient population.

Keywords: EGFR-mutated lung adenocarcinoma, postoperative recurrence, programmed cell death ligand-1

Figure



EP.07E.02 Physician Prescribing Preferences for Adjuvant Osimertinib in Early-Stage EGFR-Mutated Non-Small Cell Lung Cancer

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Introduction: Following survival benefits demonstrated in the ADAURA trial, osimertinib, a third-generation EGFR-tyrosine kinase inhibitor (TKI), was approved for early-stage EGFRm non-small cell lung cancer (NSCLC) in many countries and recommended by major clinical guidelines as standard of care for adjuvant treatment. However, some eligible patients might not receive adjuvant osimertinib due to physician or patient prescribing barriers. Understanding the influence of treatment- and patient characteristics on physician prescribing preferences may help address such barriers. We aimed to understand physician preferences in prescribing adjuvant osimertinib for early-stage EGFRm NSCLC.

Methods: A two-phased study was conducted among board certified/eligible surgeons and medical oncologists (MOs) in the USA with experience treating NSCLC patients. Phase 1 included in-depth interviews to identify treatment- and patient-attributes influencing physicians' treatment decisions; phase 2 utilized a cross-sectional, internet-based survey to quantify the influence of those attributes. For MOs only, the survey included a rank-ordering exercise to evaluate treatment attributes relative to osimertinib prescribing behaviors and a Discrete Choice Experiment (DCE) to assess the influence of patient characteristics on prescribing osimertinib verses choosing to not prescribe osimertinib. Survey variables were analyzed descriptively and attribute-level preference weights from the DCE were estimated using hierarchical Bayesian models.

Results: Qualitative findings noted that MOs were the primary decision-makers for treatment selection, though surgeons were important for determining patients' eligibility for adjuvant treatment. In total, 154 physicians participated in the quantitative phase. Surgeons (N=54) perceived patients' NSCLC stage and resection margins as the most important factors for determining eligibility. The DCE found that 95% of the time, MOs chose to prescribe osimertinib over opting out, regardless of the combination of patient characteristics shown. MOs' preferences for prescribing adjuvant osimertinib were most influenced by patient hesitancy, NSCLC staging, and age, and least influenced by patients' prior treatment with neoadjuvant chemotherapy, with or without immuno-oncology agents (Table). Five-year overall survival of 85% and disease-free survival of 66 months were treatment characteristics most frequently ranked as facilitators to prescribing adjuvant osimertinib; costs (to patients and healthcare systems) were most frequently ranked as prescribing barriers.

Conclusions: MOs are key decision-makers on patients' eligibility for adjuvant osimertinib, and their decisions are predominately influenced by survival benefit from treatment and patients' willingness to adhere to treatment regimens. These results highlight the importance of ensuring clear patient communication and education on the benefits of adjuvant osimertinib.

Keywords: early-stage NSCLC, osimertinib, physician preferences

Table. Patient Attribute & Levels Influencing Preferences to Prescribe Adjuvant Osimertinib[1]

Patient Attributes & Levels	Mean Preference Weight (95% CI)
NSCLC Stage	
IB	-0.99 (-1.19, -0.79)
IIA	-0.47 (-0.61, -0.33)
IIB	0.33 (0.21, 0.45)
IIIA	0.82 (0.68, 0.96)
IIIB	0.32 (0.16, 0.48)
Resection Margins	
Resection with Negative Margins	-0.57 (-0.77, -0.37)
Resection with Positive Margins	0.57 (0.37, 0.77)
Neo Adjuvant Chemotherapy	
No neoadjuvant therapy	-0.02 (-0.16, 0.12)
Treated with neoadjuvant IO + chemotherapy	-0.04 (-0.16, 0.08)
Treated with neoadjuvant chemotherapy alone	0.07 (-0.03, 0.17)
Age	
45 years	0.33 (0.19, 0.47)
61 years	0.25 (0.15, 0.35)
78 years	-0.58 (-0.74, -0.42)
ECOG Status	
ECOG 0	0.40 (0.30, 0.50)
ECOG 1	0.17 (0.07, 0.27)
ECOG 2	-0.57 (-0.69, -0.45)
Patient Willingness by Treatment Duration	
Patient is willing to follow 3-years on osimertinib	1.18 (0.90, 1.46)
Patient is willing to try osimertinib for at least a year	0.45 (0.37, 0.53)
Patient is hesitant to try osimertinib	-1.64 (-1.94, -1.34)

[1]In the DCE, medical oncologists were shown a series of choice tasks with 2 hypothetical patient profiles that varied on the 6 attributes above. Oncologists were prompted to select which profile they were more likely to prescribe osimertinib to as adjuvant therapy, either alone or sequentially after chemotherapy. The absolute difference between the most and least preferred levels for each attribute represent the magnitude of influence an attribute had on preferences, relative to other attributes assessed.
Abbreviations: DCE: discrete choice experiment; NSCLC: non-small cell lung cancer; IO: immuno-oncology; ECOG: Eastern Cooperative Oncology Group

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EP.07E.03 TP53 Co-Mutations Increase Risk of Recurrence in EGFR-Mutated Stage I Lung Adenocarcinoma

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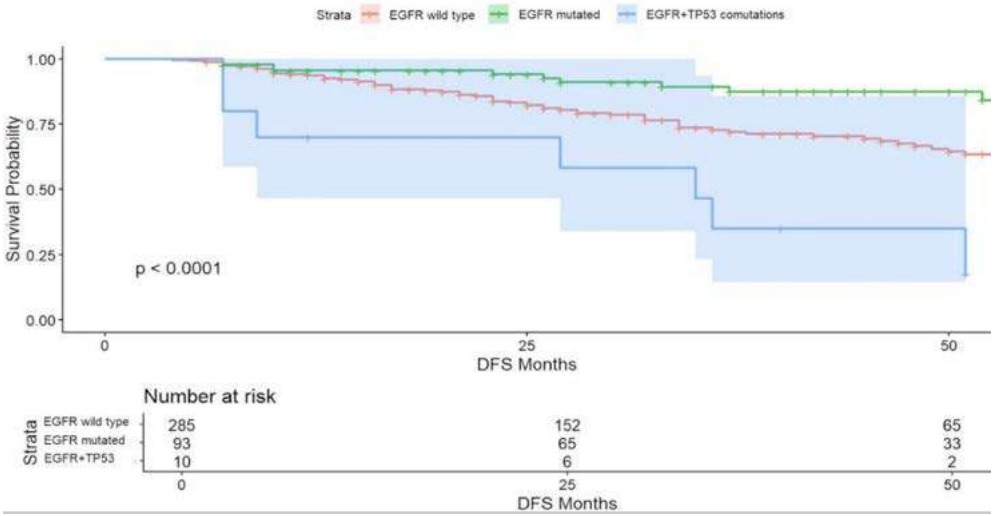
Introduction: EGFR mutations are the most prevalent oncogenic driver with a frequency in advanced LUAD ranging from around 10% in Western Europe to as high as 64% in East Asia. The ADAURA trial demonstrated significant clinical benefits in disease-free survival (DFS) and overall survival (OS) with the addition of adjuvant osimertinib in patients with resected EGFR-mutated stage IB to IIIA lung adenocarcinoma. However, beyond the ADAURA trial, the understanding of the prognostic implications of EGFR mutations in early-stage NSCLC remains rather limited. This study aims to assess the survival outcomes among patients with resected stage I LUAD with EGFR mutations by conducting a retrospective analysis using a multi-center cohort of patients.

Methods: Patients who underwent radical surgical treatment for stage I LUAD in two high volume centers with available postoperative molecular testing were collected between January 2017 to December 2022. Multivariate Cox regression was used to quantify the association between clinical and biological variables and the disease-free survival, in addition to hazard ratios and their 95% confidence intervals. Survival analysis and curves were achieved according to the Kaplan-Meier method. Disease-free survival (DFS) was compared using a log rank statistic.

Results: A total of 389 patients were included from two high volume centers. 73% of patients were male and a history of smoking was found in 301 patients. Most surgeries were performed via minimally invasive approaches (170 VATS and 98 Robot). The most frequent predominant histology was acinar LUAD (36.2%). On surgical pathology, 66 patients had lympho-vascular (LV) invasion and 83 had visceral-pleura (PL) invasion. EGFR mutation was found in 81 patients of which 10 harboured EGFR+TP53 co-mutations. In multivariable analysis, history of smoking (HR 2.35 95%CI 1.26-4-4, p=0.007), pT3 (HR 1.79 95%CI 1.04-3.1, p=0.035), MET amplification (HR 3.27 95%CI 1.14-9.4) and EGFR+TP53 co-mutation (HR 3.84 95%CI 1.32-11.2, p=0.013) were significantly associated with worse DFS. The survival analysis showed a significantly worse DFS for EGFR+TP53 co-mutation when compared to EGFR wild-type and EGFR single-mutation (fig 1, p=0.0001).

Conclusions: Our results suggest that TP53 co-mutation with EGFR for patients with completely resected stage I LUAD is a risk factor for early recurrence or death. These findings corroborate the aggressive biology associated with these molecular findings in metastatic patients.

Keywords: Lung Adenocarcinoma, Stage I, EGFR



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EP.07E.04 Efficacy and Safety of Anlotinib Plus EGFR-TKIs in Slowly or Locally Progressing NSCLC after Adjuvant Therapy with EGFR-TKIs

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Introduction: Anlotinib, a small molecule multi-targeting tyrosine kinase inhibitor (TKI), exhibits anti-tumor angiogenesis and inhibits malignant tumor progression. Due to the unclear mechanism of resistance to epidermal growth factor receptor (EGFR)-TKIs, new treatment strategies after resistance to EGFR-TKIs are continuously being explored in clinical practice. Combination therapy with EGFR-TKIs and anlotinib has been shown to inhibit tumors through multiple signaling pathways and improve the efficacy of EGFR-positive non-small cell lung cancer (NSCLC). This study evaluated the efficacy and safety of anlotinib combined with EGFR-TKIs for patients with NSCLC who developed resistance after postoperative adjuvant therapy with EGFR-TKIs.

Methods: From January 1, 2020, to December 31, 2023, 48 patients who underwent surgery at the Department of Thoracic Surgery, the First Affiliated Hospital of Zhejiang University School of Medicine and received adjuvant therapy with EGFR-TKIs but developed resistance (experiencing slow progression or local progression, or having a risk of potential disease progression) were included in this retrospective study. All patients were treated with anlotinib (10 mg, po, d1-14, q3w) plus EGFR-TKIs (original medication regimen). The primary endpoint was progression-free survival (PFS). Secondary endpoints included the 6-month and 12-month PFS rates, overall survival (OS), and safety. PFS was defined as the time from the start of treatment to disease progression or death. OS was defined as the time from the start of treatment to death from any cause.

Results: Of the 48 patients, 23 previously received first- or second-generation EGFR-TKIs, and 25 received third-generation EGFR-TKIs. As of March 25, 2024, the median follow-up time was 33.3 months (95% CI: 23.2-43.3). Thirty-three patients experienced disease progression or death, with a median PFS of 9.5 months (95% CI: 4.8-14.3), a 6-month PFS of 70.8%, and a 12-month PFS of 47.9%. For patients previously treated with first-/second- and third-generation EGFR-TKIs , median PFS were 10.3 months (95% CI: 6.1-14.4) and 7.7 months (95% CI: 4.8-10.6), with 6-month PFS of 69.6% and 72.0%, and 12-month PFS of 47.8% and 48.0%, respectively. The median OS was 31.0 months (95% CI: not reached [NR]-NR), with 6-month, 12-month, and 24-month OS rates of 91.7%, 85.4%, and 62.5%, respectively. For patients previously treated with first-/second- and third-generation EGFR-TKIs, median OS were NR and 20.3 months (95% CI: 10.7-30.0), respectively. Besides, OS rates were 95.7% and 88.0% at 6 months, 91.3% and 80.0% at 12 months, and 60.9% and 64.0% at 24 months. The incidence rates of any grade and grade ≥3 treatment-related adverse events (TRAEs) were 75.0% (36/48) and 10.4% (5/48), respectively . The most common TRAEs included hypertension (35.4%, 17/48), proteinuria (31.3%, 15/48), rash (22.9%, 11/48), fatigue (10.4%, 5/48), and diarrhea (8.3%, 4/48), with no new safety events reported. Dose reduction and discontinuation of anlotinib were reported in 4 (8.3%) and 5 (10.4%) patients, respectively.

Conclusions: For patients with NSCLC who experienced slow or local progression after postoperative adjuvant therapy with EGFR-TKIs, anlotinib in combination with EGFR-TKIs showed promising efficacy and manageable safety, providing such patients with a longer treatment window and survival opportunity.

Keywords: Anlotinib, NSCLC, EGFR-TKIs

EP.07E.05 Prevalence of EGFR Mutations (EGFRm)in Patients with Early-Stage NSCLC - Results from EARLY-EGFR Thailand Study

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Introduction: There is limited data on prevalence of EGFRm in early-stage NSCLC in Thailand. We report the prevalence of EGFRm and treatment patterns in patients with stage I-III NSCLC in the Thai subset of the EARLY-EGFR study.

Methods: EARLY-EGFR (NCT04742192), a prospective, multicountry, non-interventional study, enrolled patients with resected stage IA-IIIB (per AJCC 8th edition) non-squamous NSCLC from Mar 2021 to Oct 2022. The primary endpoint was EGFRm prevalence. Secondary endpoints included demographics, clinicopathological characteristics, EGFRm subtypes and treatment patterns. Categorical variables were compared with EGFRm using Fisher's exact test with Monte Carlo and logistic regression model to evaluate potential factors associated with having EGFRm.

Results: A total of 145 patients (median [range] age 64.0 [32.0-86.0] years) were enrolled at 3 centers; 70.3% were females and 77.2% were never-smokers. Of 145, most patients had stage I NSCLC (IA: 57.9%, IB:20.0%), tumor in right lung (70.3%), T1 tumor (60.0%), pN0 (88.3%), and adenocarcinoma histology (99.3%). High-risk pathological features were reported in 63.5% (61/96) of patients. The majority (69.0%; 100/145) of patients were diagnosed through a screening program. Multidisciplinary team discussions were conducted for 49.3% (71/144) patients. The overall prevalence of EGFRm was 63.4% (92/145) without significant differences between the stages and clinicodemographic characteristics. The prevalence of Exon-19 deletions and Exon-21 L858R were 44.6% (41/92) and 46.7% (43/92), respectively. Uncommon mutations included INS20 (n=2) and G719X, G719X+L861Q, G719X+S768I and other (n=1 each). Eight of 12 patients tested were PD-L1 positive (≥1%), of which 5 patients had EGFRm. Women had higher EGFRm rate than men (70.6% vs 46.5%; p=0.006). Most patients (87.6%) underwent only surgical resection with lobectomy (83.4%) with R0 resection (98.6%). Overall, adjuvant systemic therapy was prescribed in 18/145 patients (platinum-based chemotherapy [n=15], EGFR-TKI [n=2], immune checkpoint inhibitor [n=1]). In patients with stage IIA-IIIB NSCLC, adjuvant systemic therapy was prescribed in 46.9% (15/32). In the regression analysis, female gender was associated with an increased EGFRm rate (unadjusted odds ratio [OR], 2.76 [95% CI, 1.32-5.76], p=0.007; adjusted OR, 2.99 [95% CI, 1.07-8.34], p=0.036).

Conclusions: This real-world study reported a high prevalence (63.4%) of EGFRm in Thai patients with resected early-stage NSCLC, which was similar to the prevalence in metastatic disease. Majority of patients were stage I which demonstrated the early detection and treatment, but less than 50% of patients with stage IIA-IIIB were prescribed adjuvant systemic therapy, thus increasing access to adjuvant treatment in our population may help to optimize patient outcomes.

Keywords: Early-stage NSCLC, EGFRm, Thailand

Table: Proportion of EGFRm by demographic and clinical characteristics

Features		N=145 n (%)	*EGFRm* (N=92), n	*EGFR wild type* (N=53), n	Mutation rate (%)
Age (years)	<60	41 (28.3%)	27	14	65.9
	60-80	99 (68.3%)	60	39	60.6
	>80	5 (3.4%)	5	0	100
Gender	Female	102 (70.3%)	72	30	70.6
	Male	43 (29.7%)	20	23	46.5
Smoking	Current	9 (6.2%)	3	6	33.3
	Ex	24 (16.6%)	14	10	58.3
	Never	112 (77.2%)	75	37	67.0
Pathological stage (AJCC 8th edition)	I	113 (77.9)	73	40	64.6
	II	20 (13.8)	13	7	65.0
	III	12 (8.3)	6	6	50.0
Histology	Adenocarcinoma	144 (99.3)	92	52	63.9
	Mix	1 (0.7)	0	1	0
Lymph node metastasis	N0	128 (88.3%)	84	44	65.6
	N1	9 (6.2%)	5	4	55.6
	N2	8 (5.5%)	3	5	37.5
Primary tumor	T1	87 (60.0)	57	30	65.5
	T2	42 (28.9)	24	18	57.1
	T3	13 (9.0)	9	4	69.2
	T4	3 (2.1)	2	1	66.7

Note: No significant difference was reported for *EGFRm* rate as per smoking status, pathological stage, and lymph node metastasis. p-value not calculated for rest of the parameters.

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EP.07E.06 Long-Term Outcomes of Resected EGFR-Mutated Lung Adenocarcinoma - A Single Centre UK Experience

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Introduction: Epidermal growth factor receptor (EGFR) mutations are highly prevalent in specific lung adenocarcinoma subpopulations, including those with never-smoker status, East Asian ethnicity, and female gender1. Adjuvant third-generation Tyrosine Kinase Inhibitors (TKIs) improves survival in patients with resected EGFR mutation-positive NSCLC compared to adjuvant chemotherapy or placebo2. Despite their significance, limited data exists about the disease pattern of EGFR-mutated lung cancer in the United Kingdom (UK). This study aimed to identify patient characteristics and long-term outcomes after resection in patients with EGFR-mutated adenocarcinoma.

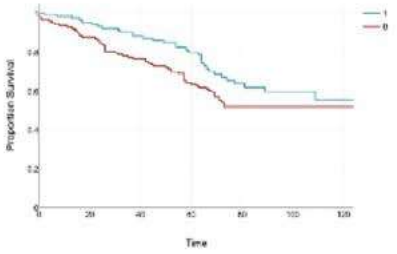
Methods: We conducted a retrospective, single-centre analysis of a prospectively maintained database. All EGFR-mutated resected lung cancers between 2013-2024 were included. A comparative group of EGFR-negative patients resected between 2017-2018 was used. Data collected included patient demographics, smoking history, EGFR status, treatment, recurrence, and survival. Primary outcomes were overall and disease-free survival. Statistical analysis employed Kaplan-Meier curves, log-rank tests, and Cox regression models to assess risk factors associated with mortality.

Results: We retrieved data for 135 EGFR-positive and 129 EGFR-negative patients with resected lung adenocarcinoma. Over 99% of patients were Caucasian and the incidence of EGFR mutation was 9.7%. Patients with EGFR-positive disease were more likely to be female (p=0.02) and never-smokers (p<0.001). 13.3% of EGFR mutation patients received adjuvant TKI therapy. After a mean follow-up of 55.5±30.26 months (median - 64 months), 94 (35.6%) patients had died, with significantly lower mortality in the EGFR-positive group (12.9% vs. 22.7%, p<0.001). EGFR-positive status was associated with improved overall survival (86.6 vs. 56.9 months, p=0.046) and cause-specific mortality (p=0.008) [see Figures 1&2]. Recurrence rates were similar between groups (p=0.24) as was recurrence-free survival (75.6 vs 58.3 months; p=0.95) [Figure 3]. Salvage TKI therapy was used in 54.1% of EGFR-positive patients with recurrent disease.

Conclusions: Our findings in this UK cohort align with reported epidemiologic trends in EGFR-mutated lung cancer. Although there was no difference in disease-free survival, overall survival was longer in EGFR-positive patients. This is likely, at least in part, due to salvage TKI therapy. This study underscores the prognostic significance of EGFR mutation in resected lung cancer. Limitations This study was single-centre and retrospective. The majority of patients underwent lung resection in the pre-adjuvant TKI era.REFERENCES1. Shigematsu H, Gazdar AF. Somatic mutations of epidermal growth factor receptor signaling pathway in lung cancers. Int J Cancer. 2006;118(2):257-262. Wu YL, Tsuboi M, He J, et al. Osimertinib in Resected EGFR -Mutated Non-Small-Cell Lung Cancer . New England Journal of Medicine. 2020;383(18):1711-1723.

Keywords: EGFR mutation, Survival, Tyrosine Kinase Inhibitors

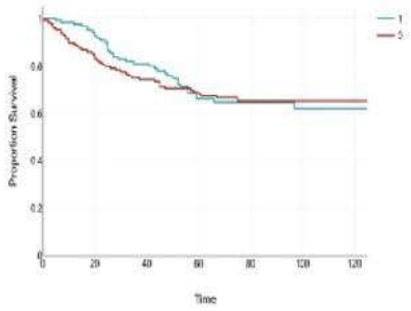
Figure 1: Kaplan-Meier survival plot between EGFR-positive and negative patients



0 = EGFR-negative, 1 = EGFR-positive

	Time	N of Remaining Cases	Event	Censored	Survivor Function	Std. Error	Lower 95% CI	Upper 95% CI
1	1	135	0	0	1	0	1	1
	12	127	1	9	0.98	0.01	0.96	1
	24	101	1	0	0.93	0.02	0.89	0.98
	60	60	1	0	0.8	0.04	0.72	0.88
0	0	129	0	0	1	0	1	1
	1	126	1	0	0.97	0.02	0.94	1
	12	121	1	0	0.93	0.02	0.89	0.97

Figure 2: Period of freedom from disease recurrence in EGFR-positive vs negative patients



	Time	N of Remaining Cases	Event	Censored	Survivor Function	Std. Error	Lower 95% CI	Upper 95% CI
1	1	135	0	0	1	0	1	1
	12	124	1	4	0.98	0.01	0.95	1
	60	54	2	3	0.66	0.05	0.57	0.76
0	1	129	1	0	0.99	0.01	0.98	1
	12	116	1	0	0.89	0.03	0.84	0.96
	60	89	1	0	0.68	0.04	0.6	0.76

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EP.07E.07 Adjuvant Aumolertinib in Patients with Completely Resected, Stage IA2-IIIA Non-Small-Cell Lung Cancer with Uncommon EGFR Mutations

Q. Zhang[1], L. Ke[1], S. Huang[2], Y. Yang[1], T. He[1], H. Sun[3], Z. Wu[1], X. Zhang[4], W. Lv[1], J. Hu[1], J. Ye[1], [1]The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou/CN,[2]Sir Run Run Shaw Hospital, Zhejiang University, Hangzhou/CN,[3]Taizhou Hospital, Zhejiang University, Taizhou/CN,[4]The First Affiliated Hospital of Wenzhou Medical University, Wenzhou/CN

Introduction: Epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs) exhibit reduced sensitivity and suboptimal treatment outcomes in non-small cell lung cancer (NSCLC) patients with uncommon EGFR mutations (EGFRm) compared to those with common EGFRm. Several real-world studies have demonstrated that adjuvant aumolertinib treatment exhibits excellent efficacy and safety among stage I to III NSCLC patients who have undergone complete tumor resection. However, Data on adjuvant aumolertinib treatment in NSCLC with uncommon EGFRm is not available. Therefore, this study aims to assess the efficacy and safety of adjuvant aumolertinib in completely resected NSCLC patients with uncommon EGFRm.

Methods: Completely resected, histologically confirmed stage IA2-IIIA non-squamous NSCLC patients with any uncommon EGFRm except EGFR Ex19del/L858R will be eligible for enrollment. Patients will receive oral aumolertinib at a dose of 110 mg once daily for 6 months to 3 years, depending on the pathological stage and individual physical conditions, until the discontinuation criteria are met. Disease-free survival (DFS), safety, and tolerability will be assessed, with patterns of recurrence and central nervous system (CNS) DFS designated as prespecified exploratory endpoints.

Results: We retrospectively collected the data of 8 patients with stage IA2-IIIA NSCLC patients and uncommon EGFRm. Among them, 5, 1, and 2 patients had G719X/L861Q/S768I, exon 20 insertion, and other mutations, respectively. The median age was 68.5 years (range 59-75), with 50% being female. At the data cutoff, the median follow-up duration was 18.9 months, and only one patient with exon 20 insertion mutations experienced mediastinal lymph node recurrence. No CNS recurrence was observed. DFS has not yet been reached, with 1- and 2-year DFS rates of 100% and 80% in the overall population, respectively. For stage I disease, the 2-year DFS rate was 100%. During aumolertinib treatment, no adverse events of grade ≥3 were reported. There were no new safety signals or concerns identified. Two patients (25%) experienced drug-related adverse reactions, presenting with rash (1/8, 12.5%) and cough (1/8, 5.5%).

Conclusions: This study represents the first investigation of third-generation EGFR-TKI adjuvant therapy in uncommon EGFR mutations. These findings highlight the promising efficacy of aumolertinib in the postoperative adjuvant treatment of NSCLC with uncommon EGFRm, coupled with an excellent safety profile. Long-term follow-up for our study is ongoing to explore additional survival outcomes.

Keywords: Aumolertinib, Adjuvant, Uncommon EGFR mutations

EP.07F EARLY-STAGE NON-SMALL CELL LUNG CANCER - MOLECULAR, MUTATIONAL, AND IMMUNOLOGIC FACTORS
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EP.07F.01 Extracellular Matrix in Early Lung Tumors Drive FAK Activation and Tumor Progression

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Introduction: Pre-cancerous lung lesions are initiated by activating mutations in upstream components of the RAS/ERK pathway, but do not transition to lung adenocarcinomas (LUAD) without additional mutations and events. Alterations in the tumor microenvironment can contribute to early progression and are interesting for their potential to be modified by environmental exposures. The extracellular matrix (ECM) glycoprotein Tenascin-C (TNC) promote epithelial cell division and migration and is normally expressed by lung fibroblasts during developmental branching morphogenesis and alveolarization. Exposure to particulate matter and fibrosis reactions can induce transient re-expression of TNC. Given the potential for pathological lung states to increase TNC expression, we investigated the role of TNC in early LUAD.

Methods: Using a KRAS-driven genetically engineered mouse model and clinical samples, we tested if TNC has a role in the transition of pre-neoplastic lesions to early LUAD. We deduced the mechanism of TNC signaling using a combination of direct in vitro assays and studies in precision cut lung slices and tumor tissue.

Results: We show that TNC is increased in the earliest stages of mouse model and human LUAD. TNC is produced by resident fibroblasts surrounding early LUADs, as well as tumor cells in some patients. KRAS-driven GEMMs of LUAD lacking TNC exhibit reduced tumor progression. Without TNC, the tumor cells at the tumor-stroma interface exhibited reduced FAK activity and S phase entry. TNC-mediated tumor cell FAK activation required integrin signaling, but not structural or mechanical changes in the tumor microenvironment.

Conclusions: We conclude that the activation of resident fibroblasts to produce TNC can drive early tumor growth and dissemination before the development of desmoplastic stroma. This suggests that TNC status could be used to prevent the overtreatment of early LUADs detected in early screening.

Keywords: early, extracellular matrix, Tenascin-C

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EP.07F.02 Preoperative Tumor-Derived Exosomes Enhanced the Accuracy of Identifying Spread Through Air Spaces from Intraoperative Frozen Sections

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Introduction: Lobectomy has been recommended as the preferred surgical procedure on stage IA patients with lung cancer spreading through air spaces (STAS). However, it posed an obstacle to identify STAS-positive disease intraoperatively as frozen sections were reported to have a low sensitivity. Our study aimed to establish a paradigm for recognition of STAS by combining preoperative blood test for tumor-derived exosomes with intraoperative frozen sections.

Methods: Blood samples were collected from a total of 700 patients with stage IA lung cancer in the Second Affiliated Hospital of Soochow University during August 2020 to August 2022 for detecting candidate genes within tumor-derived exosomes. Logistic regression analyses were performed to determine independent predictors of STAS. ROC curves were adopted to determine whether preoperative blood test could help improve the accuracy of intraoperative frozen sections for identifying presence of STAS.

Results: From our data, the sensitivity and specificity of intraoperative frozen section STAS were 46.3% and 92.2%, respectively. Regarding the candidate genes within tumor-derived exosomes, multivariable logistic regression confirmed MTA1, Twist, Slug and β-Catenin expression and ALK mutation were predictors of presence of STAS. Combination of preoperative blood test with intraoperative frozen sections significantly ameliorated the accuracy for identifying STAS with an area under curve of 0.937 (95% CI: 0.891-0.946).

Conclusions: A promising paradigm was established to recognize STAS in stage IA disease by detecting the five-gene signature within tumor-derived exosomes preoperatively combined with intraoperative frozen sections.

Keywords: lung cancer, spreading through air spaces, tumor-derived exosomes

EP.07F.03 The Mutation Landscape & Clinical Features of Taiwanese NSCLC Detected by Low-Dose CT

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Introduction: Low-dose CT(LDCT)' role in early lung cancer detection had been well established in heavy smoker. Taiwan Lung Cancer Screening in Never-Smoker Trial (TALENT) had also showed LDCT can be beneficial for non-smoker with family history. Health Promotion Administration, Ministry of Health and Welfare (HPA) of Taiwan, had conducted a free LDCT program for people for both heavy smokers and non-smokers with family history since July, 2022. This policy had drawn public awareness of LDCT application. Hence, we would like to explore the clinical features and mutation landscape of NSCLC patients detected by LDCT.

Methods: Taipei Veterans General Hospital NSCLC Cancer Database will be used to search from May 2021 to December 2022. De-identification paired genomics, pulmonary CT findings and patients' clinical factors were reviewed. For whole exome sequencing (WES) analysis, predefined pipeline was applied for sequence quality control, sequence alignment and variant calling.

Results: A total of 235 patients were included in this study, 169(69.4%) were non-smoker, 149 were female(63.6%), and 219(93.2%) were adenocarcinoma. Seventy-nine patients were detected by LDCT. There were no difference regarding age, sex, tobacco use and family history among patients detected by LDCT or not detected by LDCT. However, in LDCT group, there're more ground glass nodules (GGN) on CT (p<0.001), more early stage (p <0.001), and lower grading of adenocarcinoma (p <0.001). As for WES analysis, mutation counts was significantly lower in LDCT group; while single base substitution (SBS) 2 and SBS13, indicating the activity of APOBEC family of cytidine deaminases, were higher among non-LDCT group.

Conclusions: NSCLC patients detected by LDCT are clinically earlier in the disease status, and most patients detected by LDCT in our institute are never smokers. The WES analysis showed differenced among 2 groups, which should be further elucidated the underlying causes.

Keywords: low-dose CT, Whole exome sequencing, Non-smoker

Table 1. Demographic characteristics of patients in different detection methods.

	Overall patient	Disease detection methods		*p* value
	n=235	Detected by LDCT n=79	Not detected by LDCT n=156	
Age(range)	61(31-88)	57(31-79)	64.5(38-88)	0.578
Sex				0.262
Male	86 (37%)	25 (32%)	61 (39%)	
Female	149 (63%)	54 (68%)	54 (61%)	
Tabaco use history				0.718
Never	163 (79%)	56 (71%)	107 (69%)	
Current or Previous	72 (30%)	23 (29%)	49 (31%)	
Chest CT feature				<0.001
pure GGO	62 (26%)	34 (43%)	28 (18%)	
part-solid	72 (31%)	29 (37%)	43 (28%)	
solid	101 (43%)	16 (20%)	85 (84%)	
Family history of lung cancer				0.121
present	202 (86%)	15 (19%)	18 (12%)	
absent	33 (14%)	64 (81%)	138 (88%)	
Stage				<0.001
Tis	59 (25%)	34 (43%)	25 (16%)	
stage IA (MIA)	132 (42) [56 (18)%]	39(20) [49(25)%]	93(22) [60(16)%]	
stage II	16 (7%)	4 (5%)	12 (8%)	
stage III	22 (9%)	2 (3%)	20 (13%)	
stage IV	6 (3%)	0 0	6 (4%)	
Histology				0.034
Adenocarcinoma	220 (93%)	79 (100%)	140 (90%)	
Squamous cell carcinoma	8 (3%)	0 0	7 (5%)	
Adenosqaumous	4 (2%)	0 0	4 (3%)	
Others[#]	3 (2%)	0 0	5 (3%)	
WHO grading of adenocarcinoma				<0.001
grade 1	123 (52%)	63 (82%)	60 (41%)	
grade 2	32 (14%)	5 (7%)	27 (19%)	
grade 3	64 (27%)	8 (10%)	56 (39%)	
NA*	3 (1%)	1 (1%)	2 (1%)	

Data are median (range) or n(%). #1typical carcinoid tumor, 1 lymphoepithelioma-like carcinoma, and 1non-small cell carcinoma, subtype cannot be determined. *2 adenosquamous cell carcinoma, 1 enteric adenocarcinoma.

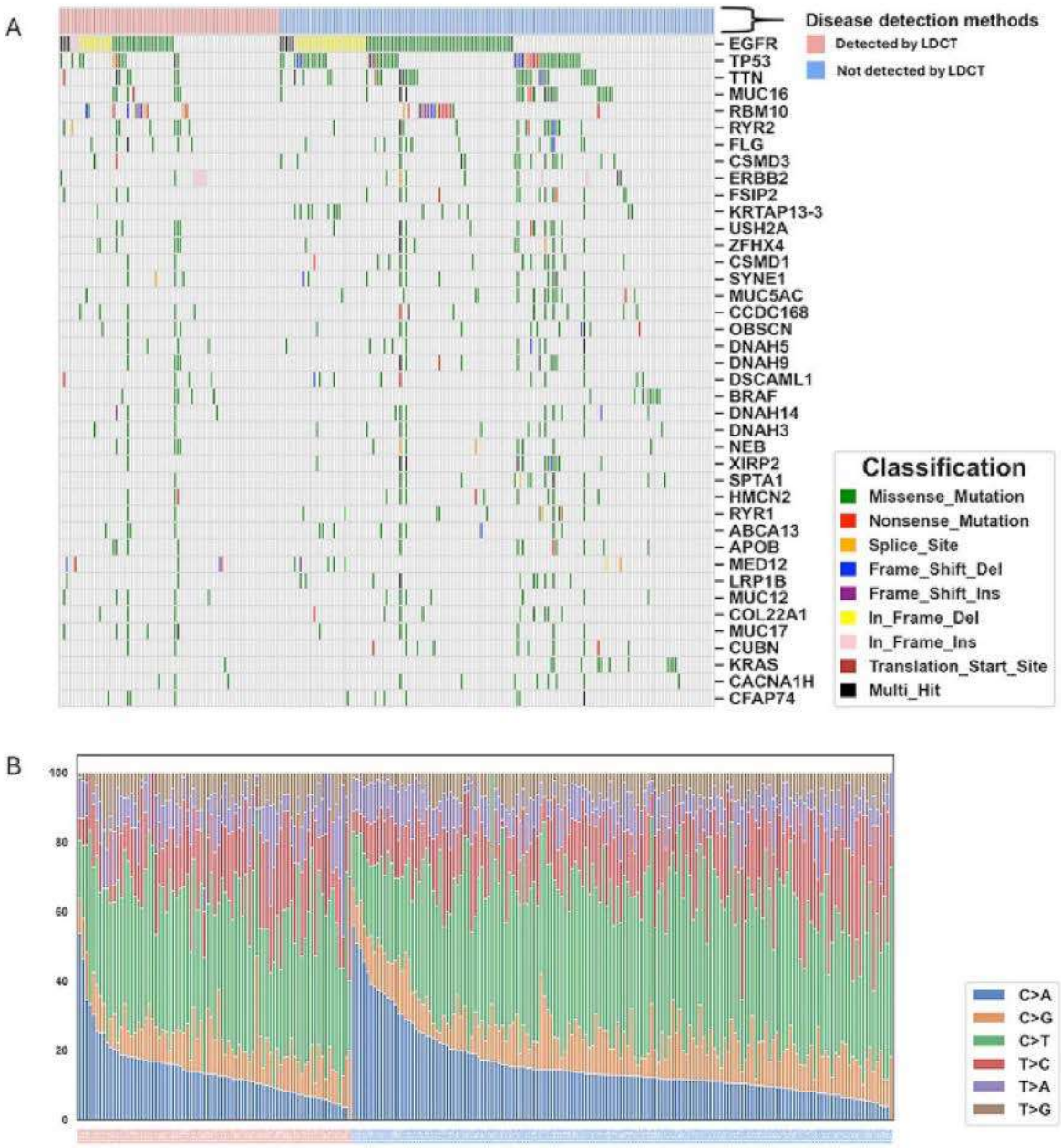

Figure 1. The mutation land scape of 235 patients.
A. Mutation color map of common cancer gene.
B. The percentage of single nucleotide variants (SNVs).

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EP.07F.04 Differences in High-Order, Three-Dimensional Chromatin Structure Between Tumor and Adjacent Normal Tissues in Lung Adenocarcinoma

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Introduction: Lung adenocarcinoma (LUAD) involves a complex interaction of gene expression alterations, resulting in variable modulation of key pathways that contribute to tumor cell growth. The higher order, three-dimensional (3-D) chromatin structure is often disturbed in cancer, and differences in genome-wide, higher-order 3-D chromatin structures in LUAD have yet to be characterized.

Methods: Thirty patients who had tumors occupying lung space on chest computed tomography (CT) and were prepared for prospective surgical treatment were prospectively enrolled. Sixteen paired tumor and adjacent normal tissue samples were included in the final analysis. One patient's (No. 10) samples were collected for Hi-C chromosome conformation experiments, and variances in 3-D chromatin structure and interactions in comparison to adjacent tissues were profiled. Long non-coding RNA (lncRNA)/RNA-seq data for all patients' samples were integrated to explore functional roles and mechanisms. Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes Genes and Genomes (KEGG) pathway enrichment analyses were used to investigate their underlying functions.

Results: Hi-C heatmaps comparing the whole genome between adjacent normal and tumor tissues revealed interactions between chromosomes 6 and 8 and chromosomes 13 and 15 in tumor tissues. Analysis of inter-chromosomal interactions by Circos plot demonstrated increased interactions from chromosome 17 to 11 and chromosome 15 to 5 in the tumor versus adjacent normal tissues. Chromosome X was confirmed to have decreased interaction with chromosomes 2 and 3 compared to the adjacent normal tissues. According to Hi-C analyses, chromosomes 11, 15 and X had a greater number of topologically associated domains (TADs) that were merged and shifted to intra-TAD boundaries in tumor tissues. The computerized Pearson correlation matrix indicated increases in component A/B location switching in chromosomes 11, 15 and X in tumor tissues. Especially in chromosome X, over 40% of the A compartment was switched to the B compartment in tumor tissues, indicating the gene loci may be switched from activated to inactivated.More up-regulated lncRNAs than down-regulated lncRNAs were found in chromosomes 15 and X in tumor tissues according to RNA-sequencing analysis. GO and KEGG pathway enrichment analyses demonstrated that many genes differentially expressed in tumor tissues were significantly enriched in biology regulation and metabolic processes. The 10 most up-regulated lncRNAs were located in the A compartment and shifted TAD boundaries of chromosomes 11, 15 and X.

Conclusions: Analyzing chromatin structure may be a potential method for identifying candidate biomarkers and molecular targets for gene therapies, and thus, may provide a valuable tool to better understand the gene and lncRNA regulatory networks responsible for LUAD.

Keywords: 3-D chromatin structure, lung cancer, Hi-C

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EP.07F.05 The Neutrophil/Lymphocyte Ratio Predict Lymph Node Metastasis in Patients with Clinical Stage T2 Non-Small Cell Lung Cancer.

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Introduction: Interest in the relationship between systemic inflammation and the development of cancer is increasing. The neutrophil-lymphocyte ratio (NLR) is used as an systemic inflammation marker, and its prognostic value in lung cancer patients has been recently reported. However, its impact on preoperative staging is still unknown. We investigated whether preoperative NLR can predict lymph node metastasis in patients with completely resected clinical T2 non-small cell lung cancer (NSCLC).

Methods: We performed 1019 lung cancer surgeries (tumor diameter between 3 cm and 5 cm) between 1993 and 2017. Patients with partial resection, bilobectomy, pneumonectomy, resection of surrounding organs, neoadjuvant therapy administration, loss of blood examination within 1month prior to surgery and those without radical mediastinal lymph node dissection were excluded from the study. Ultimately, the records of the 540 remaining patients (365 male and 175 fema1e, median age 69 years; range, 31-88) with clinical T2 NSCLC were evaluated retrospectively. Patients were divided into two groups according to lymph node metastasis: pathological nodal negative (pN0, n=373) and positive (pN1-3, n=167). We evaluated clinicopathological characteristics and preoperative NLR between the two groups.

Results: Median tumor diameter was 38 (31-50) mm. Median preoperative NLR, CEA, CRP and CRP/Alb ratio were 2.21 (range; 0.38-19.3), 4.5 (0.6-478) ng/ml, 0.13 (0-16.4) mg/dl, and 0.033 (0-5.11), respectively. There was no difference in age, gender, tumor size, tumor location, histological type, CRP, and CRP/Alb ratio between pN0 and pN1-3 groups. The ratio of lobectomy (91.4 vs 96.4%) and CEA (4 vs 5.6 ng/ml) were significantly lower in pN0 group compared to those of pN1-3 group, respectively. Median NLR were significantly lower in the pN0 group (2.14; range 0.34-19.3) compared to pN1-3 group (2.30; range 0.87-10.2) (p=0.045). When preoperative NLR were stratified by CRP, of the 395 patients with low CRP (≦0.5mg/dl), preoperative NLR was significantly lower in the pN0 group (1.99; range 0.38-6.12) (n=270) compared to those (2.22; range 0.59-7.64) in the pN1-3 group (n=125) (p=0.016). Although NLR increases with elevated CRP, there was no difference between two groups in patients with intermediate CRP (0.5-1 mg/dl) (2.39 in pN0 versus 2.94 in pN1-3, p=0.106) and high CRP(>1mg/dl) (3.09 in pN0 versus 2.86 in pN1-3, p=0.585), respectively.

Conclusions: Preoperative NLR, systemic inflammatory status, may be a predictor of lymph node metastasis in clinical T2 non-small cell lung cancer, especially in groups stratified by low CRP.

Keywords: Neutrophil/lymphocyte ratio, lymph node metastasis, systemic inflammation status

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EP.07F.06 Prospective Study of Breath Hold During SBRT Treatment of the Lung: Analysis Reliability of Surface Guidance Alone for Breath Hold

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Introduction: Respiratory motion management with breath hold (BH) is one technique to limit normal lung and other organ dose during SBRT treatments of the lung. Surface guidance (SGRT) using non ionizing 3D stereoscopic cameras to track the patient surface has been utilized for BH in larger targets such as breast cancer, but its reliability in BH treatments of small targets has not been investigated. We report the results of the reliability of utilizing SGRT alone as a technique for BH during a prospective study of treatment of primary and metastatic lung tumors.

Methods: An IRB approved prospective study was conducted in patients (pts) with primary NSCLC or lung metastasis undergoing SBRT. Eligible pts had at least 1 cm of respiratory associated motion on free breathing 4DCT. Pts underwent planning CT with BH either in end inspiration or expiration per investigator choice. During each SBRT treatment, pts performed BH and were aligned within tolerance based on the reference BH surface capture created from the BH planning CT. Pts underwent short-arc cone beam CT (CBCT) during BH for volumetric match of the target. Pts were then treated in BH with a tolerance of 3mm translations and 2 degree rotations. Treatment was stopped if pts fell outside of the predefined tolerances. Midway through treatment, pts underwent a second short arc CBCT during BH to verify the reliability of target position during BH treatment utilizing SGRT. Any subsequent shifts on target volumetric match after the second CBCT were recorded. Linear mixed models for repeated measures were used to analyze rotational and translational shift measurements.

Results: 21 pts and 65 SBRT fractions were treated utilizing SGRT alone for BH. 20 pts were treated with 54 Gy in 3 fractions and one patient had a central tumor treated to 50 Gy in 5 fractions. Mean free breathing range of motion (4D ROM) was 1.5 cm. Mean displacements after mid-treatment CBCT were minimal in all directions as shown in Table 1. Factors evaluated for association with shift magnitude included age, BMI, gender, tumor location, 4D ROM, and GTV and PTV size, but none of these were associated with increased shift amounts.

Conclusions: SGRT provides a reliable technique for BH SBRT treatments of the lung. Minimal target displacements on mid treatment BH CBCT were observed. Patients will be followed for toxicity and local control with comparison to free breathing SBRT to be reported in a subsequent analysis.

Keywords: Lung cancer, SBRT, breath hold

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EP.07F.07 Role of Microbiome in the Outcome of the Preinvasive Lung Cancer Lesions

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Introduction: Lung microbiota has received a lot of attention recently due to its potential role in the development and progression of many respiratory diseases, including lung cancer. However, the mechanisms by which the lung microbiota can influence lung cancer progression are not fully understood. Before the development of lung squamous cell carcinoma (LUSC), pre-invasive lesions can be observed in the airways. Longitudinal bronchoscopic surveillance of such lesions showed that the progression of these CIS lesions to cancer is not inevitable; only 50% of high-grade CIS lesions will progress to cancer within two years, whereas 30% will spontaneously regress. In this project, we aimed to dissect the role of the pre-invasive LUSC lesions' microbiome microenvironment in influencing the outcome of these lesions.

Methods: To identify the microbiome profile in pre-invasive CIS lesions, our whole-genome sequencing (WGS) data of 29 progressive and 10 regressive pre-invasive CIS samples (Teixeira VH et al, 2019) was analysed using different bioinformatic tools. Using 16S rRNA gene sequencing, the microbiome profile was identified in a new cohort of 30 progressive, 26 regressive CIS lesions and 21 matched normal lung epithelial tissue. Longitudinal microbiome changes were also defined in progressive preinvasive lesions (62 samples) in four different patients who underwent bronchoscopy every 6 months throughout 3 years. Bioinformatic analysis was done using Qiime2 platform. All statistical analysis was conducted in R (V4.1).

Results: Analysis of WGS data revealed that regressive CIS lesions exhibited higher bacterial alpha diversity compared to progressive CIS lesions. Furthermore, there was a difference in bacterial composition (beta diversity) between regressive and progressive CIS lesions. Regressive lesions displayed a higher abundance of Staphylococcus and Neisseria spp., while Haemophilus influenzae and Pseudomonas aeruginosa were predominant in progressive samples. These findings were consistent with the results of 16S rRNA gene sequencing, showing higher alpha diversity in regressive CIS lesions compared to progressive CIS lesions, and a difference in bacterial composition (beta diversity) between both groups. Significant differences were found in alpha and beta diversity between CIS lesions and normal epithelium, where normal samples showed higher diversity compared to CIS lesions. Moreover, variations in relative abundance and diversity were observed among longitudinal patient samples. the enrichment of the bacterial genera Sphingomonas, Corynebacterium, Staphylococcus, Enterococcus, and Streptococcus were found in CIS lesions. Additionally, the Cutibacterium genus was present in all CIS samples and increased during the transition to invasive cancer.

Conclusions: The difference in the bacterial diversity and composition between regressive and progressive CIS lesions might predict the outcome of these lesions. Regressive lesions have higher diversity, which might be correlated with immune surveillance. Certain bacterial species such as Haemophilus influenzae and Pseudomonas aeruginosa that identified in our study may contribute to lung cancer development and progression. Further experiments and data analysis are needed to validate the whole-genome and 16S rRNA gene sequencing analysis findings.

Keywords: Lung microbiome, Per-invasive CIS, lung squamous cell carcinoma

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EP.07F.08 Clinical Significance of Endothelial Programmed Cell Death Ligand 1 Expression in Patients with Non-Small Cell Lung Cancer

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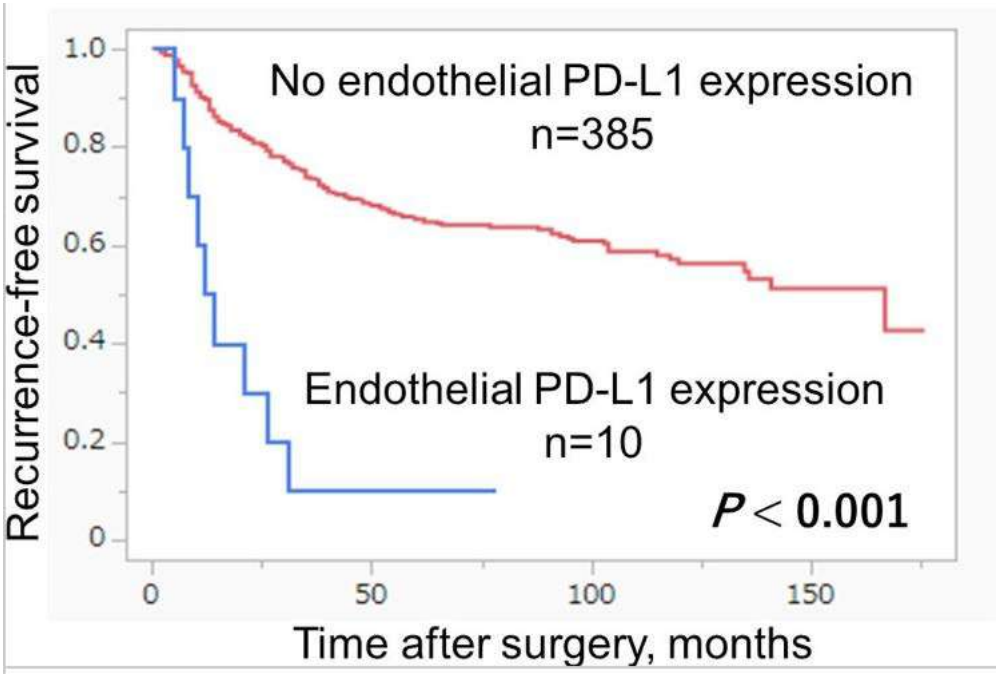
Introduction: Tumor endothelial cells (TECs) have been shown to promote immunosuppressive microenvironment by expressing co-inhibitory molecules such as programmed cell death ligand 1 (PD-L1). Our aim was to investigate clinical significance of PD-L1 expression on TECs in patients with lung cancer.

Methods: Three hundred and ninety-five patients with completely resected pathological stages IA to IIIA invasive non-small cell lung cancer (NSCLC) were investigated. Tumoral and endothelial expressions of PD-L1 were evaluated by immunostaining with 22C3 antibody. Primary endpoint was recurrence-free survival (RFS). The Kaplan-Meier estimation curve was used to visually analyze the RFS. The log-rank test was used to determine differences in RFS. Univariate and multivariate Cox proportional hazard models were used to evaluate association of RFS with clinical and pathological characteristics. Patients' characteristics included age, sex, body mass index, smoking status, carcinoembryonic antigen level, histologic type, pathological stage, vascular invasion, lymphatic permeation, tumoral PD-L1 expression, and endothelial PD-L1 expression. Multivariate analysis included the factors showing P < 0.05 in univariate analysis. P < 0.05 was considered as statistically significant.

Results: : Median age was 69 years (range, 37 to 88), and male accounted for 63.8% (252 of 395). Pathological stages IA and IB accounted for 51.4% (203 of 395) and 26.1% (103 of 395), respectively. Adenocarcinoma accounted for 72.9% (288 o 395). Hundred and sixty-two (41.0%) out of 395 patients experienced postoperative recurrence. Endothelial PD-L1 expression was observed in 10 (2.5%) of 395 patients, whereas tumoral PD-L1 expression (≥1%) was detected in 142 patients (35.9%). Univariate analysis detected age, sex, smoking status, serum carcinoembryonic antigen level, pathological stage, vascular invasion, tumoral PD-L1 expression, and endothelial PD-L1 expression as potential prognosticators. Multivariate analysis revealed age, pathological stage, vascular invasion, and endothelial PD-L1 expression as independent prognostic factors (P = 0.028, < 0.001, < 0.001, and 0.008, respectively). Hazard ratio of endothelial PD-L1 expression was 2.69 with confidence interval of 1.30-5.58.

Conclusions: Our results indicated that endothelial PD-L1 expression might be associated with poor prognosis. Further investigation is necessary to validate our results.

Keywords: PD-L1, Endothelial cell, non-small cell lung cancer



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EP.07G.01 Computed Tomography Features of Pathological Stage IA Lung Adenocarcinoma Showing Spread Through Air Spaces.

T. Saito[1], Y. Kono[1], Y. Ueno[1], N. Maru[1], T. Utsumi[1], H. Matsui[1], Y. Taniguchi[1], H. Hino[1], K. Tsuta[1], O. Honda[1,2], T. Murakawa[1], [1]Kansai Medical University, Osaka/JP,[2]Himedic Clinic WEST, Osaka/JP

Introduction: Our aim of this study was to characterize radiological features on computed tomography of pathological stage IA lung invasive adenocarcinoma showing spread through air spaces (STAS).

Methods: Hundred and ninety-five patients undergoing complete resection with lobectomy for pStage IA lung invasive adenocarcinoma were included in this study. Following radiological characteristics on preoperative computed tomography (CT) were retrospectively reviewed: total size, solid size, consolidation-to-tumor ratio, vascular convergence, air bronchogram, cavitation, lobulation/notch, pleural indentation, and spiculation. In this study, two radiologists (Y.K. and O.H.) independently assessed the CT characteristics. If the initial assessments showed disagreement, a final decision was made by the third radiologist (Y.U.). All the three radiologists were blinded to the STAS status of the assessed patients. Univariate regression analysis was used to explore association between STAS and patients' characteristics (i.e. CT features and baseline characteristics [age, sex, body mass index, preoperative carcinoembryonic antigen level, and cStage]). Multivariate logistic regression analysis that included the factors showing $P < 0.05$ in univariate analysis was used to identify independent factors associated with STAS. $P < 0.05$ was considered as statistically significant.

Results: Median age was 69 years (range, 38 to 84), and male accounted for 53.3% (104 of 195). Both recurrence-free and overall survival was significantly worse in patients with STAS ($P < 0.001$ and $P = 0.009$, respectively). Univariate analysis revealed presence of vascular convergence, absence of air bronchogram, presence of cavitation, and presence of ground-glass opacification as candidate predictive factors of STAS. Multivariate analysis revealed presence of vascular convergence, absence of air bronchogram, and presence of cavity as independent predictors of STAS (odds ratio, 3.48, 95% confidence interval, 1.61-7.72, $P = 0.001$; odds ratio, 2.92, 95% confidence interval, 1.23-6.93, $P = 0.012$; odds ratio, 3.01, 95% confidence interval, 1.04-8.72, $P = 0.048$, respectively).

Conclusions: Our results indicated that vascular convergence, air bronchogram, and cavity might be predictive of STAS in pStage IA lung adenocarcinoma. Further investigation with prospective study is necessary to identify preoperative predictors of STAS.

Keywords: STAS, Vascular convergence, pStage IA

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EP.07G.02 Nomogram Model for Predicting Risk of Spread Through Air Space in Stage IA Sub-centimeter Non-Small Cell Lung Cancer

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Introduction: To investigate the correlation between spread through air space (STAS) of stage IA sub-centimeter non-small cell lung cancer and clinical features and imaging features, constructing a nomogram risk prediction model to provide a reference for the preoperative planning of sub-centimeter lung cancer patients.

Methods: The data of patients with stage IA sub-centimeter non-small cell lung cancer who underwent surgical treatment in Nanjing Drum Tower Hospital Nanjing University from January 2022 to October 2023 were retrospectively collected. Based on the presence or absence of STAS in pathology results, they were divided into STAS positive and STAS negative groups. The independent risk predictors of STAS in clinical and imaging characteristics were selected by univariate and multivariate logistic regression analysis and then used to construct a nomogram. The sensitivity and specificity were calculated based on the Youden index, concordance index (C-index), receiver operating characteristic (ROC) curve and calibration plots were used to evaluate the performance of the model.

Results: A total of 112 patients were collected, including 17 patients in the STAS positive group and 95 patients in the STAS negative group. Univariate logistic regression analysis showed that male, anti-GAGE7 antibody positive, mean CT value and spiculation were associated with the occurrence of STAS; multivariate logistic regression analysis showed that male(OR=5.974, 95%CI: 1.495-23.872), anti-GAGE7 antibody positive(OR=11.760, 95%CI: 1.619-85.408) and mean CT value (OR=1.008, 95%CI: 1.004-1.013) were independent predictors of STAS positivity. The nomogram based on the above factors achieved good predictive performance for STAS; C-index was 0.890, sensitivity was 0.765, specificity was 0.916 and calibration curve was well-fitted.

Conclusions: Male, anti-GAGE7 antibody positive and mean CT value were independent predictors of STAS positivity of stage IA sub-centimeter non-small cell lung cancer, the nomogram model established in this study had good predictive performance, and provide reference significance for preoperative planning of patients.

Keywords: Sub-centimeter lung cancer, Spread through air space, Nomogram

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SATURDAY, SEPTEMBER 7, 2024 - 11:58 - 11:59

EP.07G.03 Radiologic Predictors of Angiolymphatic Invasion in Patients with Non-Small Cell Lung Cancer (3.0mm-30.0mm)

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Introduction: Angiolymphatic invasion (ALI) has been recognized as an important prognostic indicator for NSCLC patients. However, few studies focus on radiologic features for predicting ALI for patients with small-sized NSCLCs (3.0mm-30.0mm). The aim is to identify radiologic features for predicting ALI in patients with non-small cell lung cancer (NSCLC) (3.0mm-30.0mm).

Methods: Retrospective review of patients enrolled in XXX Hospital between 2016 and 2023. Preoperative diagnostic radiologic features suggestive of ALI were evaluated. Multivariable logistic regression analysis, adjusted for sex, age, nodule size, and smoking status, was used to determine predictors of ALI. Model performance was analyzed with the area-under-the-receiver-operating-characteristic-curve (AUC).

Results: Of 778 NSCLC patients with resected NSCLCs 3.0mm -30.0mm in maximum diameter, 715(92%) had solid NSCLCs, 41(5%) had part-solid NSCLCs and 22(3%) had nonsolid NSCLCs. 271(34%) of 778 had documented ALI, all in solid NSCLCs, none in subsolid NSCLCs. For these 715 solid NSCLCs (41% male and 59% female, median age 69 years [IQR: 63-76]), multivariable logistic regression analysis showed that lollipop sign (OR=4.12, P<.001) and spiculation (OR=2.13, P=.004) were independent predictors of ALI, with AUC of 0.77. When considering only patients on whom volume doubling time (VDT) could be calculated, multivariable logistic regression suggested that VDT was also a significant predictor for ALI (OR=0.96, P<.001) and incorporating VDT into the model led to an improved ALI prediction (AUC=0.82, P<.001)

Conclusions: For patients with NSCLC ≤30.0mm, ALI was only present in solid NSCLCs. Among solid NSCLCs, lollipop sign, spiculation and volume doubling time were independent radiologic predictors of ALI.

Keywords: Radiologic, Angiolymphatic invasion, Non-small cell lung cancer

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EP.07G.04 Clinical Implications of Spread Through Air Spread as Prognostic and Predictive Factors for Patients with Stage IA-B Non-Small Cell Lung Cancer

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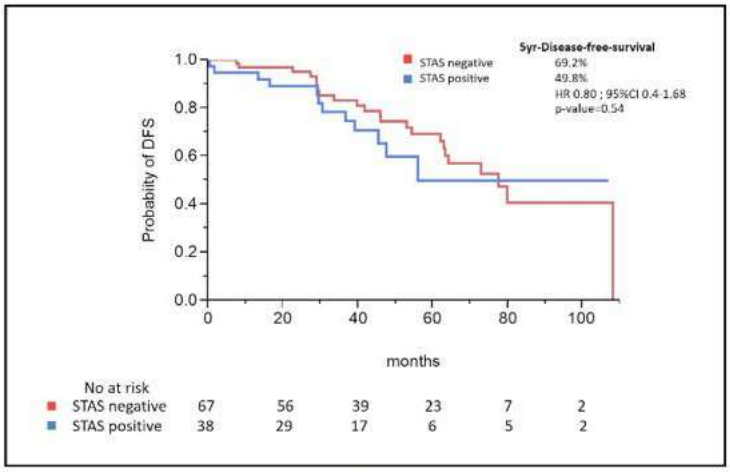
Introduction: Spread through airspaces (STAS) is recognized in the new 2021 WHO Classification of Lung Tumors as a histological feature with worse prognostic significance in early stage of adenocarcinoma of lung. This study aimed to elucidate the correlation between the histological feature of STAS and survival outcomes, and to investigate the effect of adjuvant chemotherapy in stage IA/B of adenocarcinoma of lung with STAS-positive patients.

Methods: This study was historical (retrospective) cohort design with data collected via chart and histology reviews of patients with stage IA/B of NSCLC who were undergone resection in Phramongkutklao hospital between January 2013 and December 2021. Demographics, comorbidities, pathological findings were collected. Disease-free survival was compared among patients stratified by STAS subtypes as primary endpoint. Secondary end points were univariate and multivariate correlations between clinicopathological features and DFS.

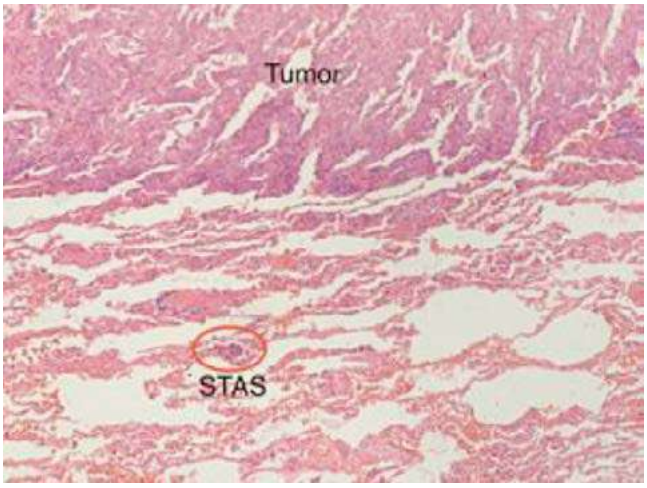
Results: One hundred and five eligible patients were enrolled. 67 of 105 patients (63.8%) were STAS-negative, and 38 of 105 patients (%36.2) STAS-positive. There was no significant difference among other aggressive histologic features between two groups. The 5-year DFS of patients with STAS-negative, and -positive were 69.2%, and 49.8%, respectively. The difference between patients with STAS-negative, and -positive was not statistically significant in either group (p-value = 0.23). Univariate analysis showed a statistically significant association with stage IA-IB, well-, moderate-differentiation, number of lymph node involvement, ALK status, receiving adjuvant chemotherapy, and schedule of follow-up visits with imaging. Multivariate analysis showed that well-differentiation, number of lymph node involvement, and schedule of follow-up visits with imaging were independent prognostic factors on DFS.

Conclusions: Patients with STAS-positive was insignificant correlated with worse DFS. The presence of STAS may be useful in predicting the clinicopathological significance and prognosis of patients with early stage of NSCLC. Therefore, STAS status might be another significant impact on decision marking for patients with early-stage NSCLC.

Keywords: Spread through airspaces (STAS), Non-Small Cell Lung Cancer (NSCLC), progression free survival (PFS)



Kaplan-Meier curves for disease-free survival (DFS). Patients with stage I NSCLC; patients with the STAS-positive (group A), and patients with STAS-negative (group B).



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EP.07G.05 Maximum Standardized Uptake Value and Cell-Free DNA to Predict Adjuvant Therapy in Resectable Non-Small Cell Lung Cancer

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Introduction: Non-small cell lung cancer (NSCLC) represents 80% of newly diagnosed lung cancers. Accurate staging is critical for prognosis. The maximum standardized uptake value (maxSUV) is a semiquantitative measure of tissue uptake of Fluorine-18 fluorodeoxyglucose (18F-FDG) positron emission tomography/computed tomography (PET/CT). It is used for the assessment of tumor metabolic activity and disease stage. Increased levels of circulating cell-free DNA (cfDNA) are detected in cancer patients due to various mechanisms, including tumor cell necrosis, apoptosis, and macrophage digestion, with subsequent release of tumor DNA fragments into the bloodstream. The purpose of this study was to evaluate the relationship between maxSUV and cfDNA concentration to predict adjuvant therapy requirements in patients with early-stage, resectable NSCLC.

Methods: Patients with resectable NSCLC who underwent preoperative PET/CT scanning at the University Hospital of Cruces between 2021 and 2023 were included in this prospective cohort study. Patients were injected with 18F-FDG according to their weight and images were acquired using a GE Discovery™ MI PET/CT system. The maxSUV of the tumor was defined as the peak SUV of 1 pixel with the highest count within the tumor in chest. The software used was the advantage workstation (GE, ADW PET/CT). Prior to surgery, venous blood was collected in Streck Cell-Free DNA blood collection tubes. DNA was extracted from 3 ml of plasma using the QIAamp Circulating Nucleic Acid Kit and was measured using the Qubit™ dsDNA HS Assay Kit. The relationship between maxSUV, cfDNA and clinical variables was evaluated with Wilcoxon test or Dunn test, as appropriate. A Leave-One-Out Cross Validation (LOOCV) multivariate logistic regression was generated through a forward stepwise selection. Model performance was evaluated based on accuracy, which was considered statistically significant by a one-sample t-test if it exceeded the percentage of non-adjuvant cases.

Results: Ninety patients (37 females and 53 males) with a mean age of 65.2 ± 6.81 years in stage I (56.66%), II (26.66%) and III (16.66%) were included. The 30% of patients received guideline-recommended adjuvant chemotherapy after surgery. Analysis of maxSUV revealed significant differences ($p < 0.05$) with respect to tobacco consumption, type of surgery, histology, stage and adjuvant therapy requirements. The concentration of cfDNA was significantly associated with the type of surgery, the stage and the need for postoperative therapy ($p < 0.05$). There was no correlation (Spearman $R < 0.10$) between cfDNA concentration and maxSUV. Logistic regression models showed that stage alone could not predict the need for an adjuvant therapy. However, moderate predictive capacity was observed after adding cfDNA concentration (cfDNA-stage, accuracy = 0.78, $p = 0.04$) or maxSUV (maxSUV-stage, accuracy = 0.80, $p = 0.02$), particularly with the latter combination.

Conclusions: This work highlights the importance of combining different clinical characteristics to predict which patients will have the greatest benefit from postoperative therapies. Different but simple combinations, such as maxSUV and stage, may help to improve adjuvant therapy decision making.

Keywords: maxSUV, cfDNA, adjuvant therapy

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EP.07G.06 Utilization of Tissue-Free Minimal Residual Disease MRD Testing in Early-Stage Lung Cancer Patients from Asia and the Middle East

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Introduction: Detecting minimal residual disease in plasma is emerging prognostic biomarker for early-stage cancer patients. Few clinical trials have described MRD detection after curative-intent treatment for early-stage non-small cell lung cancer (eNSCLC). We describe real-world use of a tissue-free plasma cell-free DNA (cfDNA) next-generation sequencing (NGS) in eNSCLC patients from Asia and the Middle East.

Methods: eNSCLC patients in this region receiving Guardant Reveal testing in clinical practice were included in this retrospective analysis. This assay determines the presence of MRD by evaluating epigenomic signals in cfDNA without the need for prior tumor tissue analysis. Data analyzed for samples received from July 2023 to March 2024 and classified as post-resection (<12 weeks after surgery) or surveillance (>12 weeks after surgery). Clinical factors extracted from test requisition forms filled by physicians.

Results: 41 consecutive patients (57 samples) with stage I (n=2), II (n=12), or III (n=27). 40/41 patients had adenocarcinoma, 51% male. 60% of samples from Taiwanese patients, 40% from rest of the region. Median follow-up since testing was 4.3 months. Regardless of cancer stage, the majority of tests (75%) were ordered during surveillance up to 5 years after surgery(fig1). Overall, 12% had MRD detected in their first test, with the increasing frequency of detection in advanced tumor stage: stage I, 0%; stage II, 8%; stage III, 15% (fig 2). Median turnaround time(TAT) from sample reaching laboratory to report release was 8 days (range: 5-20). A patient with MRD detected 22 weeks after surgery was confirmed to have radiographic lymph node recurrence five days later, resulting in additional adjuvant immunotherapy. Follow-up is ongoing for all the patients to assess sensitivity and specificity of the MRD test.

Conclusions: Preliminary real-world experience with a tissue-free cfDNA MRD test in eNSCLC patients demonstrated similar performance to that reported for tissue-informed assays with fast TAT.

Keywords: MRD, ctDNA, residual disease

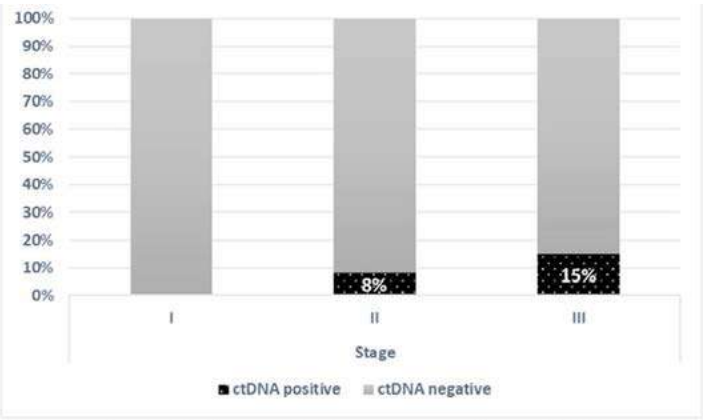

Figure 1. ctDNA positivity rate at first MRD test by cancer stage. Stage I, n=0; stage II, n=1; stage III, n=4.

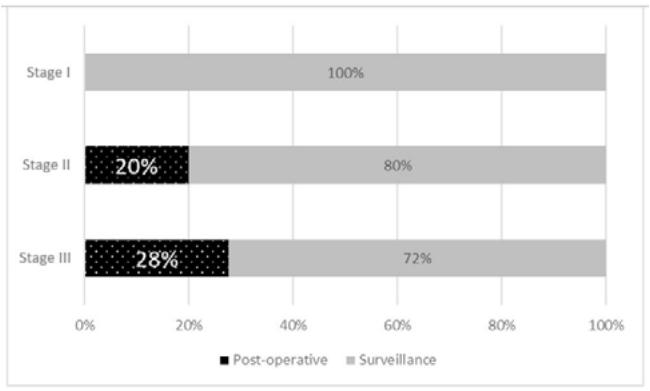

Figure 2. Timing of MRD test order for stage I (2 patients, 2 samples), stage II (12 patients, 15 samples) and stage III (27 patients, 40 samples)

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EP.07G.07 Risk and Outcomes of Secondary Malignancy Among Non-Small Cell Lung Cancer Survivors Following Definitive Treatment

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Introduction: Outcomes in non-small cell lung cancer (NSCLC) have improved over the past decade, leading to more long-term survivors. These patients remain at high risk for both disease recurrence and secondary malignancy. However, limited data exist that delineate the characteristics of non-lung secondary malignancies (NLSM) and disease outcomes for patients that develop NLSM. We assessed consecutive patients visiting a survivorship clinic in a tertiary cancer center to better characterize subtypes of NLSMs and elucidate outcomes of subsequent malignancies in this patient population.

Methods: We analyzed consecutive lung cancer survivors who visited our institutional survivorship clinic from January to May 2019 and met the following criteria: a) an initial diagnosis of stage I-III NSCLC; b) completion of definitive treatment with either surgery or radiation; and c) disease-free for at least 12 months following the completion of local therapy. Recurrence of disease, new lung primaries, and NLSM (which are not consistently detected by routine surveillance) were recorded. New lung primaries were differentiated from recurrence using the Martini and Melamed criteria in the absence of molecular sequencing data that could provide this categorization. The risk over time for developing NLSM was estimated using the Kaplan-Meier method, and clinical outcomes of these patients were collected.

Results: A total of 300 consecutive patients were analyzed, including 203 (67%) pathologic stages I, 41 (14%) II, and 56 (19%) III NSCLC survivors who completed definitive treatment. At a median follow-up of 6 years, 51 patients (17%) had cancer recurrence; of these, 35% were initially local, 25% regional, and 40% distant +/- locoregional. The median time to recurrence was 31 months (range, 12-177). Secondary malignancy occurred in 68 survivors (23%) within a median time of 58 months (range, 7-193), with second primary lung cancer being the predominant type (56% of secondary malignancies). NLSM occurred in 30 patients (10%) and emerged over a median time of 47.5 months (range, 2-84). The cumulative risk of developing NLSM was 1%, 3%, 5%, 7.3%, and 10% within the first 24, 36, 48, 60, and over 60 months post-treatment, respectively. Prostate (17%), breast (13%), pancreatic (10%), and head and neck (10%) cancers accounted for half of these cancers, with 17% of patients diagnosed with metastatic disease. Median overall survival (OS) and progression-free survival (PFS) of patients with NLSM were 26 months (range, 0.6-91) and 19 months (range, 0.6-91), respectively. The median OS of metastatic NLSM patients was 6 months (range, 0.6-26).

Conclusions: While recurrence rates decrease with time after definitive therapy for NSCLC, seven years after treatment completion, 10% of patients developed an NLSM, the majority of which were diagnosed more than 3 years post-treatment. Among patients with an NLSM, 17% were diagnosed with metastatic disease, with a median OS of 6 months. Given that the majority of the NLSMs are not captured in a routine CT scan of the chest, these findings suggest that patients should continue to be followed for second malignancies indefinitely. These data highlight the need for alternative approaches of comprehensive surveillance in this population.

Keywords: Lung cancer, survivors, secondary malignancy

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EP.07G.08 Predicting Lung Cancer Recurrence in the Pre-Operative Setting Using AI/radiomics: A Study Based on US and European Cohorts

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Introduction: Lung cancer recurrence after surgical resection presents a significant clinical challenge, with reported recurrence rates of 30%-55%. Biomarkers that allow accurate estimates of recurrence risk may provide critical evidence to inform personalized treatment decisions, such as the extent of lung resection, the use of (neo-)adjuvant therapies, and guide post-treatment monitoring. In this study, we report a novel preoperative machine learning model that leverages computed tomography (CT) images and clinical information to predict lung cancer recurrence after surgery.

Methods: We created a retrospective cohort of 947 patients with stage I-IIIA lung cancer who underwent surgical resection. 287 patients developed recurrent disease after surgical resection. The cohort includes CT images and clinical data from patients in both screening and clinical settings from the US National Lung Screening Trial (445), Stanford University School of Medicine and Palo Alto Veterans Affairs Healthcare System (180), and North Estonia Medical Centre (322). The model was trained to predict the likelihood of recurrence using radiomic features extracted from CT images and relevant pre-operative clinical variables. The model training employed using 8-fold cross-validation, where, in each fold, 6 of the subsets were used for training, one for model tuning and one held out for validation. We compare the resulting model to a clinical TNM staging. Performance was evaluated using the Area-Under-the-ROC-Curve (AUC).

Results: Lung cancer recurrence prediction results are tabulated below for the overall cohort, stratified by US and European subpopulations. The machine learning model performs significantly better than staging alone (AUC 0.66 vs 0.59, p-value=0.008). The improvement in recurrence prediction was similar in both the US and European sub-populations.

Conclusions: This analysis demonstrates that a radiomic model can more accurately predict lung cancer recurrence after surgical resection compared to cancer stage. With further development, this approach may provide a valuable tool to guide treatment of patients with Stage I-IIIA lung cancer.

	AUC		
Predictor	Whole cohort	US cohort	EU cohort
cTNM	0.59	0.58	0.65
Radiomic model	0.66	0.64	0.70

EP.07H EARLY-STAGE NON-SMALL CELL LUNG CANCER - CLINICAL TRIALS IN PROGRESS
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EP.07H.01 Analysis of Variables Predicting pCR and irAEs in Resectable NSCLC Receiving Neoadjuvant Immunotherapy with Chemotherapy (Pre-PLaN)

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Introduction: Neoadjuvant (NA) chemo-immunotherapy (C-IO) has shown an improved event-free survival (EFS) and markedly increased pathological complete responses (pCR), vs chemo-alone, in resectable non-small cell lung cancer (NSCLC) in recent trials. In these trials, achievement of pCR is associated with better survival. This approach is becoming the new SoC and is being widely adopted. Given the importance of achieving pCRs, there is an increasing interest in predicting its occurrence. Also, around one in three patients has grade 3 immune related adverse events (irAEs) with this approach. The response as well as toxicity are related to interplay between host's immunity and tumor variables. We propose to analyze the predictors of pCR and irAEs with NA C-IO in resectable NSCLC, employing a range of wider and more sophisticated parameters (utilizing ctDNA, radiomics, body composition, spatial transcriptomics, proteomics, genomics, microbiome, immune cell subsets etc.), that reflect both the tumor and the integrity of host's immune system. We will then seek to develop an initial integrated predictive model for pCR/non-pCR, and irAEs, with a good sensitivity/specificity, as a prelude to testing (and if necessary, refining) the model in future. Such a model can inform patient selection.

Methods: This is single center, prospective cohort study enrolling patients with stage IB-IIIA NSCLC, ECOG performance status (PS) 0-2 without EGFR and ALK alterations/fusions. Patients will be treated with NA nivolumab plus platinum doublet chemotherapy. The planned accrual is for 60 patients. The primary hypothesis is that a model combining predictive variables for pCR in patients with resectable NSCLC treated with NA C-IO can predict a pCR with an AUC of at least 0.8. The primary objectives are to explore the feasibility of acquiring a combination of baseline and treatment-emergent potentially predictive variables (listed below); to determine the predictive power of these variables; and to develop a precise model to predict pCR and irAEs. The secondary objectives are to assess pCR, major pathological response (MPR), objective response rates (ORRs), and irAEs; to evaluate exploratory and entirely novel potential biomarkers for predicting responses and irAEs and to assess if a post-treatment (pre-surgery) complete metabolic response by F18-FDG-PET-CT and a blood-only molecular residual disease assay can accurately predict a pCR.

Keywords: NSCLC, neoadjuvant, immunotherapy

Category	*Variables*
Demographic	age, gender, ethnicity, smoking status, vaccination, COVID status
Clinical	comorbidities, medications (steroids and proton pump inhibitors), weight loss, stage, body mass index
Radiology	body composition, CT scan, SUV (PET/CT), radiomics, volumetrics
Blood-based biomarkers and proteomics	flowcytometry (immune cell subsets), immune activation markers, LDH and its isoenzymes, CEA, CA199, CA125, leukemia inhibitory factor (LIF), CRP, IL6, IL7, growth differentiation factor 15 (GDF-15), circulating tumor DNA
Pathology and genomics	histology, PD-L1, mulitiplex immunohistochemistry (IHC) for tumor microenvironment cell types and proteins (LAG3, lysine specific demethylase (LSD1), and CD47), next generation sequencing (NGS) (Tumour Mutational Burden), spatial transcriptomics, pCR, MPR, faecal and tumour microbiome

EP.08A LOCAL-REGIONAL NON-SMALL CELL LUNG CANCER - ADJUVANT THERAPY
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EP.08A.01 Impact of Locoregional Recurrence Versus Distant Metastasis on Survival in Patients with NSCLC after Surgery: A Secondary Analysis of PORT-C RCT

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Introduction: The therapeutic advantage of postoperative radiation therapy (PORT) for non-small cell lung cancer (NSCLC) has not been shown to benefit overall survival (OS) according to two randomized controlled trials (RCTs), albeit an enhancement in locoregional-free survival was observed. We aimed to evaluate the relative influence of locoregional recurrence (LR) and distant metastasis (DM) on OS for patients with NSCLC after surgery.

Methods: This was a secondary analysis of PORT-C RCT. Patients with pN2 NSCLC undergoing complete resection followed by chemotherapy were included. A dynamic prediction model was developed to evaluate the impact of LR and DM on OS. The endpoint was OS. Age, sex, smoking history, histology, Karnofsky Performance Status, tumor side, T stage, and positive lymph node were baseline factors, whereas LR and DM status were time-dependent covariates.

Results: In total, 364 patients were eligible, including 214 and 150 in the non-PORT and PORT groups, respectively. DM significantly decreased OS in both the non-PORT (odds ratio [OR], 4.74; 95% CI, 2.70-8.30; P<0.01) and PORT (OR, 5.43; 95% CI, 2.56-11.48; P<0.01) groups. LR also significantly impacted OS in the non-PORT (OR, 2.09; 95% CI, 1.12-3.93; P=0.02) and the PORT (OR, 3.44; 95% CI, 1.53-7.75; P<0.01) groups. Multivariate Cox analysis identified the pT stage, positive lymph nodes, and histology as variables correlated with DM. A nomogram was developed to estimate the risk of DM. PORT did not significantly enhance OS in either the low (HR, 1.42; 95% CI, 0.63-3.19, P=0.40) or high-risk (HR, 0.62; 95% CI, 0.35-1.09, P= 0.10) subgroup but in the medium-risk subgroup (HR, 0.20; 95% CI, 0.05-0.86, P=0.02).

Conclusions: DM and LR significantly impacted OS in patients with NSCLC after surgery. DM emerged as the dominant failure pattern, emphasizing more effective control of DM. PORT was beneficial for patients with a medium risk of DM.

Keywords: Survival, Locoregional recurrence, Distant metastasis

EP.08A LOCAL-REGIONAL NON-SMALL CELL LUNG CANCER - ADJUVANT THERAPY
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EP.08A.02 Adherence to Adjuvant Immunotherapy and Target Therapy Protocols Inpatients with Resected NSCLC: A Meta Analysis

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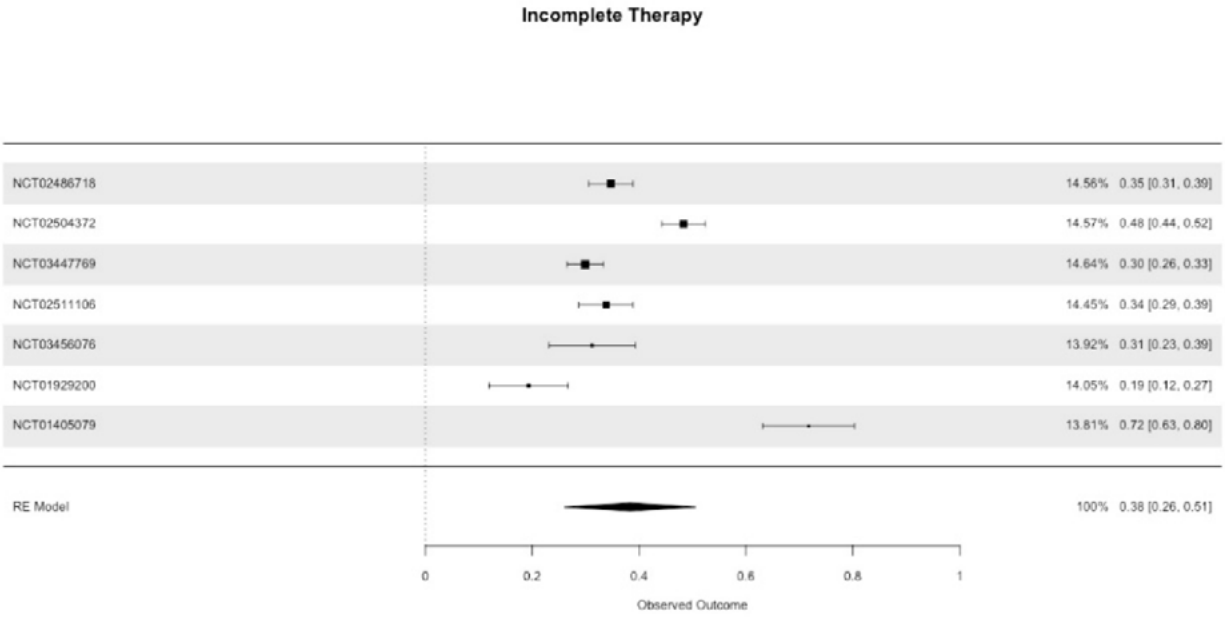
Introduction: Recently, the introduction of immunotherapy (IO) and target therapy with tirosin-Kinase inhibitors (TT) in the treatment of all stages of Non-Small Cell Lung cancer has been radically changing the standards of care. Nevertheless, adherence to post-operative adjuvant treatment protocols has been often limited by patients' performance status after surgery.We aim to verify the adherence to protocols of adjuvant therapy in recent trials using IO or TT.

Methods: A systematic review of PubMed and Embase with meta-analyses was performed. Included studies were prospective clinical trials of postoperative IO or TT alone or in combination with chemotherapy in resected NSCLC. Studies of perioperative therapy were exclude and research cutoff was March 2023. Two authors (P.B. and F.G.) independently and in duplicate screened the abstracts of all publications obtained by the search strategies to identify studies. Primary outcomes were adherence to medical treatment (calculated as omission of therapy rate and incomplete therapy rate) and posttreatment severe adverse events.

Results: We included 7 studies with a total of 2479 patients; 6 studies were phase 3 and one phase 2. The list of all included study is reported in figure 1. All studies were started in the time frame between 2013 and 2018. IO was investigated in three studies, while the remaining 4 studies used TT. Complete omission of adjuvant therapy was found in 1.3% of patients (95% CI 0.8-1.7), while 37.2% (95% CI 35.3-39.1, figure 1) of patients required a reduction of number of cycles originally planned by the protocol. Concurrently, severe adverse events (AEs) were seen in 21.5% of patients (95% CI 19.8-23.1). When we compared IO and TT no significant difference in omission of therapy rate, incomplete therapy rate or severe AEs rate was observed.

Conclusions: The adherence to treatment protocols is a critical point in NSCLC patient's after surgery. Data from the current available literature showed that adjuvant IO or TT therapy is plagued by a high rate of incomplete therapy rate. Nevertheless, when we compared outcomes of IO and TT, we did not observe significant difference in outcomes.The role and the duration of adjuvant therapy should be careful evaluate in the era of IO and TT to reduce AEs and improve completion rate.

Keywords: Immunotherapy, target therapy, Adjuvant therapy



EP.08A LOCAL-REGIONAL NON-SMALL CELL LUNG CANCER - ADJUVANT THERAPY
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EP.08A.03 Real World Outcomes of Adjuvant Atezolizumab in NSCLC: A Single Institution Study

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Introduction: Adjuvant immunotherapy versus best supportive care after adjuvant chemotherapy has shown disease-free survival (DFS) benefit in patients with resected NSCLC per IMPOWER-010; however, it also has significant associated adverse events. We sought to evaluate the tolerability and effectiveness of adjuvant atezolizumab in a real-world setting.

Methods: We performed a retrospective analysis of patients initiating adjuvant immunotherapy for stage IB-IIIB NSCLC in an NCCN-designated Cancer Center between 2021-2023 treated with 1200 mg or 1680 mg atezolizumab every 3 weeks or 4 weeks, respectively, for one year. We described immune-associated adverse events (irAEs) and DFS.

Results: Thirty-six patients underwent adjuvant immunotherapy with atezolizumab after resection of Stage IB-IIIB NSCLC. 72% (26/36) of patients were able to complete or are continuing to undergo atezolizumab maintenance. 14% of patients (5/36) discontinued therapy due to irAEs while 3% (1/36) of patients discontinued due to disease progression. Grade 3/4 colitis (6% of patients; 2/36) and grade 3/4 pneumonitis (6% of patients; 2/36) were the most common irAEs resulting in early cessation of treatment. There were no Grade 5 irAEs. 80% (29/36) of patients received adjuvant platinum-based chemotherapy (one to four cycles) prior to adjuvant atezolizumab. At time of review, only 19% (7/36) of patients had disease progression after starting adjuvant atezolizumab therapy.

Conclusions: Adjuvant atezolizumab appears well-tolerated in a diverse, real-world population. The toxicity profile and discontinuation rates were similar to that reported in the global IMpower010 study, suggesting good applicability of evidence from this trial to real world context. Further follow-up will be required to assess the ability of adjuvant atezolizumab to promote DFS.

Keywords: NSCLC, adjuvant, atezolizumab

Table 1: Real World Vs IMPOWER-010 Atezolizumab Intention-to-Treat Group Demographics

	Real World Population (n=36)	IMPOWER-010 Atezolizumab Group (n=507)
Race		
White	30 (83%)	362 (71%)
Black	3 (8%)	5 (1%)
Asian	2 (6%)	130 (26%)
Other / Unknown	1 (3%)	10 (2%)
Ethnicity		
Hispanic or Latino	12 (33%)	-
Non-Hispanic or Latino	21 (58%)	-
Unknown	3 (8%)	-
Stage		
IB	1 (3%)	65 (13%)
IIA	3 (8%)	147 (29%)
IIB	11 (31%)	90 (18%)
IIIA	17 (47%)	205 (40%)
IIIB	4 (11%)	-
Histology		
Squamous	8 (22%)	179 (35%)
Non-Squamous	28 (78%)	328 (65%)

Table 2: Comparison of Immune-Mediated Adverse Events

	Real World Population (n=36)	IMPOWER-010 Atezolizumab Group (n=495)
Any Grade	15 (42%)	256 (52%)
		p-value = 0.2232
Grade 3–4	4 (11%)	39 (8%)
		p-value = 0.5619
Led to Discontinuation	5 (14%)	52 (11%)
		p-value = 0.6243

EP.08B LOCAL-REGIONAL NON-SMALL CELL LUNG CANCER - BIOMARKERS FOR NEOADJUVANT
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EP.08B.01 Heterogeneity of Peripheral Blood Cell Dynamics and Oncologic Outcomes Between LUAD and LUSC Receiving Neoadjuvant Immunochemotherapy

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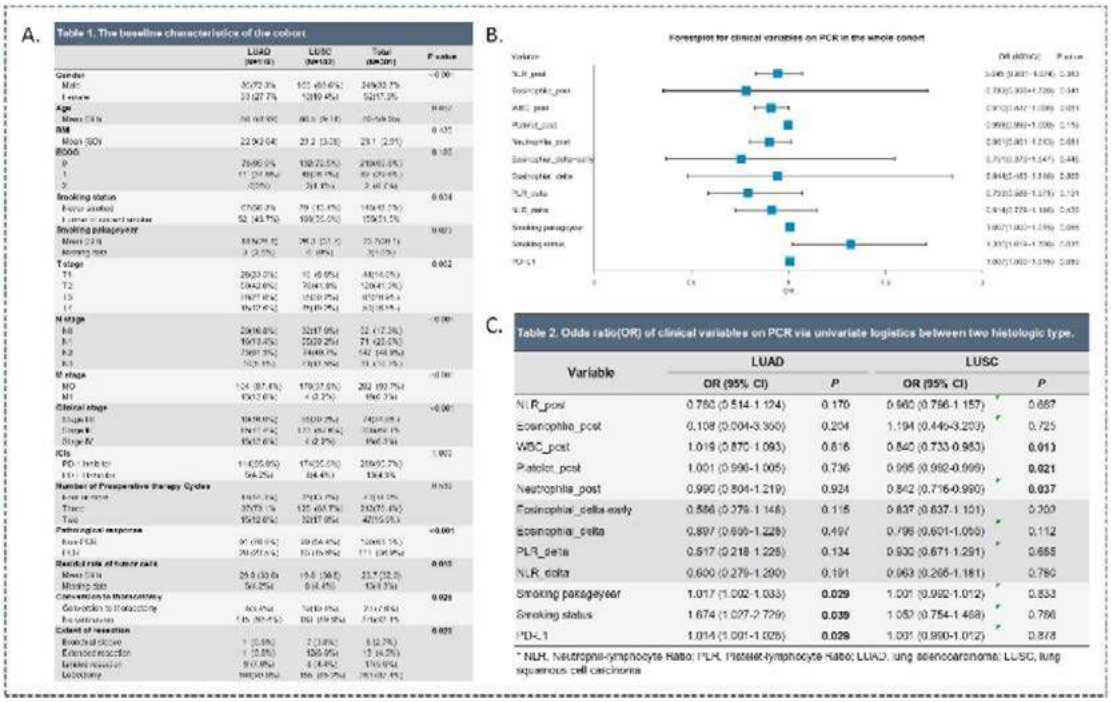
Introduction: Immune checkpoint inhibitors (ICIs)-based neoadjuvant chemotherapy has been approved by the FDA to treat resectable NSCLC with significant benefit over chemotherapy alone. Lung squamous cell carcinoma (LUSC) and adenocarcinoma (LUAD) have distinct biological behaviors and different treatment responses. Studies on of these two pathologic types in the context of neoadjuvant immunotherapy (NAIT) have not yet been explored. Besides, the role of Programmed Cell Death-Ligand 1 (PD-L1) expression and serum tumor markers in this setting is still uncertain, especially for LUSC or LUAD. Therefore, we aimed to evaluate the baseline characteristics and peripheral blood immune cell dynamics in a comparative strategy for these two histologic subtypes.

Methods: This retrospective study collected data from patients with LUAD and LUSC who received NAIT at Guangdong Provincial People's Hospital from May 18, 2019 to December 30, 2023. The oncologic and surgical outcomes were evaluated between LUAD and LUSC groups. In addition to baseline clinical variables such as PD-L1 expression, absolute counts of blood cells in peripheral blood both before and after treatment, as well as the neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR), were calculated and analyzed. These factors, along with their changes, were assessed for impact on pathological complete response (PCR) via univariate and multivariate analysis of logistics regression.

Results: A total of 301 cases (182 LUSC, 119 LUAD) were included. Of these, 111 of 301 (36.9%) patients achieved PCR. No significant differences were found in age, BMI, ECOG, ICIs type and the number of therapy cycles between two groups. LUSC group showed superior PCR rate and less residual tumor cells but higher conversion rate and more extended range of surgical resection, like bilobectomy. Neither PD-L1 expression nor serum markers were associated with PCR in the whole cohort. For LUAD group, only PD-L1 expression (OR=1.019, 95%CI: 1.004-1.033, p=0.013) and smoking status (OR=2.103, 95%CI:1.352-4.484, p=0.013) could independently predict PCR. In contrast, these two factors were less correlated with response for LUSC group. The absolute counts of white blood cell (WBC), platelet and neutrophils after first cycle is significant correlated with PCR, where WBC count is an independently predictor for PCR (OR=0.840, 95%CI: 0.733-0.963, p=0.013).

Conclusions: Patients receiving NAIT in this real-world study exhibited promising pathological remission rates, especially for LUSC subset. Higher PCR rate was observed in LUAD patients with higher PD-L1 expression whereas higher WBC counts after therapy could predict a less probability of PCR for LUSC patients.

Keywords: Neoadjuvant immunotherapy, Peripheral blood tumor markers, LUAD and LUSC



EP.08B LOCAL-REGIONAL NON-SMALL CELL LUNG CANCER - BIOMARKERS FOR NEOADJUVANT
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EP.08B.02 The Impact of C-Met Expression on the Immune Microenvironment and Survival in Locally Advanced Non-Small Cell Lung Cancer

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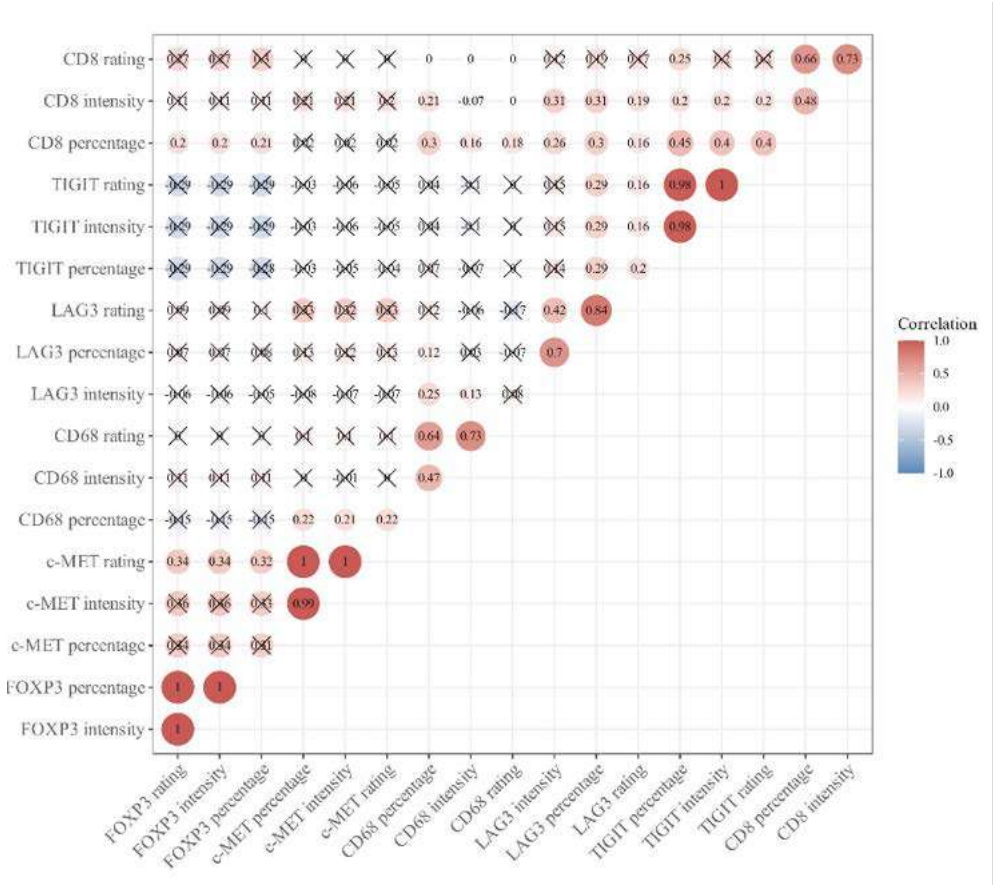
Introduction: The c-MET gene is emerging as a crucial therapeutic target owing to its diverse dysregulation in non-small cell lung cancer (NSCLC). Overexpression of the MET gene has been implicated in modulating the tumor immune microenvironment and affecting treatment responses to immunotherapy. This study aims to explore the association between c-MET expression and the immune microenvironment in NSCLC patients treated with radiochemotherapy followed by sequential immunotherapy, along with its clinical implications.

Methods: Clinical information of patients, along with the expression intensity and percentage of c-MET and specific immune microenvironment profile, including CD8, CD68, LAG3, FOXP3, and TIGIT, were collected (Table1) in 60 locally advanced NSCLC patients with radiochemotherapy followed by sequential immunotherapy. Categorical variables were compared using the Chi-square test. Survival curves were computed using the Kaplan-Meier method, and Cox proportional hazard regression was performed to evaluate factors independently associated with overall survival (OS) and progression-free survival (PFS).

Results: This investigation enrolled a cohort of patients diagnosed with NSCLC at Shanghai Pulmonary Hospital who had undergone a combination treatment regimen consisting of chemoradiotherapy and sequential immunotherapy. The median PFS and OS among all enrolled patients were 24.0 months and 34.0 months, respectively. OS was significantly associated with high c-MET expression (P = 0.02) and reduced macrophage (CD68+) infiltration (P = 0.01). PFS was significantly associated with high c-MET expression (P = 0.03). Correlation analysis shows a significant correlation (P = 0.01) between c-MET expression and macrophage (CD68+) infiltration (Figure 1).

Conclusions: Our research has identified expression of c-MET and macrophage (CD68+) infiltration as potential predictors of survival. Moreover, there is a significant correlation between the expression of c-MET and macrophage (CD68+) infiltration. The subsequent intricate mechanisms of interaction between c-MET and macrophage infiltration warrant further exploration.

Keywords: Non-Small Cell Lung Cancer, Immune Microenvironment, c-MET



EP.08B LOCAL-REGIONAL NON-SMALL CELL LUNG CANCER - BIOMARKERS FOR NEOADJUVANT
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EP.08B.03 Prognostic Value of Irradiated Cardiac and Metabolic Tumor Volume in Unresected LA-NSCLC Treated with Concurrent Chemo-Radiotherapy.

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Introduction: Treatment toxicity and poor survival outcomes highlight an urgent need to identify reliable prognostic markers in unresected locally advanced non-small cell lung cancer (LA-NSCLC). Earlier studies suggested that metabolic tumor volume (MTV) has prognostic value in LA-NSCLC treated with standard-of-care concurrent chemo-radiotherapy (cCRT), while recent work points to the detriment of effect of radiation doses reaching the heart. We compared the prognostic value of 18F-fluoro-deoxy-glucose positron emission tomography (FDG-PET) metabolic parameters [metabolic tumor volume (MTV), total lesion glycolysis (TLG), maximum standardized uptake value (SUVmax)], radiotherapy planning [gross tumor volume (GTV), planning target volume (PTV)] and normal tissue (lung, heart and esophagus) radiotherapy volumes.

Methods: A retrospective analysis of institutional health records (Juravinski and Walker Family Cancer Centers, Ontario, Canada) was pursued to identify patients with unresected stage III (AJCC 7th edition) using brain MRI, CT of the chest, abdomen and pelvic and FDG-PET) and treated with cCRT, between January 2007 and December 2017. Overall survival (OS) data were obtained from local and provincial clinical records. Radiotherapy plans - with fused FDG-PET imaging were pulled from Pinnacle databases, reviewed for tumor and normal tissue volume delineation and subjected to dosimetric data extraction using locally developed algorithms. The MIM-Vista© Encore module was used to evaluate tumor MTV, TLG and SUVmax values using appropriate workflows. OS was estimated using the Kaplan-Meier method. Cox regression was used to explore whether factors were prognostic for OS.

Results: Of 186 consecutive patients who met eligibility criteria, 90 were female and 96 male with a median age of 67. Median OS after completion of cCRT was 36.3 months [95%CI, (28.5-45.4)] and 1-, 2- and 5-year OS rates were 81.6%, 64.0% and 36.7% [95%CI (75.0-86.5), 95%CI (56.4, 72.6) and 95%CI (28.2, 45.1)], respectively. In uni-variable analysis pre-treatment MTV and TLG were prognostic for OS [HR:1.33, 95%CI (1.05-1.68), p=0.018 and HR:1.26, 95%CI (1.03-1.55), p=0.027)] but not SUVmax. The cardiac volume receiving 5-45Gy (cV5 - cV45) and radiotherapy mean heart dose (MHD) were also equally prognostic [HRs:1.28 - 1.42, p=0.044 - 0.002; HR:1.33, 95%CI (1.07, 1.64), p=0.011], respectively. No significant predictive value was found for PTV, GTV, normal lung, and esophagus volumes and radiation doses. Further, combining MTV with MHD did not improve significance.

Conclusions: In this institutional series of well-staged patients with unresected LA-NSCLC, exhibiting contemporary survival outcomes after cCRT, baseline volumes of the tumor with metabolic activity (MTV, TLG) and volumes of heart receiving radiotherapy (cV5-cV45, MHD) illustrate similar prognostic value, in agreement with earlier observations. Recognizing the complexity arising from the typical anatomical distribution of LA-NSCLC, these results suggest that, i) metabolic tumor volume could have greater prognostic value compared to clinical tumor volumes and ii) irradiating the heart may be equally detrimental for survival as tumor burden. Future studies should examine these concepts in larger datasets.

Keywords: Cardiac irradiation, Metabolic Tumor Volume (MTV), prognosis

EP.08C LOCAL-REGIONAL NON-SMALL CELL LUNG CANCER - BIOMARKERS IN UNRESECTABLE NSCLC
SATURDAY, SEPTEMBER 7, 2024 - 11:58 - 11:59

EP.08C.02 Impact of Non-Coplanar Radiation Beam Geometry on Effective Dose to Immune Cells (EDIC) In Stage III NSCLC

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Introduction: Effective dose to immune cells (EDIC) models the effect of radiation on the immune system. Sub-analysis of RTOG 0617 led to the creation of a frequently utilized model measuring EDIC in radiation treatment plans and found EDIC to be an independent prognosticator of survival outcomes in stage III non-small cell lung cancer (NSCLC). Further studies have confirmed the utility of EDIC in prognosticating lymphopenia and survival outcomes in patients treated for stage I-III NSCLC and small cell lung cancer.Despite the prognostic value of EDIC, there have been few studies investigating methods of reducing EDIC in the treatment planning setting. In this study we describe how altered radiation beam geometry can improve EDIC in patients treated with radiation for stage III NSCLC and we model its potential impact on overall survival.

Methods: This single-institution retrospective study included 35 patients treated for stage III NSCLC with definitive chemoradiation in the years 2016 to 2023. All patients received a radiation course of 60Gy in 30 fractions using photon based volumetric modulated arc therapy (VMAT) with coplanar arcs. These clinically delivered plans (CDPs) were replanned using novel non-coplanar oblique arc based VMAT plans (NCPs). These NCPs utilized VMAT arcs with strategic couch rotations limiting entrance dose through the heart. VMAT optimization software and planning objectives remained consistent in replans relative to CDPs. EDIC was calculated for all plans using the Jin model derived from RTOG 0617 sub-analysis which incorporates mean heart dose (MHD), mean lung dose (MLD), and integrated total body dose (ITBD).Two-year overall survival (OS) was modeled for each patients CDP and NCP EDIC values using the previously described Jin model. EDIC, MHD, MLD, ITBD, and two-year OS were compared between CDPs and NCPs using the Wilcoxon signed-rank test.

Results: EDIC and MHD were significantly lower in NCPs relative to CDPs (table 1). MLD was not significantly different between NCPs and CDPs. ITBD numerically improved in NCPs relative to CDPs with a trend towards significance. Modeled two-year OS was significantly improved with NCPs relative to CDPs with a 2.9% projected OS improvement for the cohort.

Conclusions: Using a non-coplanar oblique VMAT beam geometry in radiation planning for the treatment of stage III NSCLC resulted in significant improvement in MHD, EDIC, and modeled two-year OS without significant increase in MLD. Implementing this VMAT planning technique may improve these outcomes and further investigation of the real-world significance of these findings is warranted.

Keywords: Lung, Radiation, EDIC

Table 1	Clinically Delivered Plan	Non-coplanar Replan	p
Mean Heart Dose (Gy)	13.5 (0.8-33.1)	7.2 (0.6-16.7)	<0.00001
Mean Lung Dose (Gy)	15.9 (9.6-20.8)	16.4 (8.7-23.6)	0.17
Integral Total Body Dose (Gy·L)	253 (106-1288)	215 (95-498)	0.06
EDIC (Gy)	5.5 (2.6-8.8)	4.9 (2.2-8.6)	<0.00001
Modeled 2 year OS	54.60%	57.50%	<0.00001

EP.08C LOCAL-REGIONAL NON-SMALL CELL LUNG CANCER - BIOMARKERS IN UNRESECTABLE NSCLC
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EP.08C.03 To Construct Multi-Omics Modelfor Predicting Prognosis of Definitive Chemoradiotherapyin Locally Advanced Non-Small Cell Lung Cancer

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Introduction: This study aimed to construct a multi-omics model integrating baseline clinical data, computed tomography (CT) images and genetic information to predict the prognosis of dCRT in locally advanced non-small cell lung cancer (LA-NSCLC) patients.

Methods: The study retrospectively enrolled 105 stage III LA-NSCLC patients who had undergone dCRT. The primary tumor was delineated as a region of interest (ROI) on the CT image using 3D-Slicer, and radiomics features were extracted. The Least Absolute Shrinkage and Selection Operator (LASSO) was employed for dimensionality reduction and selection of features. Genomic information was obtained from the baseline tumor tissue samples. The predictive performance of the model was evaluated by the area under the curve (AUC) of the Receiver operating characteristic (ROC) and the concordance index (C-index).

Results: The median follow-up time was 30.1 months, and the median progression-free survival (PFS) was 10.60 months. Four features were made to construct the radiomics model. Multivariate analysis demonstrated the Rad-score, KEAP1 and MET mutations were independent prognostic factors for PFS. The C-index of radiomics model, genomics model and radiogenomics model all performed well in the training group (0.590 vs. 0.606 vs. 0.663) and the validation group (0.599 vs. 0.594 vs. 0.650).

Conclusions: The radiomics model, genomics model and radiogenomics model can all predict the prognosis of dCRT for LA-NSCLC, and the radiogenomics model maybe superior to other two models.

Keywords: non-small cell lung cancer, definitive chemoradiotherapy, radiogenomics

EP.08D LOCAL-REGIONAL NON-SMALL CELL LUNG CANCER - CLINICAL NEOADJUVANT
SATURDAY, SEPTEMBER 7, 2024 - 11:58 - 11:59

EP.08D.01 Neoadjuvant Chemoimmunotherapy for Potentially Resectable IIIA/IIIB NSCLC(Neo-Pre-IC): Survival Updates and Predictive Effect of MRD

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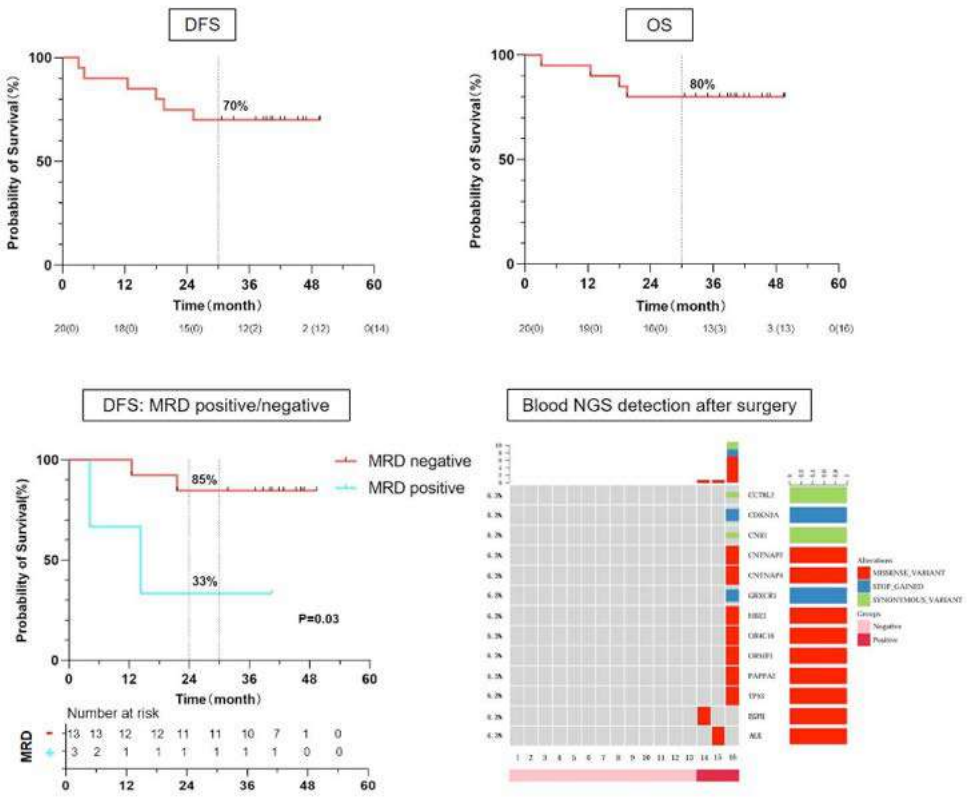
Introduction: Neoadjuvant chemoimmunotherapy for potentially resectable IIIA/IIIB NSCLC significantly improved the pathological remission rate. However, information regarding the long-term survival benefits of neoadjuvant chemoimmunotherapy for potentially resectable IIIA/IIIB NSCLC is limited. Meanwhile, the predictive role of minimal residual disease (MRD) in the prognosis for these patients is not clear.

Methods: This prospective, single-arm, phase 2 clinical trial (NCT04326153) enrolled treatment-naïve patients with 'potentially resectable' IIIA/IIIB NSCLC who were deemed unsuitable for complete (R0) resection upon initial diagnosis. Patients underwent neoadjuvant chemoimmunotherapy (sintilimab combined with nab-paclitaxel and carboplatin) for two to three cycles prior to surgical resection of the lung carcinoma and systematic nodal dissection within 30-45 days. The primary endpoint was the 2-year DFS rate, with secondary endpoints encompassing MPR rate, pCR rate, OS, ORR, downstaging rate, and AEs. Meantime, the tissue samples and blood samples retained before treatment were subjected to NGS sequencing. Plasma ctDNA testing was performed again every six months after surgery to analyze the relationship between ctDNA-MRD and survival.

Results: Between 20 March 2020, and 20 August 2021, 30 patients diagnosed with stage IIIA/IIIB NSCLC were enrolled in the study, and 20 patients underwent complete resection. As of March 31, 2024, the median follow-up time is 46.7 months. The median DFS and OS of the surgical patients is still not achieved. The 2-year DFS rate was 75%, and the 30-month DFS rate was 70%. The 2-year and the 30-month OS rate were both 80%. In 16 patients who underwent secondary plasma ctDNA testing after surgery, 3 patients turned positive and 13 patients were still negative. 2 of 3 MRD positive patients experienced disease recurrence. The two cases of radiological recurrence were found 4.1 and 5.9 months after MRD positive detected, respectively. The MRD negative group benefits more from DFS compared to the MRD positive group. Further survival follow-up is needed to clarify the predictive role of MRD on patient survival.

Conclusions: Neoadjuvant chemoimmunotherapy markedly enhanced the rate of pathological response and 2-year DFS in patients with potentially resectable IIIA/IIIB NSCLC. MRD may serve as a potential predictive biomarker for DFS.

Keywords: neoadjuvant chemoimmunotherapy, potentially resectable, MRD



EP.08D LOCAL-REGIONAL NON-SMALL CELL LUNG CANCER - CLINICAL NEOADJUVANT
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EP.08D.02 Adjuvant Treatment Options after Neoadjuvant Chemotherapy Combined with Immunotherapy and Surgery in Patients with Non-Small Cell Lung Cancer

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Introduction: A large number of studies have confirmed the place of neoadjuvant immunotherapy combined with chemotherapy (NICT) in patients with non-small cell lung cancer (NSCLC), however, controversy still exists regarding postoperative adjuvant therapy after NICT and surgical treatment. Therefore, this study aimed to explore the continuation of the addition of immunotherapy as adjuvant therapy after NICT and surgical treatment.

Methods: Patients with NSCLC treated with NICT and surgery at our study institution from January 2019 to December 2022 were retrospectively analyzed. Patients were divided into Chemo and Immuno+Chemo groups according to whether the adjuvant therapy after NICT and surgical treatment was chemotherapy or chemotherapy combined with immunotherapy to analyze the disease-free survival (DFS) and overall survival (OS) of the two groups.

Results: A total of 209 patients were enrolled, and compared with the Chemo group, the Immuno+Chemo group had a significant advantage in terms of DFS (1-year DFS 70.8% vs. 94.4%; 2-year DFS 58.4% vs. 69.7 %; P=0.002). There was also a significant advantage in OS (1-year OS 98.5% vs. 100.0%; 2-year OS 77.6% vs. 87.6 %; 3-year OS 64.6% vs. 78.9 %; P=0.034). Among those whose postoperative pathology reached pathological complete remission (pCR), there was no significant difference in DFS and OS between the Chemo and Immuno+Chemo groups, whereas among those whose postoperative pathology reached Non-pCR, compared with the Chemo group, the Immuno+Chemo group had a significant advantage in DFS (1-year DFS was 65.1% VS 90.2%; 2-year DFS was 55.8% VS 69.2 %; P=0.003). Compared with the Chemo group, the Immuno+Chemo group also had a significant advantage in terms of OS (1-year OS 97.7% vs. 100.0%; 2-year OS 72.9% vs. 87.3 %; and 3-year OS 64.8% vs. 76.8 %; P=0.030).

Conclusions: In the real world, patients treated with NICT and surgery can still benefit from immunotherapy after surgery, and chemotherapy combined with immunotherapy is significantly more effective than chemotherapy.

Keywords: non-small cell lung cancer, neoadjuvant, immunotherapy

EP.08D LOCAL-REGIONAL NON-SMALL CELL LUNG CANCER - CLINICAL NEOADJUVANT
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EP.08D.03 Efficacy of Neoadjuvant Immunochemotherapy in the Treatment of Stage III Non-Small-Cell Lung Cancer with Cancer-driven Gene Mutations

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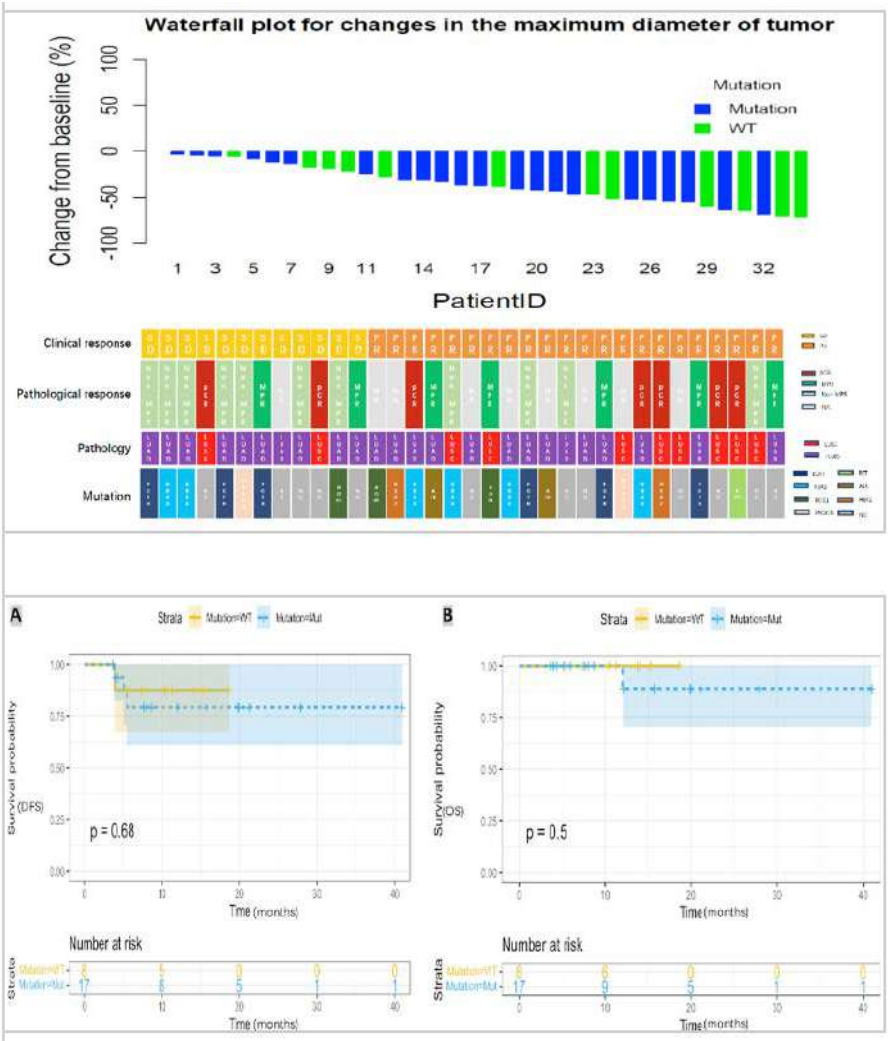
Introduction: Non-small cell lung cancer (NSCLC) patients with cancer driver gene mutations are mainly treated with targeted therapy. For NSCLC with common cancer-driven gene mutations, neoadjuvant immunochemotherapy modalit is still a field of clinical research attempt and attention. In this study, we explored the efficacy and safety of immunochemotherapy as a neoadjuvant treatment in stage III NSCLC with common cancer-driven gene mutations.

Methods: This retrospective study systematically included stage III NSCLC patients who received neoadjuvant immunochemotherapy with gene testing results (including EGFR, KRAS, BRAF, NRAS, HER2, MET, PIK3CA, ALK, ROS1 and RET). The follow-up period lasted at least 1-year post-surgery or after the patient decided to discontinue treatment. The primary endpoint is the pathological response, while secondary endpoints is objective response rate (ORR), disease-free survival (DFS), overall survival (OS), and adverse events (AEs).

Results: From 2020 to 2022, a total of 34 stage III NSCLC patients were included in this study and were categorized into two groups according to whether there were any cancer-driven gene mutations: mutation group (n=22) and wild type (WT) group (n=12). The rate of major pathological response (MPR) in the WT group was 75.0% and 47.0% in the mutation group (P=0.234). The rate of pathological complete response (pCR) in the WT group was 37.5% and 23.5% in the mutation group (P=0.640). Both groups exhibited a 100% ORR. The 1-year DFS rate in the WT group was 87.5% and 82.4% in the mutation group. The 1-year OS rate in the WT group was 100.0% and 94.1% in the mutation group. No postoperative deaths or grade 3 and 4 AEs were observed.

Conclusions: Neoadjuvant immunochemotherapy for stage III NCSLC patients with cancer-driven gene mutations is feasible and safe with considerable therapeutic effect.

Keywords: Immunochemotherapy, non-small-cell lung cancer, cancer-driven gene mutations



EP.08D LOCAL-REGIONAL NON-SMALL CELL LUNG CANCER - CLINICAL NEOADJUVANT
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EP.08D.04 Association of Lymph Node Metastatic Patterns and Neoadjuvant Immunochemotherapy Effectiveness in Resectable Non-Small Cell Lung Cancer

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Introduction: While extensively profiled in the tumor microenvironment, recent studies indicated that tumor-draining lymph nodes (TDLNs) acted as a pivotal organ for anti-tumor immunity and lymph nodes (LNs) metastasis may disrupt the effectiveness of neoadjuvant immunochemotherapy. The objective of this study was to examine the relationship between LNs metastatic patterns and neoadjuvant immunochemotherapy (ICT) effectiveness in resectable non-small cell lung cancer (NSCLC).

Methods: NSCLC patients clinically staged as T1-4N0-2M0 and received ICT followed by surgery were retrospectively reviewed from three institutions. According to the extent of TDLNs (e.g. station 2R/4R for right upper lobe, 7 for right middle lobe, 4L/5/6 for left upper lobe and 7/8/9 for lower lobe tumors), patients were further divided into three groups: uninvolved mediastinal LNs (uiMLNs/cN0-1) group, tumor-draining LNs metastasis (mTDLNs) group and non-draining LNs metastasis (mNDLNs) group. The outcomes were complete pathological response (pCR), major pathological response (MPR) and LN clearance (LN-CR) rates. Multivariable logistic regression was used to evaluate the associations between LNs metastatic patterns and pathological response.

Results: A total of 209 patients were included. Of those, 102 (48.8%) were in the uiMLNs group, 67 (32.06%) were in the mTDLNs group and the remaining 40 (19.14%) were in the mNDLNs group. The pCR, MPR and LN-CR rates in the whole cohort were 38.28%, 59.81%, and 74.64%, respectively. Compared with uiMLNs/cN0-1 group, mediastinal LNs metastasis (mMLNs/cN2) group had significantly lower pCR rate in lung squamous cell carcinoma patients (31.03% vs 51.32%, P=0.019, odds ratio [OR]=0.427, 95%CI: 0.209-0.873). In mMLNs/cN2 patients, mNDLNs group had lower pathological response rate in contrast to mTDLNs group (pCR: 7.5% vs 47.76%, P<0.001, OR=0.089, 95%CI: 0.025-0.316; MPR: 22.5% vs 74.63%, P<0.001, OR=0.099, 95%CI: 0.039-0.249; LN-CR: 40% vs 85.07%, P<0.001, OR=0.117, 95%CI: 0.046-0.294; Figure 1A-C). Taking the number of metastatic stations into consideration, patients with multiple-station TDLNs metastasis also had notably higher pCR, MPR and LN-CR rates than those with multiple-station NDLNs metastasis (pCR: 47.83% vs 7.5%, OR=11.306, 95%CI: 2.697-47.387, P<0.001; MPR: 65.22% vs 22.5%, OR=6.458, 95%CI: 2.077-20.082, P<0.001; LN-CR: 82.61% vs 40%, OR=7.125, 95%CI: 2.041-24.871, P=0.01). The pCR, MPR and LN-CR rates had no significantly statistical difference between multiple-station and single-station TDLNs metastasis groups.

Conclusions: Mediastinal LNs metastasis significantly disrupted the neoadjuvant immunochemotherapy effectiveness. In mMLNs/cN2 patients, those with tumor-draining and non-draining LNs metastasis were supposed to have poor pathological response. N-stage classification based on LNs metastatic patterns showed promising potential for neoadjuvant treatment effectiveness prediction in NSCLC.

Keywords: Non-small cell lung cancer, Neoadjuvant immunochemotherapy, Tumor-draining lymph nodes

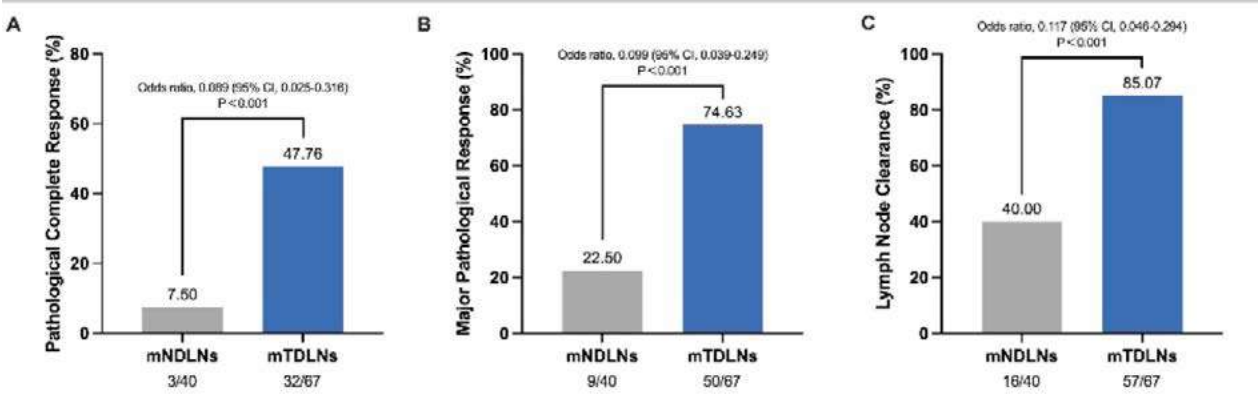

Figure 1. Differences of pathological response between non-draining lymph nodes metastasis group and tumor-draining lymph nodes metastasis group. (A) pCR rates of mNDLNs and mTDLNs groups. (B) MPR rates of mNDLNs and mTDLNs groups. (C) LN-CR rates of mNDLNs and mTDLNs groups.

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EP.08D.05 Long Term Follow-up of Two Decades Experience with Neoadyuvant Chemotherapy in Resectable Non Small Cell Lung Cancer

M. Antoñanzas, M. Amman, J.R. Jarabo, C. Aguado de la Rosa, E. Fernández, J-L. González-Larriba, C. Fraile, F. Hernando -Trancho, Hospital Clinico San Carlos, Madrid/ES

Introduction: The addition of neoadjuvant chemotherapy in locally advanced NSCLC has shown 5% absolute improvement in 5-year overall survival (OS). Clinical research indicates a strong correlation between pathological complete response (pCR) and major pathological response (MPR) with survival outcomes, yet long-term data are still required for further validation.

Methods: We retrospectively analyzed patients with stage II and III NSCLC who underwent neoadjuvant chemotherapy and complete tumor resection at Hospital Clínico San Carlos (Spain) between January 1999 and December 2019. We assessed staging, surgery data, relapse patterns, pCR, MPR, event-free survival (EFS), and OS. Log-rank tests and Cox proportional hazards models were used to estimate HR.

Results: 186 patients underwent neoadjuvant therapy. Initial staging included 20 with stage II disease and 166 with stage III disease, of which 91 were N2 positive, including 46 with multistation N2 involvement. Lobectomy, bilobectomy, and pneumonectomy rates were 64.5%, 7.5%, and 27.9% respectively. pCR was observed in 22 patients (11.8%), while MPR was observed in 37 patients (19.9%). Among the 98 patients experiencing relapse, 69 had distant relapses (36.2% in the central nervous system), and 29 were local relapses. Carboplatin plus paclitaxel was the preferred chemotherapy regimen (62.4%)We conducted statistical analyses of EFS and OS comparing patients achieving pCR versus those who did not, and patients achieving MPR versus those who did not. In the pCR scenario, estimated OS rates at 2, 5 and 10 years were 90.9%,72.2% and 45% in the pCR group, and 69.8%, 44.3% and 29% in the non-pCR group (HR 0.45, 95% CI 0.26-0.79 p < 0.001). Similarly, EFS results were statistically significant (p < 0.002) with 85.7% at 2 and 5 years and 70.7% at 10 years in the pCR group, and 53.4%, 40.4% and 33% in the non-pCR group, respectively (HR 0.27 95% CI 0.11- 0.62).EFS at 2, 5 and 10 years were 88.9%, 83.1% and 69% in the MPR group, and 48.4% and 35.5% 25 in the non-MPR group. OS rates at 2, 5 and 10 years were 94.6%, 78.4% and 55% in the MPR group, and 66.4%, 39.5% and 24.1% in the non-MPR (HR 0.40, 95% CI 0.25-0.63 p < 0.001). Figure 1.

Conclusions: In our patient cohort, achieving pCR or MPR correlated with improved EFS and OS compared to non-histological responder groups. This strong association, coupled with a lengthy follow-up period, underscores the importance of implementing immune-based neoadjuvant strategies to enhance pathological response for long-term survival.

Keywords: Neoadyuvant chemotherapy, pCR MPR, Long term survival

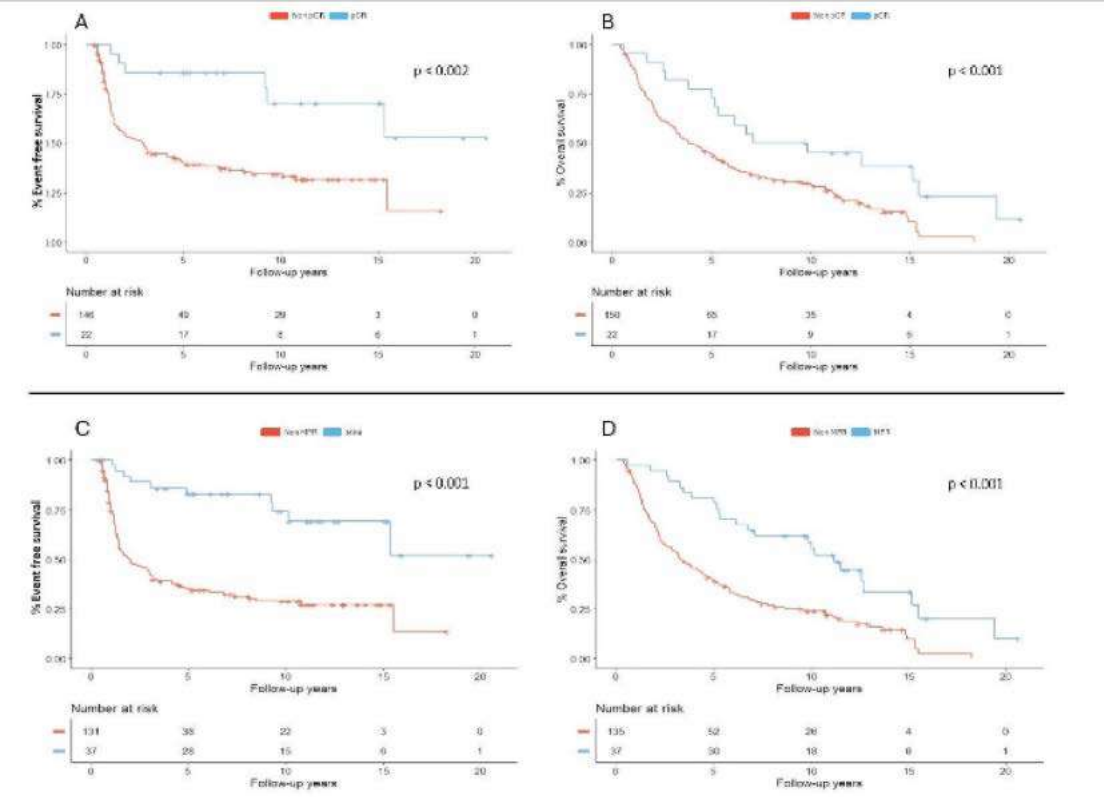

Figure 1. EFS and OS comparing patients achieving pCR versus those who did not (A,B), and patients achieving MPR versus those who did not (C,D)

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EP.08D.06 Neoadjuvant Chemoimmunotherapy Does Not Increase Postoperative Morbidity of Pneumonectomy in NSCLC Patients: A Multi-Center Psmanalysis

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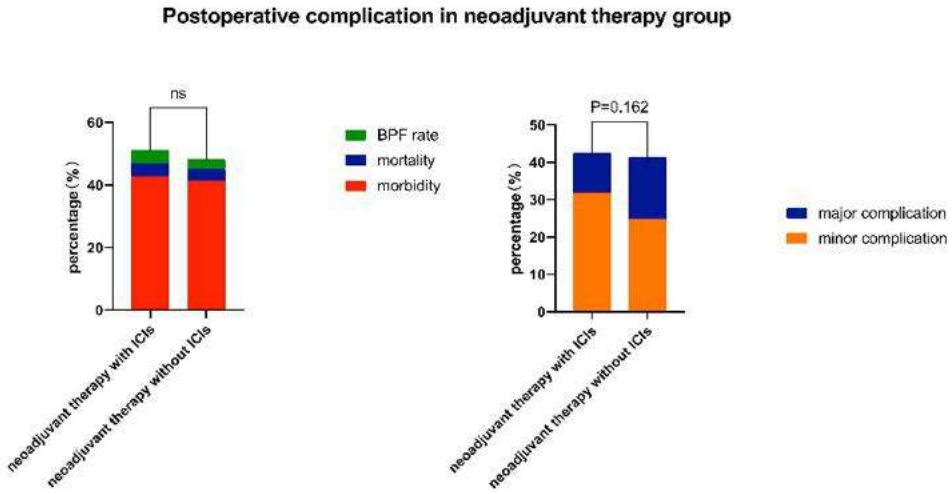
Introduction: The feasibility and efficacy of PN for locally advanced NSCLC after preoperative induction therapy especially with ICIs are uncertain and its indications after neoadjuvant therapy remain controversial.

Methods: A total of 1187 patients who underwent pneumonectomy for non-small-cell lung cancer were retrospectively analyzed from three hospitals in China, including 209 patients who received neoadjuvant therapy and 978 patients who did not. Propensity-score matching (PSM) was adopted to create a balanced cohort of 174 paired cases. The logistic regression was used in this study. The primary endpoint was the postoperative morbidity.

Results: In the unmatched cohort, univariable logistic regression analysis showed that FEV1, extended pneumonectomy, and intraoperative transfusion were risk factors for postoperative complications, and multivariable logistic regression analysis showed FEV1 (odds ratio [OR], 1.487; P=0.019) and extended pneumonectomy (OR, 1.499; P=0.007) were independent risk factors. The neoadjuvant group had larger tumors (4.7±2.2 vs. 3.9±1.9cm, P<0.001; cT4: 36.3% vs. 19.1%, P<0.001), had a greater rate of N2 metastases (64.5% vs. 33.3%, P<0.001), and were at a more advanced clinical TNM stage (stage III: 89.4% vs. 58.6%, P<0.001). However, no significant difference in postoperative morbidity was observed between the two groups before and after PSM (43.5% vs. 42.9%, P=0.975; 49.4% vs. 41.9%, P=0.162). The complete pathologic response of chemoimmunotherapy was significantly superior to chemotherapy alone (27.7% vs. 2.0%, P<0.001), and no significant difference in postoperative morbidity was noted in different neoadjuvant therapy modalities.

Conclusions: After neoadjuvant therapy with ICIs, pneumonectomy can be safely performed in selected patients without increased postoperative morbidity.

Keywords: pneumonectomy, non-small cell lung cancer, Neoadjuvant chemoimmunotherapy



EP.08D.07 Pathological Response to Neoadjuvant Tislelizumab Plus Chemotherapy in Potentially Resectable Stage IIIB NSCLC

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Introduction: In patients with resectable stage II-IIIA non-small cell lung cancer (NSCLC), neoadjuvant tislelizumab plus chemotherapy showed clinically meaningful improvements in major pathological response (MPR) and pathological complete response (pCR) rates compared to chemotherapy alone. However, the clinical benefit of neoadjuvant tislelizumab plus chemotherapy for potentially resectable stage IIIB NSCLC remains to be determined. This exploratory analysis retrospectively evaluated the pathological response of neoadjuvant tislelizumab plus chemotherapy for patients with potentially resectable stage IIIB NSCLC.

Methods: Between August 2020 and January 2024, 75 patients with potentially resectable stage IIIB NSCLC from 4 centers (West China Hospital, Sichuan University; Fujian Medical University; Fujian Province University; The Second Affiliated Hospital of Zhejiang University of Medicine Affiliated Hospital of Zunyi Medical University) were included in this retrospective study. All patients received 2-4 cycles of neoadjuvant tislelizumab plus chemotherapy (nab-paclitaxel/pemetrexed and cisplatin/carboplatin) followed by surgery and optional adjuvant therapy. The primary endpoint was MPR. Secondary endpoints included R0 resection rate, pCR, tumor downstaging, as well as objective response rate (ORR) and disease control rate (DCR) per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.

Results: Of the 75 patients, the median age was 57.0 years (range, 46.0-73.0). The majority of patients were male (74/75, 98.7%). As of January 14, 2024, 64 patients (85.3%; 95% CI, 75.3%-92.4%) completed the planned neoadjuvant therapy and underwent successful R0 resection, while 11 patients declined or were not suitable for surgery . 47(73.4,60.91-83.7)of 64 patients had an MPR, and 28 (43.7%; 95% CI, 32.4%-56.7%) had a pCR. Tumor downstaging occurred in 84.37% (54/64) of patients. The ORR and DCR were 81.3% (95% CI, 70. 7%-89.4%) and 98.7% (95% CI, 92.79%-100.0%), respectively.Table 1: Efficacy results of included patients (N=75)

Conclusions: Tislelizumab in combination with chemotherapy as neoadjuvant therapy demonstrated promising antitumor activity for potentially resectable stage IIIB NSCLC with high rates of MPR and pCR.

Keywords: stage IIIB, NSCLC, neoadjuvant

Outcomes	n/N (%, 95%CI)
Tumor response	
CR	2/75 (0.03, 0.3-9.3)
PR	59/75 (78.7, 67.7-87.3)
SD	13/75 (17.3, 9.6-27.8)
PD	1/75 (0.01, 0.03-7.2)
ORR	61/75 (81.3, 70.7-89.4)
DCR	74/75 (98.7, 92.8-100.0)
Surgical resection	
Surgery rate	64/75 (85.3, 75.3-92.4)
R0	64/64(100, 94.39-100)
Pathologic outcomes	
pCR	28/64 (43.7, 32.4-56.7)
MPR	47/64(73.4,60.91-83.7)
Non-MPR	17/64 (26.6, 16.3-30.1)
Tumor down-staging	54/64(84.37, 73.13-92.24)

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EP.08D.08 Aumolertinib as Neoadjuvant Therapy for EGFR M+ NSCLC: A Subcohort Analysis of PURPOSE Trial Data Updated

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Introduction: Recently, promising results with neoadjuvant targeted therapy and immunotherapy have been seen in resectable non-small cell lung cancer (NSCLC). Aumolertinib, a 3rd generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI), has been proven to be highly effective for postoperative and advanced NSCLC with EGFR mutations. The primary data has been published (WCLC 2023 EP07.05-17). Here, we update the data of aumolertinib as neoadjuvant treatment for resectable EGFRm+ NSCLC from the PURPOSE trial.

Methods: The PURPOSE trial is an open-label, prospective, phase II, umbrella study of precise neoadjuvant therapy for patients with stage II-IIIB resectable NSCLC. Eligible patients with EGFR 19del were given aumolertinib 110mg QD for 9 weeks followed by surgery, as one of the six cohorts in the PURPOSE trial. The primary endpoint was objective response rate (ORR). The secondary endpoints were major pathologic response (MPR) rate, pathological complete response (pCR) rate, event-free survival (EFS) and overall survival (OS).

Results: Up to March 26, 2024, 9 patients have completed the neoadjuvant treatment and received radical surgery. The median follow-up time were 12 months. 6 patients were females and 3 patients were males, 8 patients were lung adenocarcinoma and 1 was squamous cell carcinoma, 2 patients were stage II and 7 patients were stage III, 2 patients were N1 and 7 patients were N2. Remarkably, the ORR was 100%. Serious adverse event was not observed. All patients achieved R0 resection, 8 patients received VATS lobectomy (88.9%) and 1 underwent open bi-lobectomy. Importantly, 2 patients achieved pCR (pCR rate 22.2%, including one squamous cell carcinoma) and 1 achieved MPR (MPR rate 33.3%). 3 patients had pathological response (Tumor residual <50%). 3 patients pN2 and 6 patients pN0. The rate of N1 and N2 mediastinal lymph node downstage was 100% and 57.1%, respectively. After surgery, 7 patients received aumolertinib maintenance therapy and 2 patients received 4 cycles of chemotherapy combination with aumolertinib maintenance therapy. No intraoperative and postoperative complication was occurred. MRD detection were performed in all patients, MRD was detected before the treatment of aumolertinib neoadjuvant therapy and surgery, 3 months, 6 months, and 1 year after surgery. 5 patients completed MRD detection at 1 year, 4 patients completed MRD detection at 6 months after surgery. 7 patients were MRD positive and 2 patients were MRD negative before the treatment of aumolertinib neoadjuavant therapy, and later MRD were negative in all patients.

Conclusions: The subcohort analysis from the PURPOSE study has illustrated that aumolertinib as neoadjuvant therapy is effective and feasible for locally advanced EGFR 19del NSCLCs. The rest results of this study will be released in the future. Clinical trial information: ChiCTR2100053021

Keywords: Aumolertinib, Neoadjuvant targeted therapy, EGFR-mutated NSCLC

EP.08D.09 Efficacy and Safety of Neoadjuvant Tislelizumab Plus Chemotherapy for the Treatment of Non-Small Cell Lung Cancer: a Pooled Analysis

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Introduction: Although various effective Immune checkpoint inhibitors for the neoadjuvant treatment of non-small cell lung cancer (NSCLC) improved MPR/pCR rate, the optimal regimen remains controversial. Previous studies revealed that PD-1 inhibitor tislelizumab had extensive antitumor activities. However, the majority of studies on neoadjuvant tislelizumab in NSCLC are non-randomized controlled trials with small sample sizes, different treatment modes and uncontrolled statistical analysis. Here, this meta-analysis aims to evaluate the efficacy and safety of neoadjuvant tislelizumab plus chemotherapy in patients with NSCLC.

Methods: We performed a systematic literature review of trials reporting outcomes of neoadjuvant tislelizumab-based therapy on PubMed, Embase and the proceedings of the most relevant international conferences before December 2023. Eligibility criteria: Animal experiments, cell research, reviews, meta-analyses, duplicates, case report or letters were not in consideration; studies with less than 10 patients were excluded. The study was registered on the International Platform of Registered Systematic Review and Meta-analysis Protocols (INPLASY202430114). The statistical analysis was performed using R version 4.1.2 statistical computing software.

Results: A total of 9 studies with 280 patients were included in the meta-analysis. For neoadjuvant tislelizumab plus chemotherapy in NSCLC pts, the pooled pCR and MPR rate was 0.40 (95% CI 0.33-0.46) and 0.65 (95% CI 0.59-0.71) respectively, with an ORR 0.76 (95% CI 0.68-0.83). R0 resection rate was 1.0 (95% CI 0.98-1). The pooled incidence of all grade TRAEs was 0.89 (95% CI 0.69-1.00), and that of >= grade 3 TRAEs was 0.17 (95% CI 0.05-0.33).

Conclusions: According to our analysis, reliable efficacy and safety of neoadjuvant tislelizumab plus chemotherapy for NSCLC were demonstrated across multiple clinical trials.

Keywords: Neoadjuvant immunochemotherapy, Non-small cell lung cancer, Tislelizumab

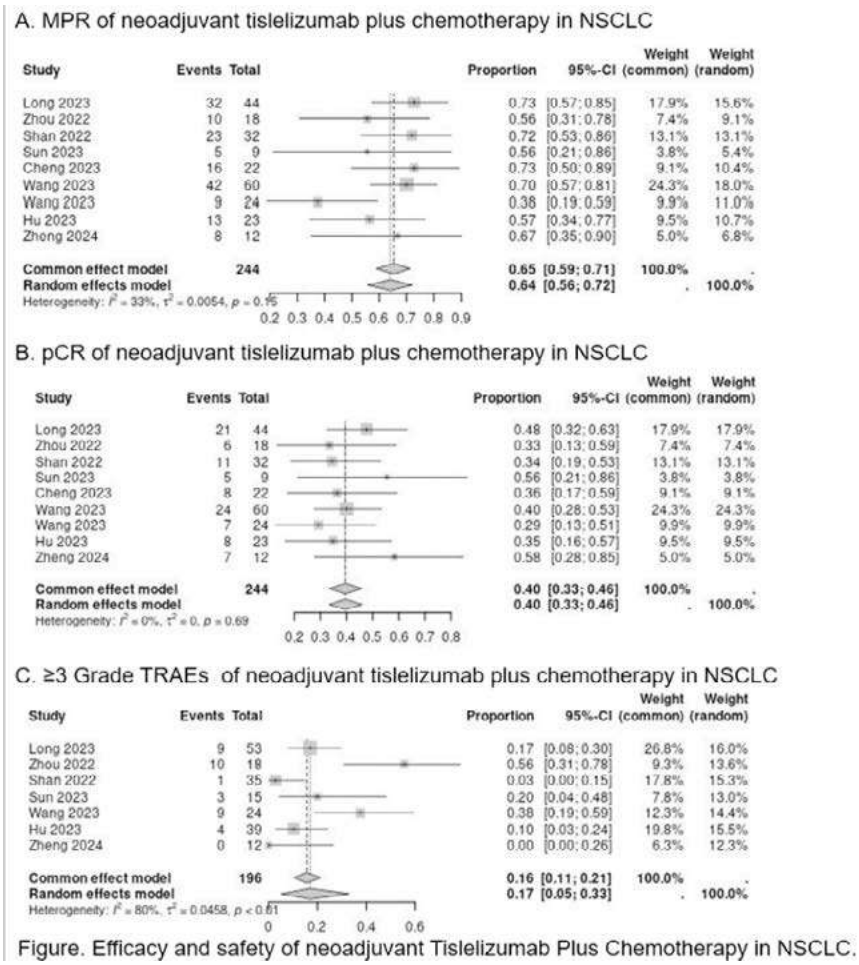

Figure. Efficacy and safety of neoadjuvant Tislelizumab Plus Chemotherapy in NSCLC.

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EP.08D.10 Outcome after Preoperative Chemoradiotherapy for Non-Small Cell Lung Cancer with Chest Wall Invasion

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Introduction: Multimodality treatment including anatomic lung resection and chest wall resection is recommended for patients with chest wall-invasive non-small cell lung cancer (NSCLC). Surgery after chemoradiotherapy (CRT) for chest wall invasive cancer has been reported to be safe and effective. On the other hand, there are few reports showing the outcomes of preoperative treatment for chest wall invasive cancer, excluding SST. We will clarify the outcomes of preoperative CRT for NSCLC with chest wall invasion at our institution.

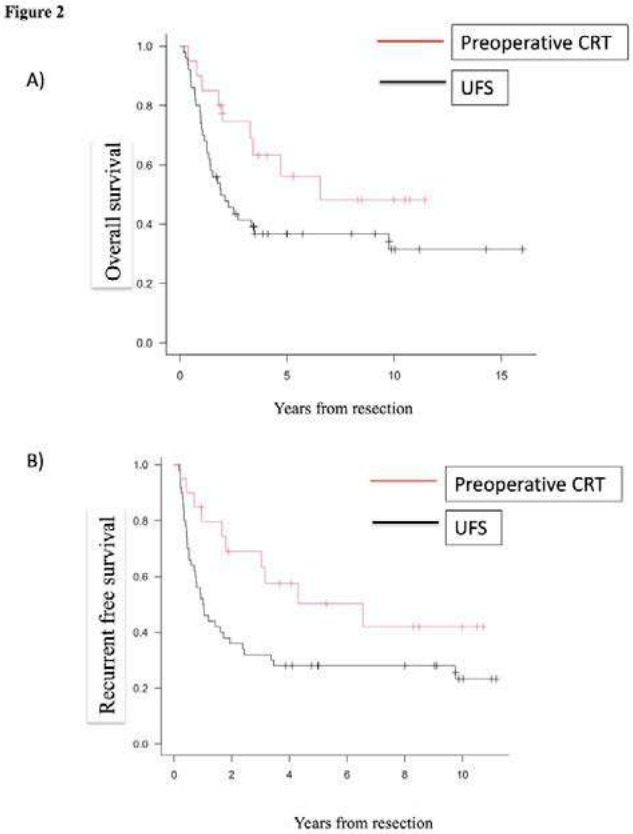
Methods: From 2000-2020, Seventy patients who underwent lobectomy or more for chest wall invasive cancer (NSCLC) with rib involvement on CT images were included in this study. The clinicopathological characteristics between the two groups, 20 patients in the preoperative CRT group and 50 patients in the upfront surgery (UFS) group, were clarified, and the 3- and 5-year OS, RFS prognosis, recurrence format, and cause of death were comparatively analyzed.

Results: The preoperative CRT group was more likely to be younger and cN0 with good PS and fewer serious postoperative complications than the UFS group. Five patients (25%) in the preoperative CRT group had pathologic complete response; 13 patients (25%) in the UFS group received postoperative adjuvant therapy. About 15% of patients in both groups were not curative. Median follow-up was 33.7 months. 3/5-year OS was 74/53% in the preoperative CRT group and 41/37% in the UFS group (HR=0.51, p=0.05). 3/5-year RFS was 63/42% in the preoperative CRT group and 30/28% in the UFS group (HR=0.49, p=0.04). As for recurrence, there was 1 (5%)/8 (16%) chest wall margin recurrence, 4 (20%)/23 (46%) distant recurrence, and 5 (20%)/27 (54%) lung cancer deaths.

Conclusions: The preoperative CRT group had a better prognosis than the UFS group. Future prospective studies examining the efficacy and safety of preoperative CRT (±ICI) for chest wall invasive cancer excluding SST need to be considered.

Keywords: Chest Wall Invasion, Chemoradiotherapy, Upfront surgery

Figure 2



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EP.08D.11 Redefining Prognosis in NSCLC after Neoadjuvant Immunotherapy: The Predictive Power of Pathologic Response and Lymph Node Status

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Introduction: This study evaluates the predictive value of pathologic response and lymph node status on progression-free survival (PFS) in patients with non-small cell lung cancer (NSCLC) undergoing neoadjuvant immunotherapy.

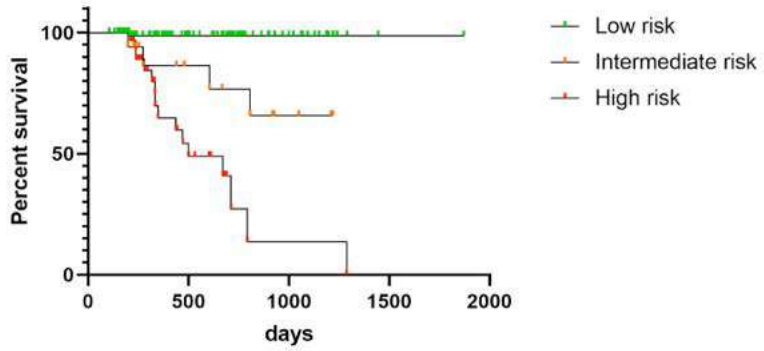
Methods: We conducted a retrospective analysis of 143 patients with potentially resectable NSCLC who underwent neoadjuvant immunotherapy followed by surgical resection. Data on pathologic response, lymph node involvement, and clinical outcomes were collected and analyzed. Kaplan-Meier analysis and Cox regression were used to evaluate the association between these factors and PFS.

Results: Both major pathological response (MPR) and complete pathological response (CPR) were significantly associated with improved PFS (p<0.01), with no statistical difference observed between them (p=0.15). Lymph node involvement adversely affected PFS (p<0.01). A novel risk stratification based on pathologic response and nodal status effectively distinguished prognosis (3-year PFS: 98.9%, 78.9%, 53.3%). Adjuvant immunotherapy did not demonstrate a clear benefit for PFS (p=0.62). Gender (p=0.02) and total pneumonectomy (p=0.04) emerged as prognostic factors.

Conclusions: MPR and CPR confer similar survival benefits in NSCLC after neoadjuvant immunotherapy. Lymph node status significantly influences prognosis. The proposed risk stratification provides a valuable tool for personalized management.

Keywords: neoadjuvant Immunotherapy, non-small cell lung cancer (NSCLC), Objective Response

Neoadjuvant immunotherapy's effects on NSCLC: Pathologic and nodal responses stratify PFS



	CPR	MPR	OR not achieved
N0	Low risk	Low risk	Intermediate Risk
N1	Low risk	Low risk	High Risk
N2	High Risk	High Risk	High Risk

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EP.08D.12 Comparision of Neoadjuvant Chemoimmunotherapy and Chemotherapy for Potentially Resectable Stage IIIA/B NSCLC

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Introduction: Currently, the treatment of stage III non-small-cell lung cancer (NSCLC) remains a significant challenge. It has been reported that the 5-year survival rate following surgery in patients with stage III NSCLC is only 13-36%. However, patients who received neoadjuvant chemoimmunotherapy could improve pathological response and downstaging of the tumor compared to neoadjuvant chemotherapy alone. However, most of these studies are single-armed trials with small sample sizes. Consequently, this study aimed to compare the real-world efficacy and safety of neoadjuvant chemoimmunotherapy to chemotherapy alone in patients with potentially resectable stage III NSCLC.

Methods: We retrospectively analyzed patients with newly diagnosed stage III NSCLC in our institution during 2018-2023. A total of 71 patients were finally selected including 46 patients in the neoadjuvant chemoimmunotherapy group and 25 patients in the neoadjuvant chemotherapy group. All patients were followed up to collect perioperative pathology and clinical data. SPSS 27.0 was used for statistics.

Results: Patients who received perioperative chemoimmunotherapy had significantly longer disease-free survival (DFS) (median DFS: NR vs. 15 months; hazard ratio [HR]=0.186, 95CI: 0.073-0.479, p=0.001). Patients who received neoadjuvant chemoimmunotherapy performed better overall survival (OS) (p=0.193). The objective response rate (ORR) in the combination group was higher compared with that of the chemotherapy group (73.9% vs. 60.0%), but without statistical significance (P = 0.123). The major pathological response (MPR) and pathological complete response (pCR) were significantly higher in the neoadjuvant chemoimmunotherapy group than in the neoadjuvant chemotherapy group (65.9% vs. 16.7%, 36.4% vs. 8.3%, respectively; P < 0.05). In subgroup analyses by pathological response, patients with a MPR had better DFS (P = 0.016) and OS (P = 0.032) than those with incomplete pathological response. We have also found that neoadjuvant chemoimmunotherapy was more effective in nodal downstaging (61.4% vs. 41.7%, p = 0.039). Although the incidence of all grades adverse events was higher in the neoadjuvant chemoimmunotherapy group than in the neoadjuvant chemotherapy group (80.4% vs. 64.0%), and the incidence of grade 3 and above adverse events was 10.9% (5 cases) and 8.0% (2 cases) respectively, none of these reached statistically significance.

Conclusions: Overall, neoadjuvant chemoimmunotherapy is effective and safe in potentially resectable stage IIIA/B NSCLC. Compared with chemotherapy alone, neoadjuvant chemoimmunotherapy provides a significant improvement in pathological response and DFS without increasing the incidence of adverse events.

Keywords: Non-small cell lung cancer, Neoadjuvant chemoimmunotherapy, Potentially resectable

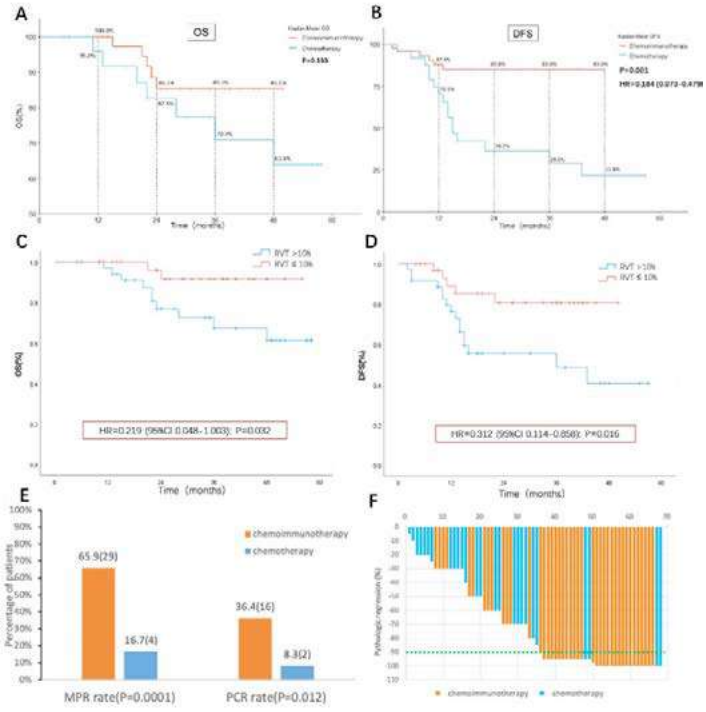

Fig.1 A-B, Kaplan–Meier curves depicting the OS (A) and DFS (B) for patients with potentially resectable stage IIIA/B NSCLC who received neoadjuvant chemoimmunotherapy or neoadjuvant chemotherapy. **C-D**, Kaplan–Meier curves show the association between MPR and OS (C) and between MPR and DFS (D). Regarding RVT, the category (0%–10%) corresponds to patients who achieved MPR; the category >10% corresponds to patients who did not achieve MPR. **E**, Comparison of pathological response between the two groups. **F**, Waterfall plot of pathological response to treatment. OS, overall survival; DFS, disease-free survival; NSCLC, non-small-cell lung cancer MPR, major pathological response; RVT, residual viable tumor cells (%); HR, hazard ratio; CI, confidence interval.

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EP.08D.13 Macrophage Polarization States Predicting the Efficacy of Neoadjuvantchemoimmunotherapyin Resectable or Potentially Resectable NSCLC

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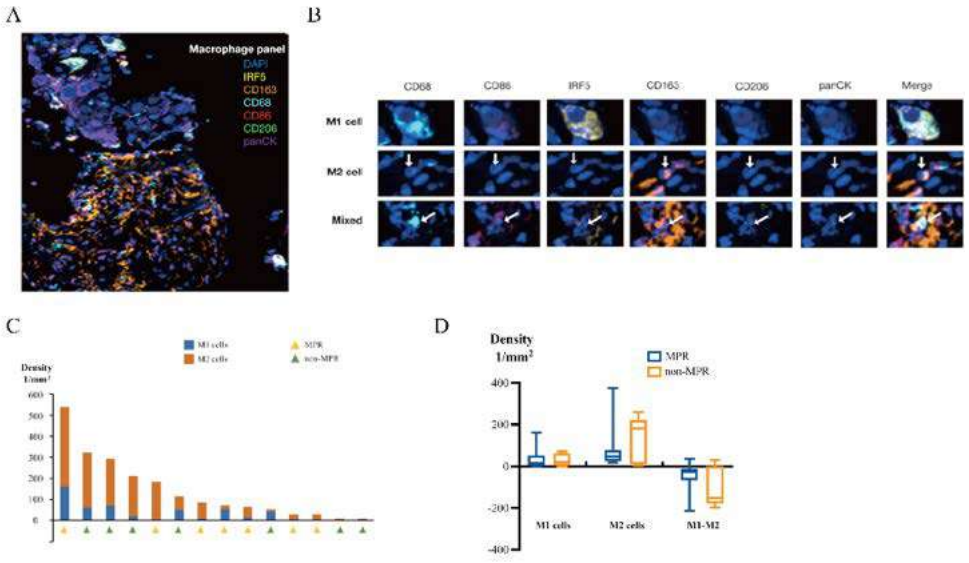
Introduction: Neoadjuvant chemoimmunotherapy has been proved beneficial for resectable or potentially resectable non-small cell lung cancer (NSCLC) in the neoadjuvant setting, while the predictive and prognostic biomarkers are still under investigation. This study aims to reveal the predictive role of macrophage polarization states in tumor microenvironment for patients who underwent neoadjuvant chemoimmunotherapy.

Methods: This study included stage I-IIIB resectable or potentially resectable NSCLC who required neoadjuvant therapy of immune checkpoint inhibitors combining with standard chemotherapy after assessment by surgeons. We classified patients into pathological response (MPR) group and non-MPR group, according to the pathological remission rate, defined by at least 90% tumor necrosis in the resected tissue. Multiple immunofluorescence (mIF) assay was performed for macrophage detection. The detected biomarker molecules included CD68, IRF5, CD86, CD206, CD163, panCK, and DAPI. The DAPI was a fluorescent dye that binds strongly to DNA and was used for preliminary identification of all cells. The panCK was a pan-cytokeratin marker used to identify lung cancer cells. The CD68 was a pan-macrophage marker. The CD86/IRF5 served as indicators of M1 macrophage polarization, while the CD163/CD206 served as indicators of M2 macrophage polarization. The relationship between the macrophage characteristics at baseline and the pathological responses was analyzed.

Results: A total of 14 samples from patients who had received 2-3 cycles of neoadjuvant chemoimmunotherapy followed by radical surgery was included for mIF analysis, with 7 cases in MPR group, and another 7 cases in non-MPR group. The distribution and characteristics of macrophage cells in one sample was shown in Fig A. As characterized by a pro-tumoral activity and the production of immune-suppressive cytokines, M2-polarized macrophages in both groups had relatively higher density than M1-polarized macrophages, characterized by having anti-tumoral activity and producing pro-inflammatory cytokines, shown in Fig B. In MRP group, the median number of M2 and M1 macrophages were 48/mm2 (range 18-376) and 16/mm2 (range 2-163), respectively (P=0.848); in non-MPR group, the median number of M2 and M1 macrophages were 181/mm2 (range 4-260) and 21/mm2 (range 3-71), respectively (P=0.949), shown in Fig C. However, the difference value in the density of M1-M2 macrophages was less than in MPR group than in non-MPR group (median difference value of 25/mm2 and 152 16/mm2, respectively).

Conclusions: Baseline M1/M2-polarized macrophages level may be related to the pathological reponses, therefore the detection of macrophage polarization states is potential in predicting the efficacy of neoadjuvant chemoimmunotherapy in resectable or potentially resectable NSCLC.

Keywords: Macrophage polarization states, Neoadjuvant chemoimmunotherapy, Predictive biomarker



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EP.08D.14 Long-Term Prognosis of Patients Undergoing Trimodality Therapy for Locally Advanced Non-Small-Cell Lung Cancer

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Introduction: Induction chemoradiotherapy (CRT) followed by surgery (trimodality therapy) is a therapeutic option for locally advanced non-small-cell lung cancer (NSCLC). In this study, we conducted a single-center retrospective analysis of the long-term prognosis of patients undergoing trimodality therapy for locally advanced NSCLC.

Methods: Patients treated with trimodality therapy between January 1999 and December 2021 were retrospectively analyzed. Overall survival (OS) and recurrence-free survival (RFS) were calculated from the initiation of induction CRT until death from any cause or the last follow-up for OS, and until confirmed recurrence at a local or distant site or death from any cause for RFS. Univariate analysis of OS and RFS was performed using the Kaplan-Meier method with the log-rank test. Multivariate analysis was conducted using the Cox proportional hazards model.

Results: A total of 206 patients underwent trimodality therapy. The median age at the time of surgery was 64.5 (range, 31-79), and 160 patients were male. The 7th edition of the TNM classification was used for disease staging, with clinical stages including II (n = 24), III (n = 178), and IV (n = 4). Tumor histology included adenocarcinoma (n = 120), squamous cell carcinoma (n = 77), or others (n = 9). The median radiation dose was 46 Gy, and 201 patients received platinum doublets. One hundred seventy-six patients completed the planned CRT, and 35 patients underwent more than lobectomy, while one patient underwent exploratory thoracoscopy solely due to pleural dissemination. Downstaging was achieved in 153 patients (74.3%), and 69 patients (33.5%) achieved a pathological complete response (pCR). Postoperative complications included pneumonia (n = 28), radiation pneumonitis (n = 32), bronchopleural fistula (n = 9), and 17 patients underwent reoperation. Adjuvant chemotherapy was administered to 92 patients (45.1%), and 89 patients (43.2%) developed recurrence. The median follow-up was 11.08 years (Kaplan-Meier estimate). Excluding the patient with pleural dissemination, the 3-, 5-, and 10-year OS rates were 77.8%, 68.2%, and 51.8%, respectively, and the 3- and 5-year RFS rates were 57.2% and 51.5%, respectively. Multivariate analysis showed that a history of other malignancy (P = 0.006), lower lobe tumors (P = 0.009), non-pCR (P = 0.004), and reoperation (P = 0.003) correlated with a worse prognosis. In non-recurrence patients, more than lobectomy (P = 0.02) and postoperative pneumonia (P = 0.04) were independent poor prognostic factors. It is considered that preserving lung function and preventing postoperative complications are important not only for short-term prognosis but also for long-term outcomes.

Conclusions: This study demonstrated the long-term prognosis of patients undergoing trimodality therapy for locally advanced NSCLC. Trimodality therapy is a feasible therapeutic option.

Keywords: Non-Small-Cell Lung Cancer, Trimodality Therapy, Long-term Prognosis

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EP.08D.15 Radical Surgery after Induction Therapy for Initially Unresectable Stage III Non-small Cell Lung Cancer

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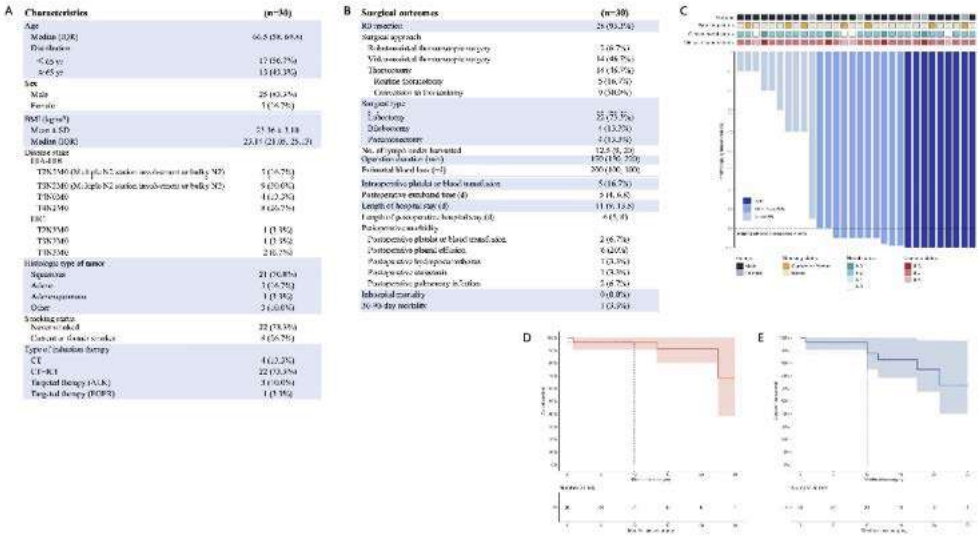
Introduction: Treatments for stage III non-small cell lung cancer (NSCLC) is controversial. Surgical resection is primarily recommended for T1-3 diseases with single station and non-bulky N2, while other stage III NSCLC are determined initially unresectable. Previous studies have shown that selective surgery after induction therapy could bring potential benefits for these patients. However, it requires strict operation indications and patient screening. This single-arm, prospective study evaluated the safety and feasibility of surgery after induction therapy for initially unresectable stage III NSCLC patients (NCT04945928).

Methods: Patients with initially unresectable stage III NSCLC who received induction therapy and evaluated operable for radical resection were included and underwent surgery. The primary endpoint is perioperative morbidity. The lymph nodes count, R0 resection rate, operation time, blood loss, operative complications, postoperative hospital stay, 30-day mortality, complete pathological remission rate (pCR) the rate of major pathological remission (MPR), one-year overall survival (OS), and one-year disease-free survival (DFS) were secondary outcomes.

Results: From August, 2021 to January, 2024, 30 patients were included (Figure 1A). Most of the patients received immunochemotherapy (23/30, 76.7%), others received chemotherapy (4/30, 13.3%) and targeted therapy (4/30, 13.3%) as induction therapy. The R0 resection rate was 93.3%. Ten out of 30 patients (33.3%) experienced post-operative morbidity with details shown in Figure 1B. No in-hospital mortality was observed, but one patient died 30-90 days after the surgery. MPR and pCR were achieved in 20 (20/30, 66.7%) and 9 (9/39, 30%), respectively (Figure 1C). The rate of one-year DFS was 87.5%, and one-year OS was 96.7% (Figure 1D-E).

Conclusions: Surgery after induction therapy was safe and feasible for initially unresectable stage III NSCLC patients, with acceptable surgical-related morbidity, MPR/pCR rate, and 1-year DFS/OS.

Keywords: stage III NSCLC, initially unresectable, surgery after induction therapy



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EP.08D.16 Neoadjuvant Chemoimmunotherapy in the Treatment of Stage III Non-Small Cell Lung Cancer: A Single-Center Initial Results.

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Introduction: Neoadjuvant immunotherapy combined with chemotherapy has demonstrated high efficacy in the treatment of patients with locally advanced non-small cell lung cancer. However, there is still not much data on the surgical feasibility as well as on the tumor response. We have analyzed our personal experience of using chemoimmunotherapy in combination therapy of patients with stage III NSCLC.

Methods: Patients with stage III resectable locally advanced NSCLC treated with neoadjuvant chemoimmunotherapy followed by surgery at The Loginov Moscow Medical Scientific Center from 2023 to 2024 were retrospectively included. Patients with activating mutations were not included in our study. Surgical, therapeutic and morphological outcomes were assessed.

Results: A total of 22 stage III locally advanced non-small cell cancer carcinoma patients were included in our study. All patients received 3 cycles of neoadjuvant chemoimmunotherapy with a subsequent assessment of the treatment response. The objective radiological response rate was 90.9% among all patients: complete response in 4 patients (18.2%), partial response in 16 patients (72.7%), and stable disease was achieved in 2 patients (9.1%). All patients underwent surgical treatment. A totally minimally invasive surgical treatment was successfully completed in 4 cases (18.2%). 7 patients (31.8%) received lobectomy with lymph node dissection, 3 patients (13.6%) underwent sleeve lobectomy with lymph node dissection, bilobectomy with lymph node dissection was performed in 4 cases (18.2%), 2 patients (9.1%) received pneumonectomy with carinal resection and both right and left pneumonectomy were performed in 6 patients (27.3%). A reduction in the volume of surgery was achieved in 7 patients (31.8%). All surgeries were performed in full and there was no residual tumor (R0). Complete pathological response was found in 8 patients (36.4%), in 13 cases (59.1%) major pathological response was achieved and only in 1 patient (4.5%) there was no pathological response. There were no significant therapeutic complications in postoperative period and no 30- or 90-day mortalities.

Conclusions: Surgical treatment after chemoimmunotherapy for resectable stage III NSCLC is feasible and safe. Moreover, neoadjuvant chemoimmunotherapy leads to a significant pathological response. This study has limitations, such as lack of PD-L1 scores and short follow-up period and further research is needed to analyze these data.

Keywords: Immunotherapy, Lung cancer

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EP.08D.17 Long-Term Survival Outcomes of Surgery after Neoadjuvant TKI for Locally Advanced Lung Adenocarcinoma Harboring Driver Gene Mutations

M. Aoki, G. Kamimura, S. Morizono, T. Tokunaga, A.H. Takeda, K. Maeda, T. Nagata, K. Ueda, Kagoshima University School of Medicine, Kagoshima/JP

Introduction: The optimal treatment for locally advanced non-small cell, including stage IIIA, remains controversial. In addition, tyrosine kinase inhibitors (TKIs) have been shown to be effective in lung adenocarcinomas with driver gene mutations, and the usefulness of surgery for lesions that remain after TKI treatment has been reported.

Methods: Between January 2016 and December 2018, ten patients with stage III lung adenocarcinoma harboring driver gene mutations were treated with TKI (EGFR-Exon19 deletion, n=5; EGFR-L858R point mutation, n=3; EGFR-L861Q point mutation, n=1; EML4-ALK rearrangement, n=1). With the exception of one patient who refused surgery, nine patients received two courses of platinum doublets and underwent surgery. Postoperatively, two to four courses of platinum doublet were added in six cases, and TKI was restarted in four cases.

Results: In all cases, the therapeutic effect of TKI was greater than a partial response (according to RECIST), and radical surgery was performed in nine cases, excluding one patient who refused surgery. Although residual cancer cells were histologically observed in the EGFR gene mutation-positive case, the expression of the EGFR-T790M point mutation was not observed. A complete pathological response was observed in the EML4-ALK rearrangement case. No major postoperative complications due to surgery were observed. One patient who refused surgery continued to receive Osimertinib for 30.1 months, but died 33.5 months after the initiation of treatment. Of the patients who underwent surgery, three were alive without recurrence, but six had distant metastases, including five with brain metastases. Among the cases in which TKI therapy was not restarted postoperatively, brain metastases were observed in three patients and lung metastasis was observed in one patient. In two of the cases in which TKI therapy was restarted, brain metastasis recurrence was observed 47.4 months after the administration of Erlotinib and 6.6 months after the administration of afatinib. In two cases who were not able to receive any adjuvant therapy, recurrence of brain metastasis was observed in the early postoperative period. At present, a median observation period of 77.2 months has passed since the initiation of treatment, and seven of the nine patients who underwent surgery are still alive.

Conclusions: We report the long-term survival outcomes of ten patients with stage III lung adenocarcinoma harboring driver gene mutations who received TKIs as neoadjuvant therapy. The treatment was feasible, and radical surgery was performed without major complications. Eight of the nine patients who underwent surgery survived for more than five years from the initiation of treatment, suggesting the usefulness of this treatment. It is difficult to completely cure EGFR mutation-positive cases with drug therapy alone, and radical surgery is desirable at some point. In addition, pretreatment radiological imaging showed locally advanced lung cancer, but a high rate of distant metastasis, mainly brain metastasis, was observed after surgery. This suggests the need for additional postoperative treatment, including TKI therapy.

Keywords: adenocarcinoma harboring driver gene mutation, neoadjuvant TKI, long-term survival outcome

EP.08E LOCAL-REGIONAL NON-SMALL CELL LUNG CANCER - CLINICAL SURGICAL
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EP.08E.01 Comparison of CT Findings Between Staple Line Granuloma and Recurrent Tumor after Sub-Lobar Resection for Lung Cancer and Pulmonary Metastasis.

T. An, Y.K. Cha, T.J. Kim, J. Lee, Samsung Medical Center, Seoul/KR

Introduction: The use of autonomous suture devices increased with the rise of thoracoscopic surgery in the treatment of lung cancer and the formation of staple line granuloma has been reported. Staple line granuloma is known to be more frequent in sub-lobar resection. Distinguishing between a recurrent tumor and staple line granuloma is clinically important. However, previous studies only included few cases of staple line granuloma. This study aimed to find CT imaging feature for differentiating staple line granuloma from recurrent tumor, especially in the case of sub-lobar resection for lung cancer and pulmonary metastasis.

Methods: A cross-sectional retrospective analysis was conducted on consecutive 57 patients, with pathologic confirmed staple line granulomas (n=21) and recurrent tumors (n=36), who underwent sub-lobar resection for lung cancer or pulmonary metastasis from 1 April 1995 to 1 May 2022. Three independent radiologists interpreted CT parameters as follows: lesion size, enhancement, internal low density, staple line abutting length, air-bronchogram, growth pattern (one side contact or radial), margin, satellite nodule, preserved vascular or lobular margin, and mediastinal or hilar lymph node enlargement. We compared CT parameters between staple line granuloma and recurrent tumor groups and analyzed univariate and multivariate logistic regression. We assessed inter-reader reliability for significant CT imaging features.

Results: For the reader 1, radial growth pattern (OR=0.014), enhancement (OR=0.943), internal low density (OR=21.000), air-bronchogram (OR=0.059), preserved vascular or lobular margin (OR=13.000) and satellite nodule (OR=31.818) were significant in univariate analysis ($p < 0.01$), while only radial growth pattern (OR=0.046) and air-bronchogram (OR=0.055) were significant in multivariate analysis ($p<0.05$). For the reader 2, internal low density (OR=24.700), air-bronchogram (OR=0.067), preserved vascular or lobular margin (OR=12.750) and satellite nodule (OR=21.538) were significant in univariate analysis but only internal low density (OR=14.142), air-bronchogram (OR=0.015) and preserved vascular or lobular margin (OR=21.019) were significant in multivariate analysis. For the reader 3, margin (smooth vs. lobulated; OR=0.123), internal low density (OR=47.5), air-bronchogram (OR=0.053), preserved vascular or lobular margin (OR=8.250) and satellite nodule (OR=31.818) were significant in univariate analysis, while only internal low density (OR=158.891) and air-bronchogram (OR=0.002) significant in multivariate analysis. Inter-reader reliability was good to almost perfect (weighted kappa=0.648-0.953).

Conclusions: If suspicious lesion is detected at suture margin after sub-lobar resection, the presence of internal low density and preserved vascular or lobular margin on CT may suggest possibility of staple line granuloma. Whereas, if the air-bronchogram or radial growth pattern is accompanied, recurrent tumor should be considered.

Keywords: lung cancer, sub-lobar resection, staple line granuloma

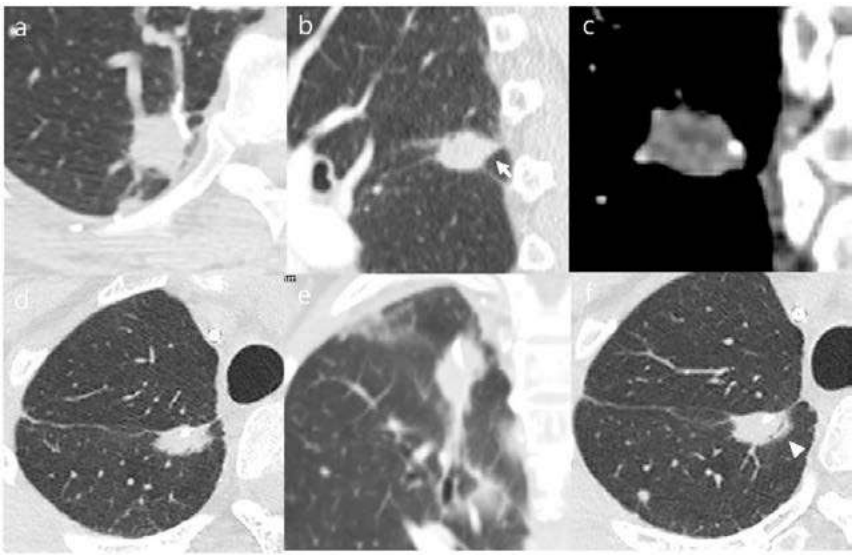

Figure 1. Representative CT image of staple line granuloma (a-c) and tumor recurrence (d-f).

Axial scan (a) with lung window setting shows staple line granuloma with one-side abutting growth pattern at staple line. Sagittal scan (b) shows preserved lobular margin (arrow) and coronal scan (c) shows internal low density of staple line granuloma. Axial (d) and coronal (e) scan with lung window setting shows recurrent tumor with radial growth pattern around the staple line. Same nodule at different slice section, axial scan with lung window setting (f) shows air-bronchogram (arrowhead).

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EP.08E.02 Long Term Impact of IASLC Uncertain Resection (Run) Definition in Surgically Resected pN2 Non-Small Cell Lung Cancer

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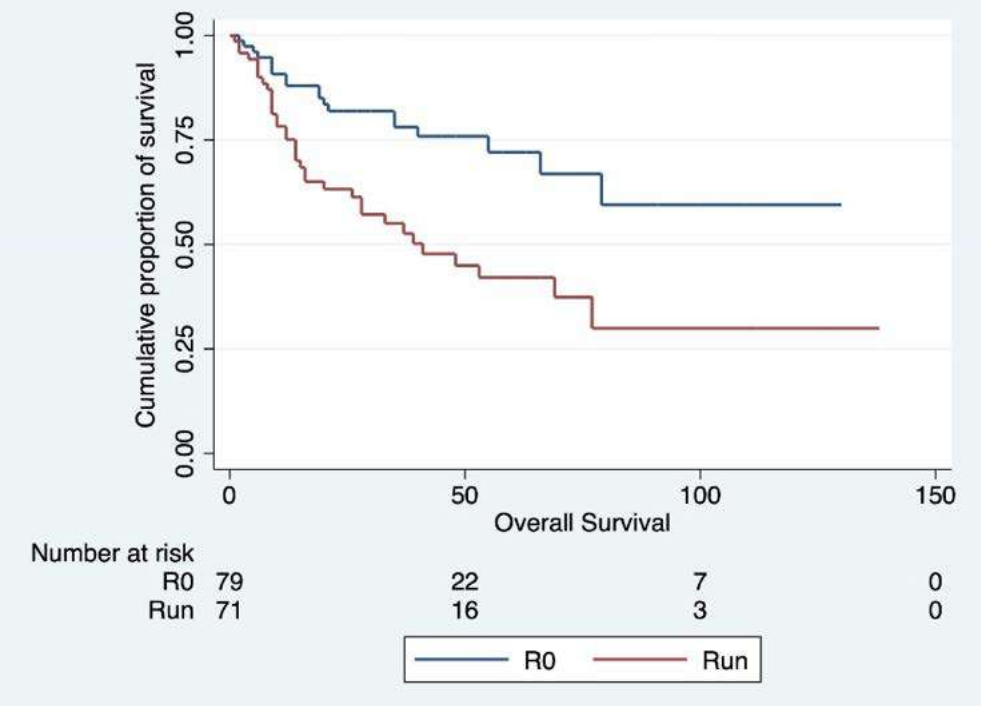
Introduction: In 2019 IASLC better defined surgical radicality for Non-Small Cell Lung Cancer (NSCLC) introducing the concept of uncertain resection (Run) in addition to R0, R1 and R2. Briefly, in case of pathological N2 patients, the presence of metastasis in the highest lymph-node resected and/or a lymphadenectomy below guidelines' standards should be defined as Run.The aim of this study is to analyze the long-term impact of Run in a cohort of surgically treated pN2 NSCLC.

Methods: We prospectively collected all consecutive surgically resected pathological N2 patients from three high-volume institutions between 2016 and 2021. All preoperative, intraoperative and long-term postoperative data were collected and analyzed. Patients with incomplete follow-up information were excluded.

Results: Among 155 patients, mean age was 67.2 years (range 38-90) and 61 (39.4%) were female. Neoadjuvant was administered to 35 patients (22.6%) and 116 (74.8%) received a lobectomy. A pathological single N2 station involvement was identified in 98 patients (63.2%) and 97 patients (62.6%) had a concomitant N1 involvement. R0 resection was seen 83 patients (53.5%) and the remaining 72 (46.5%) were classified as Run. Adjuvant therapy was administered to 99 patients. At follow up, recurrence occurred in 94 cases (60.6%) and 45 were loco-regional. Patients with a single N2 station involvement had a better overall survival (OS) compared to multiple stations, but it was not significant (p=0.163). Patients with R0 resection had a significant better OS compared to Run patients (p<0.001, figure 1) and a better disease-free survival (DFS, p<0.001). Run patients had a significant higher recurrence rate (p=0.002), but no difference in recurrence site (loco-regional or distant) was found between R0 and Run (p=0.544). Run patients exhibited a worse OS and DFS also in the subgroup of patients who received adjuvant therapy (p=0.010 and p=0.016 respectively). At multivariable analysis age (p=0.029, HR 1.036 95% CI 1.004-1.007), no adjuvant therapy (p=0.038, HR 1.902 95% CI 1.037-3.486) and Run (p=0.024, HR 1.910 95% CI 1.088-3.351) were independent prognostic factors for a worse OS.

Conclusions: In our cohort of resected pN2 NSCLC, patients with older age and no adjuvant therapy had worse long-term outcomes. Moreover, uncertain resection was significantly related to worse OS and DFS compared to R0 patients; this significant difference was confirmed in the subgroup of patients who received adjuvant therapy. Our data suggest that Run population might require a more careful and tailored postoperative management given their higher risk of recurrence and mortality.

Keywords: Uncertain resection, Non-small cell lung cancer, Thoracic Surgery



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EP.08E.03 Clinical Characteristics and Outcomes in Resectable Stage III ALK-Positive Non-Small Cell Lung Cancer: A Multicenter Real-World Cohort Study

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Introduction: Resectable stage III non-small cell lung cancer (NSCLC) needs multimodal therapy, particularly for patients harboring driver gene mutations. Nonetheless, data concerning resectable stage III ALK-positive NSCLC are limited.

Methods: This study was a multicenter real-world cohort study to examine clinical characteristics and outcomes among patients with resectable stage III ALK-positive NSCLC. Cox proportional hazards analysis was utilized to assess the impact of risk factors on clinical outcomes.

Results: Out of the 133 enrolled patients, the median age were 52.6 (19-75), 80 (59.7%) were female, and 98 (73.7%) were never-smokers. After a follow-up with 53.13 months, the 5-year overall survival (OS), 5-year progression-free survival (PFS), median OS, and median PFS were 74.8%, 14.6%, not reached, and 20.8 months, respectively. 94 (70.1%) patients relapsed, and 74 (55.2%) patients had distant metastasis, including 26 (19.4%) with brain metastasis, 16 (11.9%) with bone metastasis, and 15 (19.4%) with lung metastasis. Salvage ALK TIKs after disease progression significantly improved the OS (5-year OS, 72.5% vs. 95.4%, P = 0.015). 15 patients were treated with surgery and upfront ALK TKIs. Upfront ALK TKIs significantly prolonged median PFS (mPFS, NA vs. 17.8 months, P < 0.0001), while OS data were immature (5-year OS, 100.0% vs. 73.1%, P = 0.015). Histological type emerged as an independent prognostic factor for poorer OS (univariate Cox regression analysis: HR = 3.36, P = 0.049; multivariate Cox regression analysis: HR = 3.47, P = 0.049).

Conclusions: Patients with resectable stage III ALK-positive NSCLC are at high risk for relapse, with distant metastasis being the predominant pattern of failure. Salvage ALK TKIs can confer relatively prolonged survival for these patients. Combining surgery with upfront ALK TKIs represents a promising therapeutic strategy.

Keywords: Anaplastic lymphoma kinase, non-small cell lung cancer, surgery

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EP.08E.04 Not all pN1 Are the Same: Stations 12-14 Involvement, an Independent Prognostic Factor of Better Survival

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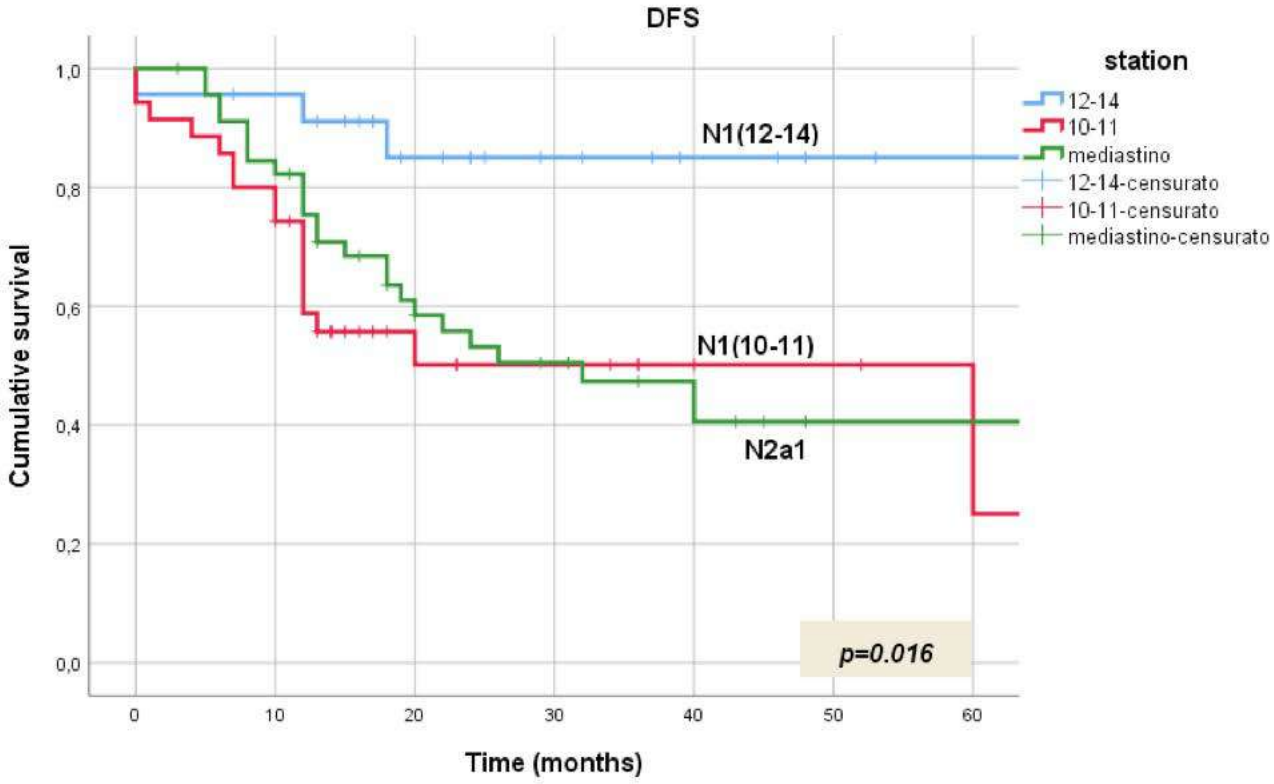
Introduction: The nodal status is still considered one of the most important prognosticators as well as crucial to establish the optimal treatment strategy for resectable NSCLC. The latest IX edition of lung TNM include only one change in N2 descriptors, but several changing proposals are under evaluation along with the role of different metastatic N1 stations (Hilar/Interlobar 10/11, Peripheral 12-14). The aim of our study was to analyse the impact of different lymph node location on overall survival (OS) and Disease-Free Survival (DFS).

Methods: A retrospective analysis of 104 patients (68% male, mean age 67 years) who underwent an anatomical resection (segmentectomy or lobectomy) and a systematic lymph node dissection for T1/T3 single station N1-N2 NSCLC (VIII TNM edition) adenocarcinoma or squamous cell carcinoma between 2013 and 2023 in a single centre, was conducted. Patients with >2 metastatic lymph nodes, who underwent induction therapies or extended/incomplete resections were excluded. All patients were divided into three groups: pN1(12-14), pN1(10-11) and pN2a1("skip N2", N2 positive node without N1 involvement). OS, DFS and risk factors of pN1(12-14), pN1(10-11) and pN2a1 were analysed

Results: An overall mean number of 11 (±5.8) lymph nodes were resected: 5.1 (±3.1) from the hilum and 6,2 (±4,1) from the mediastinum. The median lymph node ratio was 0,16. After grouping all cases according to N+ location we observed: 23 pN1(12-14) (22%), 35 pN1(10-11) (34%) and 46 pN2a1(44%). With a median follow up of 40 months, the median OS and DFS were 36 and 28 months respectively. pN1(12-14) had a significant better OS (p=0,005) and DFS (p=0,016) when compared with the other two groups. 5-year OS and 5-year DFS for pN1(12-14), pN1(10-11), pN2a1 were 91%, 31%, 41% and 85%, 25%, 40% respectively. At univariate analysis pN1(12-14) was confirmed a good prognosticator for both OS (p=0,019) and DFS (p=0,012).

Conclusions: Our data underlined the importance of peripheral N1 lymph node. Patients with metastasis in station 12-14 lymph nodes have a significant better prognosis compared both to other pN1 and pN2a1 groups

Keywords: intrapulmonary lymph node, NSCLC, long term survival



EP.08E LOCAL-REGIONAL NON-SMALL CELL LUNG CANCER - CLINICAL SURGICAL
SATURDAY, SEPTEMBER 7, 2024 - 11:58 - 11:59

EP.08E.05 The Presence of NSCLC Results in Diminished Ventilation in the Affected Lung

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Introduction: Pulmonary tumors have long been associated with hypoxic environments, yet the reciprocal relationship between tumors and local ventilation remains underexplored. Ventilation-perfusion scintigraphy (VPS) has emerged as a valuable tool for assessing pulmonary function and regional ventilation-perfusion status. This study aims to utilize VPS to investigate the impact of tumors on surrounding ventilation and understand how the oxygen environment influences tumor survival.

Methods: 365 patients diagnosed with non-small cell lung cancer with a single lesion were enrolled. Lesion characteristics (including size, location, specific pathological subtypes), VPS results, and survival data were collected. Statistical analyses including chi-square, t-tests, and Kaplan-Meier survival analysis were employed to assess the influence of tumor location on pulmonary ventilation and overall survival rate.

Results: Tumor presence significantly impacted ventilation in the corresponding lung ($\chi 2 = 17.74$, $p < 0.001$). Patients with right lung tumors exhibited a 3.82% decrease in right lung ventilation compared to those with left lung tumors (ventilation percentage with right-sided occupancy: 52.74% ± 13.11%, without occupancy: 56.82% ± 12.47%, $p < 0.05$), Similarly, patients with left lung occupancy showed a 4.08% decrease in left lung ventilation percentage compared to those with right lung occupancy (ventilation percentage with left-sided occupancy: 43.19% ± 12.47%, without occupancy: 47.26% ± 13.11%, $p < 0.05$). This trend persisted across adenocarcinoma and squamous cell carcinoma patients (adenocarcinoma: $\chi 2 = 4.81$, $p < 0.05$; squamous cell carcinoma: $\chi 2 = 16.30$, $p < 0.05$). Among 216 patients with survival data, Kaplan-Meier curves revealed that lung ventilation volume and tumor location were not independent predictors of overall survival (lung ventilation volume group HR: 0.910; 95% CI: 0.485-1.706; P = 0.087, tumor location group HR: 1.394; 95% CI: 0.778-2.500; P = 0.262). However, when tumor occupancy was present, patients with greater ventilation on the same side as the tumor exhibited a significantly higher five-year survival rate compared to those with greater ventilation on the opposite side (HR: 0.416; 95% CI: 0.198-0.874; P < 0.05).

Conclusions: This study demonstrates that tumors induce a reduction in ventilation in the corresponding lung, regardless of tumor type. This suggests that local pulmonary ventilation alterations are not solely due to the obstructive effect of tumors themselves. Furthermore, ventilation status surrounding the tumor may impact prognosis, as patients with poorer ventilation on the tumor side have a worse prognosis compared to those without significant ventilation decrease.

Keywords: Non-small cell lung cancer, Hypoxia, Ventilation perfusion scintigraphy

EP.08E LOCAL-REGIONAL NON-SMALL CELL LUNG CANCER - CLINICAL SURGICAL
SATURDAY, SEPTEMBER 7, 2024 - 11:58 - 11:59

EP.08E.06 The Peripheral Bronchial Occlusion or Stenosis after Dumon Y-stenting is Prognostic Factor in Patients with Advanced Lung Cancer

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Introduction: Dumon Y-stenting for tracheal bifurcation stenosis due to primary advanced lung cancer is useful procedure in relieving patient symptoms and leading to post-stenting chemotherapy and/or radiation therapy. However, we often encounter patients with airway stenosis ranging from the trachea to the orifice of the lobar bronchi or bronchus intermedius, which cannot be wholly covered with a simple Y-stent. We have often customized Y-stent with a small window for right upper bronchus or an additional metallic stent in bronchus intermedius to maintain peripheral bronchus patency. Despite of these efforts, insufficient patency of peripheral bronchus including stenosis or occlusion, lead to obstructive pneumonia, might be affect subsequent therapy for lung cancer. The purpose of this study was to evaluate the poor prognostic factors after Y stenting for bifurcation stenosis in patients with advanced lung cancer.

Methods: From 2012 to 2022, 116 patients who had placed Dumon Y-stent via rigid bronchoscopy under general anesthesia for tracheobronchial stenosis due to primary advanced lung cancer were examined retrospectively. This study involved 82 male and 34 female. The mean age was 67 years (range,30-91). The observation period was 229 days(range,4-1947). A two-week mortality after stenting were observed in 8 patients. In histological type, squamous cell carcinoma in 61, adenocarcinoma in 23, small cell carcinoma in 12, and others in 20 patients. The pre-stenting and post-stenting therapy for lung cancer was performed in 53(46%) and 71(61%) patients, respectively. Simple Y-stent was implanted in 78, Y-stent with small window for right upper bronchus in 9, and Y-stent with metallic stent in 29 patients. To identify prognostic factors, univariate and multivariate analysis were conducted.

Results: The respiratory symptom improved in all patients. The ratio of patients with PS3-4 (ECOG) improved to 17% (n=20/116) after stenting compared to 59% (n=68/116) before stenting. There were 53 patients (46%) of insufficient peripheral bronchial patency after stenting. Univariate analysis showed significantly worse prognosis in post-stenting PS3-4 compared to PS0-2(median survival time:1.8 vs. 4.7months), males (2.6 vs. 7.2), administration of pre-stenting therapy for lung cancer (3.0 vs. 7.0), no post-stenting therapy (1.6 vs. 7.6) and insufficient peripheral bronchial patency (2.3 vs. 7.3), respectively. There were no significant differences in histological type, type and size of Y-stent, and number of stents implanted. Multivariate analysis revealed post-stenting therapy (HR 4.7;2.6-7.7, p<0.001) and insufficient peripheral bronchial patency (HR 1.6;1.0-2.6, p=0.032) were independent prognostic factors. The insufficient peripheral bronchial patency was also significantly correlated with post-stenting chemotherapy and/or radiation therapy for advanced lung cancer.

Conclusions: The insufficient peripheral bronchial patency, such as stenosis or occlusion after Y-stenting was independent prognostic factor affecting the subsequent therapy for advanced lung cancer.

Keywords: Y-stent, prognosis, insufficient patency

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EP.08E.07 Optimal Surveillance Interval and Prediction Models of Short-term Mortality Risk for Elderly Patients (≥70) after Lung Cancer Surgery

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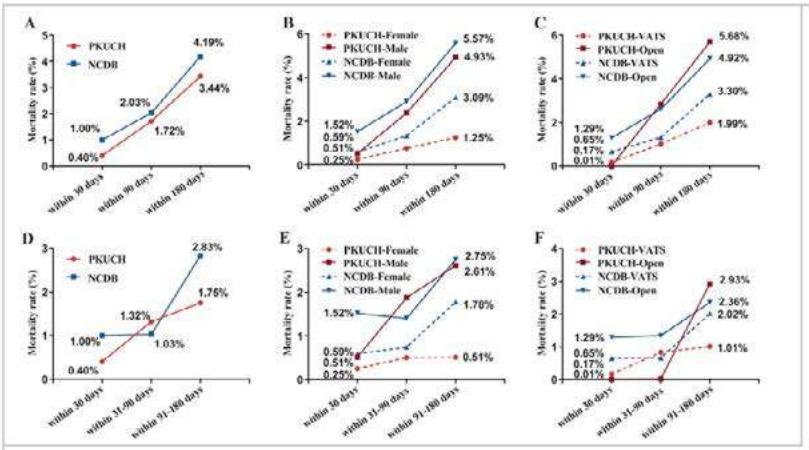
Introduction: Lung cancer surgery is now commonly adopted on septuagenarians and octogenarians. Due to increased vulnerability to surgery, geriatric patients have higher incidence of postoperative morbidity and mortality than younger counterparts. Thus, optimal surveillance interval and prediction models for mortality after surgery are needed to support decision-making and risk evaluation.

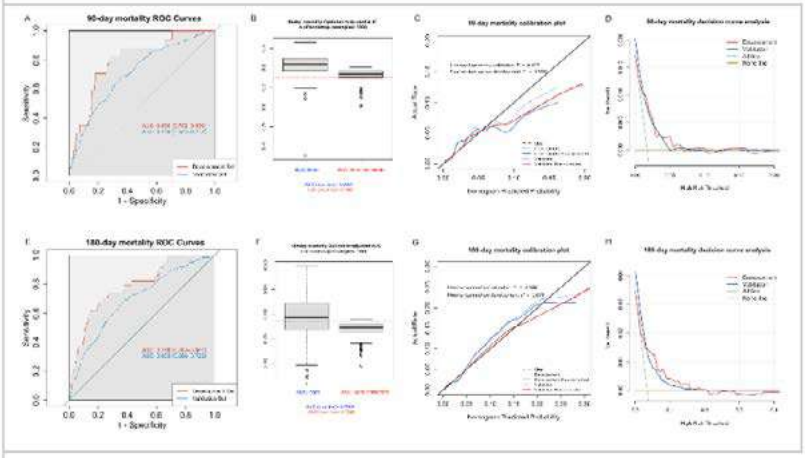
Methods: Clinical data of 989 patients (≥70 years) from Peking University Cancer Hospital (PKUCH) were collected for prediction model development and 16,321 patients were queried from National Cancer Database (NCDB) for external validation. Mortality rates were calculated for legitimate measure of optimal surveillance interval for elderly patients. Logistic regression was used to determine the structure of the prediction models and prediction performances were assessed by discrimination, calibration, and clinical utility. Meanwhile, area under the curve (AUC) of receiver operating characteristic curves and decision curve analysis (DCA) were performed for the assessment.

Results: Short-term mortality showed similar increasing trend from 30 days to 180 days after surgery in PKUCH cohort and NCDB cohort (0.40% and 1.00% within 30 days; 1.03% and 1.32 % within 31-90 days; 2.83% and 1.75% within 91-180 days; For cumulative mortality rates, 1.72% and 2.03% within 90 days, 3.44% and 4.19% within 180 days, respectively). Prediction models for 90-day and 180-day mortality consisted 4 similar predictors (age, gender, tumor diameter and surgery approach, AUC=0.80 and 0.79 in internal validation; AUC=0.71 and 0.69 in external validation). DCA proved the prediction models brought more benefit to elderly patients in clinical practice.

Conclusions: Besides of traditional 30- and 90-days mortality, 180- days mortality was suggested to complement surgical quality surveillance for elderly patients. Optimal performance of prediction models for 90- and 180-day mortality in different ethic cohorts suggest a potentially value of universal application for surgical decision-making in elderly patients. An easy-to-use online prediction model tools can be used at https://ai.dev.linkdoc.com/internal/xueke/lixiang/v2.

Keywords: Elderly lung cancer patient, Optimal surveillance interval, Mortality prediction models





EP.08E LOCAL-REGIONAL NON-SMALL CELL LUNG CANCER - CLINICAL SURGICAL
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EP.08E.08 Local Advanced Lung Cancer: Artificial Intelligence, Complex System Analysis, Simulation of Alive Supersysems for Optimal Management

O. Kshivets, Bagrationovsk Hospital, Bagrationovsk/RU

Introduction: The survival of patients with local advanced of lung cancer (LC) takes several months. Radical operations are extremely complex and remain the prerogative of several top thoracic surgeons of the world. The search of optimal treatment plan for LC patients (LCP) with stage T3-4N0-2M0 was realized. We examined factors in terms of precise prediction of 5-year survival (5YS) of local advanced LCP after complete (R0) combined lobectomies/pneumonectomies (LP).

Methods: We analyzed data of 198 consecutive LCP (age=58.1±8.2 years; tumor size=6.8±2.6 cm) radically operated and monitored in 1985-2024 (m=173, f=25; bi/lobectomies=84, pneumonectomies=114, mediastinal lymph node dissections=198; combined LP with resection of trachea, carina, atrium, aorta, VCS, vena azygos, pericardium, liver, diaphragm, ribs, esophagus=198; only surgery-S=117, adjuvant chemoimmunoradiotherapy-AT=81: CAV/gemzar + cisplatin + thymalin/taktivin + radiotherapy 45-50Gy; T3=137, T4=61; N0=94, N1=44, N2=60, M0=198; G1=42, G2=53, G3=103; squamous=118, adenocarcinoma=65, large cell=15, central=115, peripheral=83. Multivariate Cox modeling, clustering, SEPATH, Monte Carlo, synergetics, bootstrap and neural networks computing were used to determine any significant dependence.

Results: Overall life span (LS) was 1671.7±1721.6 days and cumulative 5YS reached 62.4%, 10 years - 50.4%, 20 years - 44.6%. 94 LCP lived more than 5 years without cancer (LS=2958.6±1723.6 days), 22 - more than 10 years (LS=5571±1841.8 days). 67 LCP died because of LC (LS=471.9±344 days). AT significantly improved 5YS (68% vs. 53.7%) (P=0.028 by log-rank test). Cox modeling displayed that 5YS of LCP significantly depended on: N0-N12, T3-4, blood cell circuit, cell ratio factors (ratio between cancer cells-CC and blood cells subpopulations), LC cell dynamics, recalcification time, heparin tolerance, prothrombin index, protein, AT, procedure type (P=0.000-0.031). Neural networks, genetic algorithm selection and bootstrap simulation revealed relationships between 5YS and N0-12 (rank=1), thrombocytes/CC (rank=2), segmented neutrophils/CC (3), eosinophils/CC (4), erythrocytes/CC (5), healthy cells/CC (6), lymphocytes/CC (7), stick neutrophils/CC (8), leucocytes/CC (9), monocytes/CC (10). Correct prediction of 5YS was 100% by neural networks computing (error=0.000; area under ROC curve=1.0).

Conclusions: 5YS of local advanced non-small cell LCP after combined radical procedures significantly depended on: tumor characteristics, LC cell dynamics, blood cell circuit, cell ratio factors, biochemical factors, hemostasis system, anthropometric data, adjuvant treatment and procedure type. Optimal strategies for local advanced LCP are: 1) availability of very experienced thoracic surgeons because of complexity radical procedures; 2) aggressive en block surgery and adequate lymph node dissection for completeness; 3) precise prediction; 4) AT for LCP with unfavorable prognosis.

Keywords: local advanced lung cancer, surgery, survival

EP.08E LOCAL-REGIONAL NON-SMALL CELL LUNG CANCER - CLINICAL SURGICAL
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EP.08E.09 Safety and Feasibility of Uniportal Robotic Lung Resection

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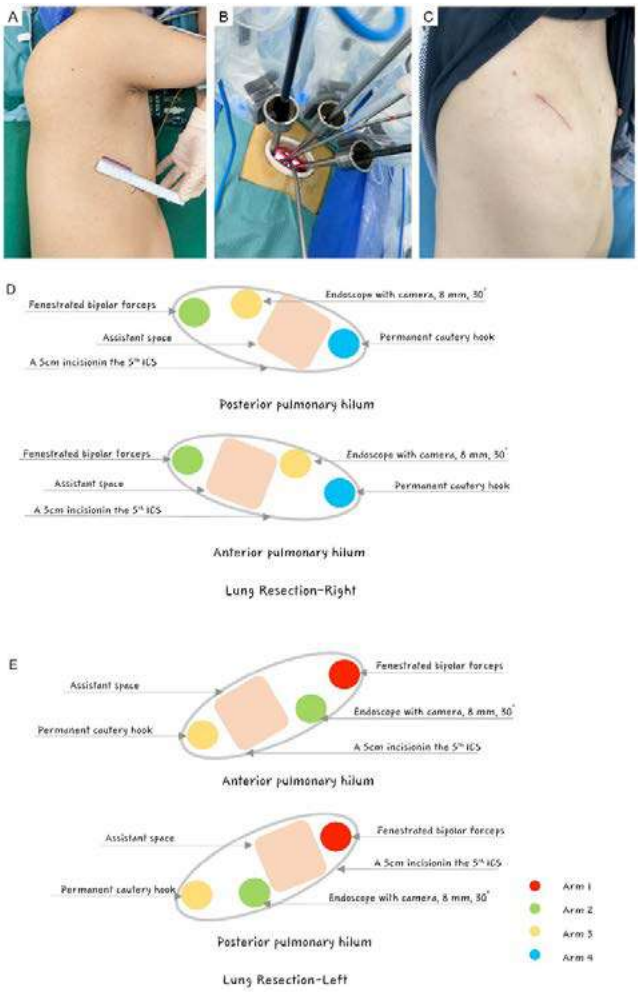
Introduction: Multi-port robotic-assisted thoracic surgery (RATS) has been comprehensively evaluated for its clinical efficacy through numerous studies. The safety and feasibility of uniportal robotic-assisted thoracoscopic surgery (U-RATS) remain further validated. We have summarized our experience in performing U-RATS via the da Vinci Xi system over the past 4 months.

Methods: Clinical data of 15 non-small cell lung cancer patients who underwent U-RATS at our hospital between November 2023 and February 2024 were reviewed retrospectively. U-RATS was conducted using the da Vinci Surgical Xi system. A utility incision of 4 to 5 cm in the mid-posterior axillary line is made between the 5th intercostal space (Figure 1A-C). Three robotic arms (1, 2, and 3 arms (for left lung resection) or 2, 3, and 4 arms (for right lung resection)) are usually selected during the procedure (Fig. 1D-G).

Results: U-RATS was undertaken in 15 patients (7 males, 46.66%, and 8 females 53.33%), and the median age was 60 years (interquartile range (IQR), 40-69 years). The median BMI of all the patients was 21.7 kg/m2 (IQR, 18.69-26.70 kg/m2). The median forced expiratory volume in 1 second (FEV1) of 90.59% (IQR, 70.95-122.05%) of predicted and median forced vital capacity (FVC) of 93.86% (IQR, 70.70-134.05%) of predicted. Lobectomy was conducted in all patients, including right upper (4/15, 26.66%), right middle (3/15, 20.00%), right lower (3/15, 20.00%), left upper (3/15, 20.00%), and left lower (2/15, 13.33%). The median U-RATS procedural duration was 151 min (IQR, 93-270 min, 162.33 ± 47.26 min), and the median intraoperative blood loss volume was 20 mL (IQR, 15-100 mL, 30.33 ± 22.08 mL) respectively. None of them were converted to thoracotomy and reoperation. The median time interval for chest tube placement and postoperative hospital stay was 4 days (IQR, 3-7 days) and 6 days (IQR, 3-14 days). Postoperative complications included pneumonia (2/15, 13.33%) and atrial fibrillation (1/15, 6.67%) graded as Clavien-Dindo I-II, while none of the patients experienced grade III-IV complications. Based on the TNM staging system, one(6.67%), ten (66.67%), two (13.33%), and two (13.33%) patients were evaluated as pathological stage 0, I, II, and III, respectively. The median number of lymph nodes dissected was 22 (IQR, 10-38), and the median station number dissected was six (IQR, 5-6). No wound infection and postoperative 30-day mortality.

Conclusions: The safety and feasibility of uniportal RATS procedures using the da Vinci Surgical Xi system have been preliminarily validated

Keywords: uniportal, Robot-assisted thoracoscopic surgery (RATS), non-small cell lung cancer



EP.08F LOCAL-REGIONAL NON-SMALL CELL LUNG CANCER - UNRESECTABLE NSCLC
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EP.08F.01 Predicting Radiation Pneumonitis with Baseline Pulmonary Function Tests in Patients with Locally Advanced Non-Small Cell Lung Cancer (NSCLC)

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Introduction: Radiation pneumonitis (RP) poses a significant challenge in the management of patients with locally advanced NSCLC undergoing chemoradiation therapy (CRT). In addition to respiratory toxicity, RP complicates decisions related to consolidation immunotherapy. We investigated the role of baseline pulmonary function tests (PFTs) in predicting RP risk by using a novel radiographic score in addition to clinical symptoms.

Methods: Unresectable stage II-III NSCLC patients who underwent CRT (50-70 Gy) without immunotherapy consolidation between 2010 to 2021 at a tertiary hospital in New York were identified. All patients had PFTs within 1 year prior to start of treatment, which included forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1), diffusing capacity (DLCO), total lung capacity (TLC), residual volume (RV), and RV/TLC. Surveillance computer tomography scans for one year after treatment completion were reviewed by a thoracic radiologist for presence of RP and graded accounting for the density (score: 0-2) and extent (score: 0-4) of opacities in each of the five lung lobes (total score: 0-40). RP was defined as radiographic score of ≥ 6 and/or by clinical documentation.

Results: Among 81 eligible patients, the mean age was 68 years old; 46% were white, 58% had stage 3A disease, and 78% and 16% were former and current smokers, respectively. The mean FVC was 83.7±20.8%, mean FEV1 was 72.9±21.1%, mean DLCO was 58.5±16.7%, mean TLC was 5.12±1.08 L, mean RV was 2.21±0.72L, and mean RV/TLC was 43.3±9.3%. We found no correlation between the radiation dose (i.e., v20) and any PFT parameter. 44.4% (n=36) had RP defined as above. Significant differences were observed in the mean DLCO (63.8±17.5% vs. 53.7±14.6%, p=.015) and RV/TLC (40.9±7.4% vs. 45.6±10.3%, p=.035) in patients who developed RP vs. no RP. Baseline DLCO showed a significant positive correlation (r:0.31, p=.015) while RV/TLC demonstrated a significant negative correlation (r:-0.25, p=.035; Table1) with RP. No other PFT parameters were significantly different or correlated between subjects with RP vs. no RP.

Conclusions: Our study demonstrates that increased functional lung volume (i.e., higher DLCO) and lower dead space volume (i.e., decreased RV/TLC) prior to CRT is associated with higher RP risk. These findings may explain prior studies demonstrating smoking as a protective factor for RP, given tobacco users generally have lower DLCO and higher RV/TLC. With the potential of RP impacting consolidation immunotherapy in locally advanced NSCLC patients, prospective evaluation of PFTs to predict RP should be undertaken to prompt closer monitoring.

Keywords: Non-Small Cell Lung Cancer, Radiation Pneumonitis, Chemoradiation

Table 1: Correlation of Baseline PFTs with Radiation Pneumonitis in Patients with Locally Advanced NSCLC

	Pearson Correlation						
	FVC%	FEV1%	DLCO%	TLC (L)	RV (L)	RV/TLC%	Radiation Pneumonitis
FVC%	1.000						
FEV1%	**0.787**	1.000					
DLCO%	**0.286**	**0.280**	1.000				
TLC (L)	-0.019	-0.020	0.045	1.000			
RV (L)	**-0.283**	-0.220	-0.245	**0.654**	1.000		
RV/TLC%	**-0.374**	**-0.294**	**-0.372**	0.074	**0.787**	1.000	
Radiation Pneumonitis	0.044	0.122	**0.306**	-0.005	-0.189	**-0.251**	1.000

* Bold; significant value (p<0.05)

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EP.08F.02 Pifenidone Prophylactic Therapy for Radiation Lung Injury in Patients Who Have Previously Received Immune Checkpoint Inhibitors

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Introduction: Our previous study found that the incidence of grade ≥2 radiation pneumonitis (RP) was 40% when lung cancer patients previously treated with immune checkpoint inhibitors (ICIs) underwent thoracic radiotherapy (TR). Therefore, we conducted an open-label, single-arm, two-stage, phase II clinical trial to evaluate the efficacy and safety of pirfenidone capsules (TGF-β inhibitor) in preventing RP in lung cancer patients who had previously received ICIs and were given pirfenidone in combination with TR treatment to provide a theoretical basis for future clinical practice.

Methods: lung cancer patients previously treated with ICIs undergoing TR and radiotherapy dose BED(β/ β =10) ≥50.0Gy. The study used a two-stage gen2stage design in R language. Based on the real-world occurrence of grade ≥2 RP of 40% with TR after treatment with ICIs, whereas this trial aimed to reduce the rate of grade ≥2 RP to 25%, β =0.1, β =0.25, the two-stage design was (6/14, 13/41). That is, 14 patients were enrolled in the first phase, and the study was stopped if the number of patients with grade ≥2 RP was ≥6; otherwise, the study entered the second phase, in which an additional 27 patients were enrolled, for a total of 41 patients. If ≥13 patients ultimately developed grade ≥2 RP, the study was considered a failure; otherwise, the study was considered a success. Pirfenidone were started on the first day of TR and dosed as follows 200 mg/dose in week 1, 300 mg/dose in week 2, and 400 mg/dose in weeks 3-12, all 3 times/day. RP grades were categorized by assessing patients in conjunction with their medical history and CT images of the lungs, and defined according to the Common Terminology Criteria for Adverse Events (CTCAE) 5.0.

Results: From 20 March 2023 to 13 October 2023, 14 lung cancer patients were enrolled, including 9 patients with non-small cell lung cancer (NSCLC) and 5 patients with small cell lung cancer (SCLC). The median age was 60 years (range: 42-73), 85.7% were male and 78.6% were receiving PD-1 inhibitors. The median number of previous ICIs cycles was 5 (range: 2-20). The median time between last ICI and start of TR was 27 days (range: 23-184). The median BED(β/ β =10) =60.0Gy (range: 50.3-64.7), the median fractional dose was 2.1Gy (range: 2-2.8), the median PTV=213.7cm3 (range: 120.1-673.7) and the median V20, V5 and Dean were 18.4% (range: 8.3-26.5), 37.0% (range: 18.7-58.1) and 10.0 58.1) and 10.0Gy (range: 4.8-16.4). The median follow-up was 5.9 months (range: 4.2-11.7). A total of 9 (64.3%) patients experienced any grade of RP, including 3 (21.4%) patients with grade ≥2 RP (two grade 2 PRs and one grade 5 PR). Pirfenidone-related adverse events (≤ grade 2) occurred in 7 patients, including six gastrointestinal reactions and one photosensitivity reaction.

Conclusions: The first phase data from this single-arm, open, phase II clinical study demonstrated that pirfenidone can safely and effectively reduce the incidence of grade ≥2 RP in lung cancer patients previously treated with ICIs undergoing TR and the study should enter the second phase (case expansion stage).

Keywords: Radiation Pneumonitis, Pifenidone, immune checkpoint inhibitors (ICIs)

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EP.08F.03 Efficacy and Safety of Aumolertinib with Radiotherapy in the Treatment of Unresectable Locally Advanced EGFR-Mutant NSCLC: A Phase II Study

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Introduction: Approximately 30% of patients have advanced to stage III in non-small cell lung cancer (NSCLC) at initial diagnosis. For the patients with stage III unresectable locally advanced NSCLC, the standard treatment is platinum-based concurrent chemoratherapy (cCRT) according to multi-disciplinary team (MDT). However, there are still about 80% patient recurrence within 1-2 year. The PACIFIC study demonstrated the consolidation therapy efficacy and safety of durvalumab after cCRT, but it seems like ineffective for the patients with epidermal growth factor receptor (EGFR) mutation. The POLESTAR and LAURA registered clinical study aim to investigate consolidation therapy efficacy and safety of third generation EGFR tyrosine kinase inhibitors (aumolertinib and Osimertinib) after cCRT. However, some patients cannot tolerate chemotherapy or refuse chemotherapy due to adverse events. A multicenter retrospective REFRACT study demonstrated that combined radiotherapy with tyrosine kinase inhibitor (TKI) are superior than cCRT for stage III NSCLC patients harboring EGFR mutations. Here, we initiate a prospective study named POLESTAR 2 designed to evaluate the efficacy and safety of aumolertinib combined with radiotherapy, which may benefit those unresectable stage III EGFR-mutant NSCLC patients who are intolerant to chemotherapy as a potential chemotherapy-free regimen.

Methods: This is a phase II single-arm clinical trial evaluating the efficacy and safety of aumolertinib combination with radiotherapy in unresectable locally advanced EGFRm NSCLC patients. We plan to accrue 27 patients (One-sample logrank tests, —=0.05, —=0.9, dropout rate 15%) confirmed stage III unresectable EGFRm patients are administrated aumolertinib (110mg, oral once daily), and concurrent radiotherapy (56-66Gy, 1.8-2.0Gy/f) are performed after 8 weeks, follow with aumolertinib after radiotherapy until to disease progression or other criteria for discontinuation. The primary endpoint of efficacy endpoint is PFS (RECIST 1.1) and secondary endpoints are investigators assessed PFS, OS, time to CNS progression, time to distant metastasis (TTDM), objective response rate (ORR), disease control rate (DCR) and during of response (DoR). The safety endpoint: all subjects were observed and recorded for any adverse events that occurred during the clinical trial.

Results: The clinical trial is ongoing.

Conclusions: The clinical trial is ongoing.

Keywords: Locally advanced NSCLC, Aumolertinib, concurrent radiotherapy

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EP.08F.04 Development of Learning-Based Predictive Models for Radiation-Induced Atrial Fibrillation in Non-Small Cell Lung Cancer

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Introduction: Despite advances in radiotherapy, the probability of atrial fibrillation (AF) occurrence still exists. By incorporating patient-specific clinical, dosimetry and diagnostic information, this work developed machine and deep learning-based predictive models for AF following chemoradiotherapy (CRT) for non-small cell lung cancer (NSCLC) with institutional and external datasets. We also investigated patient-specific key influential features associated with cardiac toxicity.

Methods: Institutional and external patient cohorts consisted of 321 and 187 NSCLC datasets who received definitive CRT, including 17 and 6 AF incidences, respectively. The network input features had 159 patient-specific information that incorporated clinical, dosimetry (dose-volume histogram), and diagnostic (coronary artery calcium (CAC) scores) information. The imbalance between AF and non-AF incidences was mitigated by synthetic minority oversampling technique (SMOTE). To handle various types of input features, machine learning-based model adopted an intervention technique in feature selection process that chose a representing feature with the largest weight at each sub-group. Deep learning-based model employed a hybrid architecture that assigned different types of networks to corresponding input paths. The performance of the developed networks was assessed by area under the curve (AUC). The key features were investigated by network coefficients at classifier and an open-source workflow (Captum) for the machine and deep learning-based models.

Results: In the internal validation, the hybrid deep learning model yielded AUC of 0.823, outperforming the machine learning-based algorithm with intervention (AUC of 0.801). The hybrid deep learning-based model produced more consistent performance (AUC of 0.806) than the machine learning model (AUC of 0.776) in the external validation. Importantly, maximum dose to heart and sinoatrial node (SAN) were found to be the key features for both external and internal validations.

Conclusions: The learning-based predictive models showed consistent prediction performance across internal and external cohorts, identifying maximum heart and SAN dose as key features for the incidence of AF.

Keywords: Learning-Based Predictive Models, Radiation-induced cardiac dysfunction, Cardio-oncology

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EP.08F.05 Real World Evidence of Long-Term Safety and Effectiveness of Durvalumab in Unresectable Stage III NSCLC in Japan: AYAME Study

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Introduction: Durvalumab is a standard of care as consolidation therapy after concurrent chemoradiation for unresectable stage III non-small cell lung cancer (NSCLC) in Japan. However, the data in the Japanese subgroup of the phase III study (PACIFIC study) are limited. This study aims to assess the long-term safety and effectiveness of durvalumab, including the post-treatment period after completion or discontinuation of durvalumab treatment, in a real-world setting in Japan.

Methods: This is a non-interventional, prospective study. Data are collected for up to 3 years from the start of durvalumab treatment. The primary endpoints are the incidence proportion of interstitial lung disease (ILD) and adverse events of special interest (AESIs, not presented in this report) within 3 years of starting durvalumab; progression-free survival (PFS); and PFS rates at 12 months, 18 months, and 24 months. The secondary endpoints include ILD in patient subset population; overall survival (OS); and OS rates at 24 months and 36 months.

Results: A total of 529 patients were enrolled at 52 sites between July 2019 and December 2020. At the third interim analysis (data cut-off in July 2023), of the 512 patients who received durvalumab treatment after chemoradiotherapy (CRT), 511 were included in the safety analysis population and 495 were included in the effectiveness analysis population. In the safety analysis population, the proportion of patients who completed durvalumab treatment was 41.1%. The incidence of any grade ILD was 74.8% (382/511 patients) in the safety analysis population, and that of grade 1, 2, 3, 4, and 5 ILD was 36.2%, 29.0%, 8.8%, 0%, and 0.8%, respectively. The median number of days to the first onset was 44 days after the first dose of durvalumab. Among 382 patients with ILD, 31.7% (121) discontinued durvalumab treatment, 29.1% (111) experienced durvalumab interruption. Of those, 89.2% (99/111) subsequently resumed the treatment. In addition, 43.7% (167/382) of the patients with ILD received steroid therapy. Of those, 68.3% (114/167) of the patients had the ILD grade 2 and 24.6% (41/167) of the patients had the ILD grade 3. The median PFS in the effectiveness analysis population was 23.5 months (95% confidence interval, 18.2 to 27.2) and the PFS rates at 12 months, 18 months, and 24-month were 62.5%, 54.6%, and 49.6%, respectively. The OS rates at 24-month and 36-month were 75.4% and 64.4%. The final analysis (data cut-off in March 2024), including multivariate analysis of the incidence of ILD, with longer follow-up is to be reported at the World Conference on Lung Cancer 2024.

Conclusions: Based on the interim analysis data obtained so far indicate that real-world durvalumab treatment outcomes are consistent with the Japanese subset in the PACIFIC study. We expect that our findings from the updated results will enhance comprehension of the long-term safety and effectiveness of durvalumab in clinical practice.

Keywords: Durvalumab, Unresectable Stage III NSCLC, RWD (Real World Data)

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EP.08F.06 Concurrent Chemoradiotherapy Followed by Durvalumab for Elderly Patients

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Introduction: Consolidation therapy with durvalumab after concurrent chemoradiotherapy (cCRT) for patients with unresectable locally advanced non-small cell lung cancer (LA-NSCLC) has become the standard of care. The PACIFIC-R study has also shown the effectiveness and tolerability of the consolidation therapy in the real world, but there are insufficient data for elderly patients aged above 75 years, especially above 80 years. There are also limited data on the incidence of pneumonitis by age. Here, we conducted a multicenter retrospective study to evaluate the effectiveness and tolerability on elderly patients.

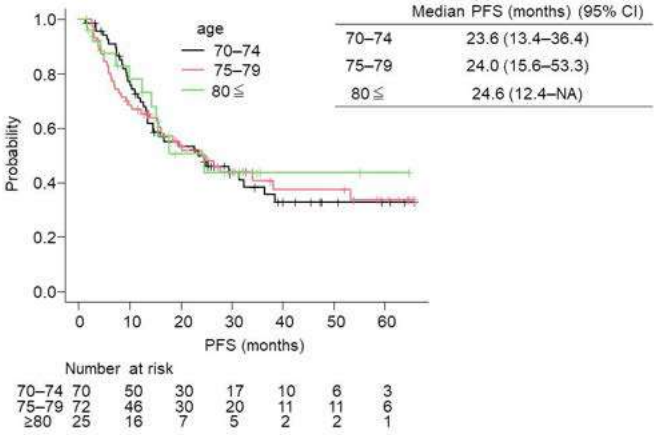
Methods: We evaluated progression free survival (PFS) as the primary endpoint in patients initiated on cCRT for unresectable LA-NSCLC from July, 2018 to March, 2023, and compared among three groups: aged 70 to 74 years, 75 to 79 years, and above 80 years. We also evaluated cCRT completion rate, overall survival (OS), and PFS in carboplatin plus paclitaxel regimen (CP)as the secondary efficacy endpoints, and the rate of initiation and compression of durvalumab, and incidence of pneumonitis as the safety endpoints among the three groups.

Results: 167 patients were included from 6 institutions in Japan. The number of patients was 70 in the group aged 70 to 74 years, 72 in the group aged 75 to 79 years, and 25 in the group aged above 80 years. Patient characteristics in each group was as follows: male 59 (84.3%) / 59 (81.9%) / 19 (76.0%), adenocarcinoma 32 (45.7%) / 36 (50.0%) / 11 (44.0%), and CP regimen in 39 (55.7%) / 61 (84.7%) / 21 (84.0%). The primary endpoint was median PFS of 23.6 / 24.0 / 24.6 months (p-value = 0.97). The secondary efficacy endpoints included cCRT completion rate of 94.3 / 93.1 / 88.0% (p-value = 0.55), median OS of 46.0 / 38.5 / NA months (p-value = 0.30), and median PFS of 24.6 / 26.4 / 17.8 months (p-value = 0.93) in CP regimen. The safety endpoints included: durvalumab initiation rate, 85.7 / 75.0 / 68.0% (p-value = 0.10); durvalumab completion rate, 37.3 / 32.4 / 20.0% (p-value = 0.29); and incidence of pneumonitis during the therapy, 66.7 / 56.6 / 58.8% (p-value = 0.53).

Conclusions: In patients aged above 80 years, consolidation therapy with durvalumab after cCRT is effective, and the completion rate and safety of this therapy are also assured. We will include more patients for further investigation.

Keywords: LA-NSCLC, elderly, durvalumab

Kaplan-Meier distribution of PFS according to age



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EP.08F.07 Induction Immunochemotherapy Before Definitive Chemoradiotherapy for Patients with Stage III Non-Small Cell Lung Cancer

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Introduction: Immune checkpoint inhibitors (ICIs) have become the standard consolidation therapy for stage III unresectable non-small cell lung cancer (NSCLC). Whether induction immunochemotherapy can further improve efficacy is unclear. In this study, we used real-world data to explore the possibility of induction immunochemotherapy before definitive chemoradiotherapy (CRT).

Methods: Patients with stage III NSCLC (including postoperative recurrence), who received definitive CRT from 2016 to 2022, were retrospective reviewed. Survival outcomes and the incidence of pneumonia were calculated and compared between patients with induction immunochemotherapy or not.

Results: A total of 156 patients undergoing definitive RCT were analyzed. Among them, 103 patients received induction immunochemotherapy followed by definitive CRT (I-CRT group), and 53 patients received sequential chemoradiotherapy or concurrent chemoradiotherapy (CRT group). The 5-year overall survival (OS) rates were 75.0% in the I-CRT group and 44.4% in the CRT group. The median OS was not reached (NR) and 36.5 months respectively, indicating a significant improvement in survival with the addition of induction immunochemotherapy (P=0.03). However, there were no significant differences between the two groups in median progression-free survival (PFS) (22.4 vs. 13.6 months; P=0.09), locoregional recurrence-free survival (LRFS) (38.0 vs. 36.9 months; P=0.73), and distant metastasis-free survival (DMFS) (37.8 vs. 25.5 months; P=0.14). Multivariate analysis showed that induction immunochemotherapy was an independent favorable prognostic factor for OS (HR 2.89; 95% CI, 1.24-6.75; P=0.01). The incidence of grade 2 or higher pneumonia in the two groups was 37.2% and 29.2%, respectively (P=0.35). Additionally, we found that patients with consolidation ICIs after induction immunochemotherapy had a better OS, with a 4-year OS rate of 90.7% versus 65.5% (P=0.03). Patients undergoing 5-6 cycles of induction immunochemotherapy seemed to have a better outcome compared to those with 3-4 cycles or 1-2 cycles (93.8% vs. 77.4% vs. 60.5%).

Conclusions: For patients with stage III NSCLC receiving definitive CRT, the application of induction immunochemotherapy improves OS without a significant increase of pneumonia in real-world practice. This treatment strategy warrants further research.

Keywords: induction immunochemotherapy, definitive chemoradiotherapy, stage III non-small cell lung cancer

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EP.08F.08 Safety and Efficacy of Durvalumab Consolidation Therapy after Chemoradiotherapy in NSCLC Patients Positive for Antinuclear Antibodies

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Introduction: Pneumonitis during durvalumab consolidation therapy after concurrent chemoradiotherapy (CRT) is a major cause of treatment discontinuation and potentially fatal. Identifying biomarkers of pneumonitis is a special concern for oncologists. Although previous studies have revealed the association between serum antinuclear antibody (ANA) levels and the safety and efficacy of immune checkpoint inhibitors in advanced non-small cell lung cancer (NSCLC), there are no reports specific to durvalumab consolidation therapy. In this study, we aimed to investigate the safety and efficacy of durvalumab consolidation therapy after CRT in patients positive for ANA.

Methods: We conducted a single-center retrospective cohort study. We reviewed patients with unresectable NSCLC treated with durvalumab consolidation therapy after CRT between August 2018 and July 2022. Serum ANA titers were assessed before durvalumab initiation and a titer of 1:40 served as the cutoff. We evaluated the association of ANA positivity with the development of treatment-related adverse events (AEs) and survival outcomes.

Results: A total of 80 patients were enrolled in this study. The median age of the patients was 71 years, and 64 patients were male. Thirty-nine patients were positive for ANA. There were no significant differences in the development of each AE, including pneumonitis, between patients positive for ANA and patients negative for ANA. The incidence of pneumonitis of grade 3 to 5 tended to be higher in patients positive for ANA than patients negative for ANA (12.8% vs. 2.4%, p = 0.10). The progression-free survival (PFS) and overall survival (OS) of the patients positive for ANA were significantly shorter than those of the patients negative for ANA (median PFS: 14.9 [95% CI, 6.9-39.3] months and not reached (NR) [95% CI, 15.5-NR], respectively; hazard ratio (HR), 2.42; 95% CI, 1.28-4.60) (median OS: NR [95% CI, 15.8-NR] and NR [95% CI, 41.6-NR], respectively; HR, 2.66; 95% CI, 1.19-5.96). Multivariate analysis using the Cox proportional hazard model revealed that the presence of ANA at pretreatment was an independent predictor of both PFS (HR, 2.23; 95% CI, 1.16-4.29; p = 0.016) and OS (HR, 2.28; 95% CI, 1.01- 5.12; p = 0.046).

Conclusions: ANA positivity was a poor prognostic factor in patients receiving durvalumab consolidation therapy after CRT, which may be due to higher frequency of severe pneumonitis. We recommend careful monitoring for pneumonitis during durvalumab consolidation therapy in patients positive for ANA.

Keywords: Durvalumab, Antinuclear antibodies, Pneumonitis

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EP.08F.10 Semi-Automated NSCLC Segmentation and RECIST Measurement: Bridging the Gap Between Speed and Radiologist-Level Accuracy

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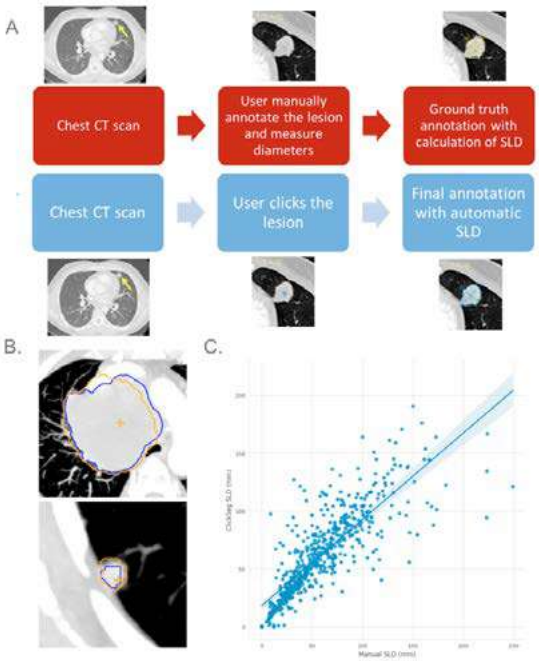
Introduction: Accurate tumor measurement is paramount for evaluating treatment response in non-small cell lung cancer (NSCLC). Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 guidelines are routinely employed by radiologists and oncologists to determine total tumor burden and monitor treatment. However, manual RECIST measurements are time-consuming and subject to inter-observer variability. This study presents evaluated a semi-automated segmentation algorithm, aiming for high correlation with experts' manual annotations of pulmonary lesions.

Methods: Retrospective CT scans obtained at a single time point from 557 stage III and IV NSCLC patients were collected from 4 institutions. For each patient, lung lesions were identified and manually segmented by two or more physicians annotating in consensus. A semi-automated interactive segmentation model ClickSeg was previously developed from ground truth annotations of 1,146 patients) using convolutional neural networks combined with morphological operations tailored for lung tumor characteristics. No patients used in ClickSeg training overlapped with the evaluation cohort of this study. From a users' click point within a lesion, the algorithm delineates tumor boundaries and identifies the longest diameters, conforming to RECIST guidelines. In the case of multiple lesions, the two largest lesions were selected as target lesions of the patient, resulting in 753 lesions. For each patient, the RECIST sum of target lesion diameters (SLD) was calculated and compared between manual and semi-automated annotations. Concordance between SLDs was quantified using the Dice coefficient, Pearson correlation, and intraclass correlation coefficient (ICC).

Results: The full ClickSeg system processed the scans with a mean time of 14.59 seconds (range: 5.04-26.15 seconds) per case, more than 60 times faster than the average manual measurement time of 15 minutes 34 seconds. The median Dice coefficient between the manual and automated segmentations was 0.66. The Pearson correlation coefficient was 0.81 (p<1e-10). The algorithm's SLDs agreed strongly with physician's measurements, achieving an ICC of 0.81 (95% CI: 0.78-0.84, p<1e-10).

Conclusions: The presented semi-automated lung tumor segmentation model demonstrates high accuracy and substantial time efficiency in deriving quality tumor segmentation and RECIST diameters for NSCLC. These promising results suggest a valuable tool for enhancing consistency and efficiency in tumor size assessment. Future work will explore its ability to distinguish RECIST labels across longitudinal, on-treatment scans, as well as its utility in clinical practice.

Keywords: Radiology, Monitoring, AI



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EP.08F.11 Development of Clinical Prediction Model Using Digital Device for ILD in the Stage III NSCLC Patients Treated with Durvalumab

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Introduction: Durvalumab serves an important role as a consolidation therapy after chemoradiation therapy (CRT) in patients with unresectable stage III non-small cell lung cancer (NSCLC), but the early detection of interstitial lung disease (ILD) is one of the urgent challenges to prevent treatment discontinuation due to worsened ILD. We aimed to develop a clinical prediction model for the grade 2 or higher ILD in those NSCLC patients, by means of machine-learning analysis on the continuously collected automatic measurements from the wearable device and mobile application.

Methods: This study was a prospective, non-interventional pilot study. We collected the patients' clinical characteristics and outcomes from electronic medical records, physiological data, such as heart rate, respiratory rate and saturation of percutaneous oxygen, from the wearable device, and the number of coughs from the mobile application. The patients were followed up to 6 months after the first dose of durvalumab, or until the start of post-treatment, death, or withdrawal of consent whichever comes first. The primary objective was development of the clinical prediction model for grade 2 or higher ILD. Secondary and exploratory objectives were development of the clinical prediction models for progression disease (PD) and grade 3 or higher ILD, respectively. Eight machine-learning or statistical prediction models were used for each objective, and each performance was evaluated with area under the receiver operating characteristic curve (ROC-AUC).

Results: A total of 145 patients were enrolled in this study from August 2021 and September 2022; 22 patients dropped out before device data acquisition, and 123 patients were included in the analysis set. The median age was 68.0 years, and the mean wearing time of the wearable device, which was used during sleep, was 7.8 hours per day. Among the 123 patients, 40 were diagnosed with grade 2 ILD, 6 with grade 3 or higher ILD (no deaths), and 16 with PD during the follow-up period. For primary objective, the XGBoost had the highest ROC-AUC among the eight predictive models [0.789 (95%CI: 0.724, 0.854)]. For secondary and exploratory objectives, logistic regression developed the prediction models with the highest ROC-AUC [0.713 (95%CI: 0.560, 0.865)] and [0.813 (95%CI: 0.672, 0.954)], respectively. The ROC-AUC decreased when the wearable device data was excluded, and the ROC-AUC was unchanged when the data of cough-counting was excluded.

Conclusions: Our findings suggest that it is possible to construct a clinical predictive model with an accuracy at clinically meaningful level for grade 2 or higher ILD in patients receiving durvalumab after CRT, using patients background information and physiological data collected from a wearable device as a feature by the machine-learning methods.

Keywords: PACIFIC Regimen, ILD Prediction Model, Machine Learning

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EP.08F.12 Toxicity and Outcomes by Radio-Sensitizing Chemotherapy Regimen for Unresectable Stage III NSCLC in British Columbia, Canada

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Introduction: Definitive chemo-radiotherapy (CRT) followed by durvalumab consolidation is the standard of care for the treatment of unresectable stage III non-small cell lung cancer (NSCLC). Platinum and etoposide (PE) every 3 weeks or weekly carboplatin-paclitaxel (CP) are commonly used radio-sensitizing protocols. The risk of toxicities, including radiation and immunotherapy-related pneumonitis, may differ based on the concurrent chemotherapy regimen. This study aimed to (i) compare toxicities associated with the use of different chemotherapy regimens and (ii) evaluate the impact of pneumonitis on patient outcomes.

Methods: Patients treated with concurrent CRT followed by durvalumab consolidation for unresectable stage III NSCLC at BC Cancer, British Columbia, Canada from January 2018 to December 2020 were identified. A retrospective analysis was performed through chart review and the outcomes database to identify various patient, tumor, and treatment factors. Overall survival (OS) was analyzed by the Kaplan-Meier method.

Results: 202 patients with unresectable stage III NSCLC treated with CRT were identified; 111 patients (55%) had stage IIIA disease. The radiosensitizing chemotherapy agents used were cisplatin-etoposide in 82 (41%), carboplatin-etoposide in 49 (24%) and weekly CP in 71 (35%). The most common reason for selecting a carboplatin-based regimen was patient comorbidities (23.3%). The median radiation dose received was 60 Gy (range 50-66) and 202 patients (100%) received at least one dose of durvalumab. CP was better tolerated with a lower incidence of grade 3-4 adverse events, including hematologic and gastrointestinal toxicities, compared to PE regimens. 47 (23%) pneumonitis events were reported (Table 1). Pneumonitis rates were similar with PE and CP and were predominantly low grade (1-2). Events occurred at a median of 49 days after durvalumab initiation (range 0-285). Despite treatment with steroids in 46 patients/47 (97.9%) who developed pneumonitis, 28 patients/47 (60%) were unable to complete one year of durvalumab consolidation due to pneumonitis. Median OS was 58.4 months (95% CI: 45.4-63.9), 45.7 months (30.0-65.9) and 37.1 months (31.1-56.3), for cisplatin-etoposide, carboplatin-etoposide and CP, respectively (p= 0.157). OS did not differ significantly in patients who developed pneumonitis (p=0.256).

Conclusions: CP is associated with a better tolerability profile and fewer high-grade adverse events when compared to PE regimens in patients with stage III NSCLC undergoing CRT. Pneumonitis occurred in 23% of our cohort and negatively impacted treatment completion but did not appear to negatively impact survival. There was no difference in pneumonitis rates and overall survival by radio-sensitizing regimen.

Keywords: NSCLC, Stage III, Chemo-radiation

Table 1. Summary of adverse events

Adverse event	Cisplatin-etoposide N=82		Carboplatin-etoposide N=49		Carboplatin-paclitaxel N=71	
Grade	Any	3-4	Any	3-4	Any	3-4
	Number of patients (%)					
Hematologic						
Anemia	38 (46.3)	1 (1.2)	22 (44.9)	0	29 (40.8)	1 (1.4)
Neutropenia	42 (51.2)	18 (22)	20 (40.8)	10 (20.4)	15 (21.1)	5 (7)
Thrombopenia	5 (6.1)	1 (1.2)	8 (16.3)	2 (4.1)	11 (15.5)	1 (1.4)
Febrile neutropenia	6 (7.3)	6 (7.3)	6 (12.2)	6 (12.2)	0	0
Non-hematologic						
Nausea & vomiting	47 (57.3)	6 (7.3)	11 (22.4)	0	21 (29.6)	1 (1.4)
Fatigue	43 (52.4)	3 (3.7)	33 (67.3)	1 (2)	36 (50.7)	0
Esophagitis	41 (50)	7 (8.5)	22 (44.9)	2 (4.1)	38 (53.5)	3 (4.2)
Mucositis	9 (11)	0	6 (12.2)	0	7 (9.9)	0
Acute kidney injury	9 (11)	0	0	0	2 (2.8)	0
AESI						
All pneumonitis	18 (22)	3 (3.7)	12 (24.5)	4 (8.2)	17 (23.9)	3 (4.2)
Radiation-related	9 (11)	0	5 (10.2)	0	7 (9.9)	0
Immunotherapy-related	4 (4.9)	1 (1.2)	6 (12.2)	3 (6.1)	5 (7)	2 (2.8)
Mixed etiology	5 (6.1)	2 (2.4)	1 (2)	1 (2)	5 (7)	1 (1.4)

AESI: adverse event of special interest

EP.08F LOCAL-REGIONAL NON-SMALL CELL LUNG CANCER - UNRESECTABLE NSCLC
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EP.08F.13 Machine Learning Analysis of Cardiac Sub-Structure Dose and Overall Survival of NSCLC Pts Treated with Concurrent Definitive Chemoradiotherapy

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Introduction: We have previously shown that cardiac substructure (CSS) dosimetric parameters (DP) lose significance in linear Cox Proportional Hazards testing after correcting for pt age, PTV volume, and receipt of durvalumab. Here, we perform a nonlinear machine learning (ML) analysis of the impact on overall survival (OS) of dose to 17 different CSS (4 chambers, 4 valves, aorta, superior vena cava, pulmonary artery, SA/AV nodes, and 4 coronary arteries (LAD, circumflex, left/right coronary).

Hypothesis: In LA-NSCLC pts receiving Concurrent Definitive Chemoradiotherapy (CDCRT), dose to individual cardiac substructures is predictive of overall survival (OS)

Methods: We culled consecutive patients with LA- NSLC treated with CD-CRT between 3/2009 and 01/2021 at a multi-site tertiary cancer center from our prospectively maintained database. Pts were excluded if they received sequential therapy, prior lung resection, or had oligometastatic disease. Pts with prior lung SBRT were allowed if prior maximum heart dose was < 1000 cGy. We used open-source software to auto-segment the CSS. In this analysis, we reviewed the DP of minimum/mean doses, D03cc, and gEUD for each CSS and its impact on OS. In this preliminary analysis, we used three ML survival analysis techniques: 1) elastic-net survival regression (ENSR), 2) gradient boosting survival (GBS), and 3) random survival forest (RSF) modeling.

Results: 418 patients met inclusion criteria. 49 (12%) received durvalumab. 56% were male. 74% received IMRT. Prescriptions ranged from 60-70 Gy, with 68% receiving 70 Gy. Median age was 67. Two pts were stage IB, 33 stage 2A/B, and 383 stages IIIA-C (AJCC 8th ed). Patients were divided into training (80%) and testing (20%) cohorts, stratified by year of treatment, to account for any evolution in treatment technique over time, as well as the receipt of durvalumab. Feature importance varied across the models. Pt age, delivered dose (< 6000 cGy vs > 6000 cGy), and ITV and/or PTV volume played a role in all models. However, the specific CSS and DP's varied across the models. ENR focused entirely on clinical features, except for Valve_Mitral_D03cc. The RSF model incorporated a variety of CSS, as well as age, ITV volume, PTV minimum dose, and dose received. Likewise, GBS utilized ITV volume, PTV minimum dose, age, and PTV volume, in addition to various CSS DP's. However, while D0.03cc of A_Aorta and mean A_Cflx dose were important in two of the three models, no single CSS DP played a sole role in all 3 ML models.

Conclusions: This is the largest ML analysis of CSS of which we are aware. In these simple ML models that do not incorporate cardiotoxicity or pt comorbidity, age and tumor volume predominate in determining OS. In ENR, clinical factors predominate, whereas in the other models, various CSS DP's are of greatest importance, though no single one predominated. Additional modeling, incorporating pt comorbidity, cardiotoxicity, and dosiomics into ensemble models, will be presented at the meeting.

Keywords: cardiac substructure dose, overall survival, machine learning

EP.08F LOCAL-REGIONAL NON-SMALL CELL LUNG CANCER - UNRESECTABLE NSCLC
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EP.08F.14 Outcomes of Durvalumab Consolidation Treatment in Stage III Unresectable NSCLC: A Retrospective Real-World Study

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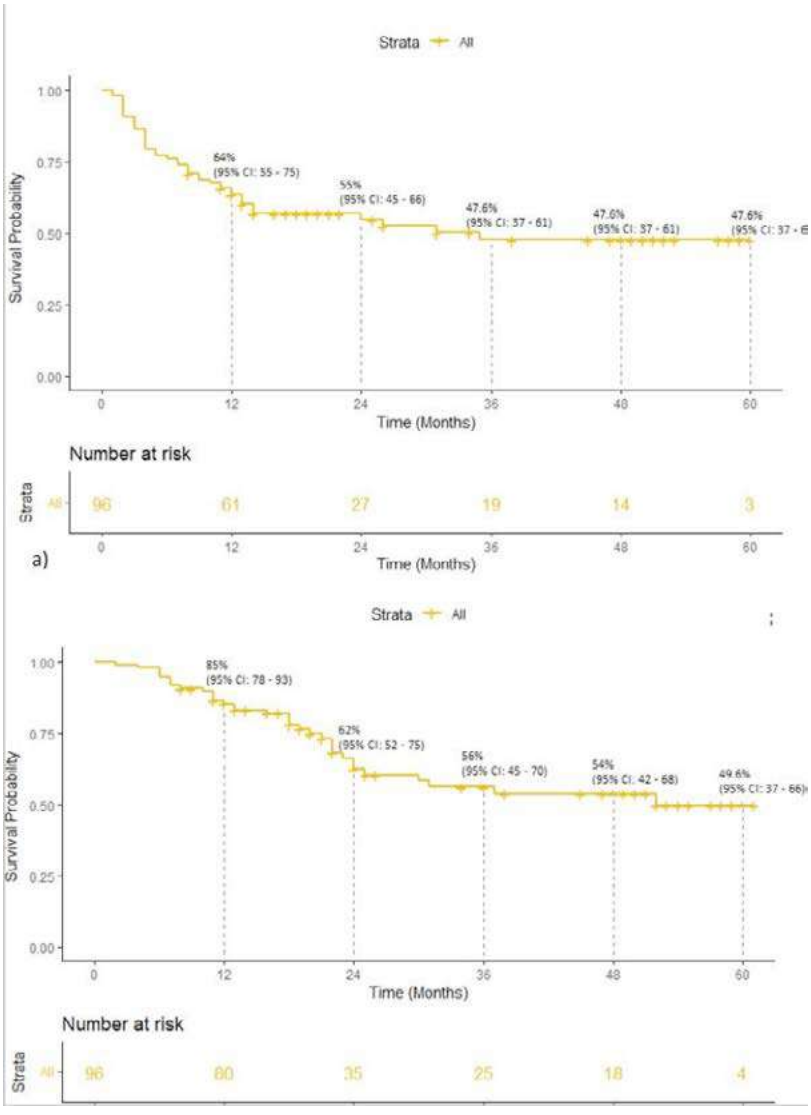
Introduction: The PACIFIC trial established concurrent chemoradiation followed by 12 months of consolidation durvalumab as the standard of care in locally advanced NSCLC, with real-world studies subsequently confirming these findings, the most extensive being the observational PACIFIC-R.

Methods: This retrospective study included ninety-six patients who received concurrent or sequential conventionally fractionated CRT with consolidation durvalumab for unresectable and locally advanced NSCLC between 2018 and 2022. To assess efficacy, we used progression-free survival and overall survival. We employed the Cox regression model to evaluate differences in OS and PFS, considering several key variables such as age, PD-L1 status, histological type, gender, time to durvalumab initiation, and the type of radiation therapy (concurrent vs. sequential).

Results: At the time of analysis, 62 out of 96 patients were alive. The median time to start durvalumab was 39 days. At the median follow-up of 22 months, median PFS was 35 months, with 1- and 2-year PFS rates of 64% and 55% (Figure 1a). The median overall survival was 52 months, accompanied by 1- and 2-year OS rates of 85% and 62% (Figure 1b). Five-year OS rate was 49.6%. Better survival outcomes were observed among patients with PD-L1≥50%, those receiving concurrent chemoradiotherapy, and patients with immune-related adverse events.

Conclusions: Our study demonstrates that our real-world data not only mirrors the outcomes observed in comparable real-world studies but also surpasses those from the PACIFIC trial regarding the survival advantage of durvalumab consolidation therapy.

Keywords: durvalumab, real-world outcomes, stage III NSCLC



EP.08F LOCAL-REGIONAL NON-SMALL CELL LUNG CANCER - UNRESECTABLE NSCLC
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EP.08F.15 A Retrospective Study of Tislelizumab Combined with Chemotherapy in Patients with Locally Advanced Lung Cancer

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Introduction: This study aimed to evaluate the downstaging and surgical rates of patients with locally advanced lung cancer treated with tislelizumab combined with chemotherapy through a retrospective collection of real-world data.

Methods: This study was a single-arm, multicenter, retrospective, real-world study. The study mainly includes patients with locally advanced lung cancer who are expected to be unable to achieve radical resection or whose surgery is more difficult and who received at least 2 cycles of tislelizumab combined with chemotherapy from October 1, 2020 to November 30, 2021. Statistically analyze the patients' baseline characteristics, R0 surgical resection rate, major pathological response rate and adverse events, and observe the efficacy and safety of tislelizumab combined with chemotherapy for downstaging and conversion therapy in patients with locally advanced lung cancer.

Results: A total of 65 patients were enrolled, with a median age of 62.0 (57.0-66.0) years, including 62 (95.4%) males and 3 (4.6%) females. Pathological diagnosis of squamous cell carcinoma, adenocarcinoma, squamous cell carcinoma with neuroendocrine differentiation, and malignant epithelial lung cancer accounted for 78.5%, 18.5%, 1.5%, and 1.5% respectively. The clinical stages of the patients were as follows: 26 (40.0%) cases were in stage IIIA, 33 (50.8%) cases were in stage IIIB, and 6 (9.2%) cases were in stage IIIC. There were 30 (46.2%) patients with ECOG PS score of 0. There were 38 (58.5%) patients with smoking history. There were 25 (38.5%) patients who had past medical history.The median treatment cycle of the treatment regimen was 3. The main adverse events related to treatment were lymphocyte count decreased (47.7%), alanine aminotransferase increased (27.7%), aspartate aminotransferase increased (26.2%), anemia (21.5%), neutrophilia granulocyte count decreased (21.5%), hypoalbuminemia (21.5%), white blood cell count decreased (20.0%), and lactate dehydrogenase increased (15.4%).A total of 55 of the 65 patients enrolled underwent surgery. The surgery rate was 84.6% (95%CI: 73.5%-92.4%). All patients who underwent surgery achieved R0 resection after surgery, the R0 resection rate was 100.0% (95%CI: 93.5%-100.0%), and the median surgical interval was 5.7 weeks. Among them, 26 cases achieved pathological complete response after surgery, and the pCR rate was 47.3% (95%CI: 33.7%-61.2%). Among them, 42 cases achieved major pathological response after surgery, and the MPR rate was 76.4% (95%CI: 63.0%-86.8%).

Conclusions: Tislelizumab combined with chemotherapy shows good anti-tumor activity in patients with locally advanced lung cancer, can reduce tumor volume, improve surgical resection rate, has a high pathological complete response rate and is well tolerated. Immunotherapy combined with chemotherapy is one of the new options for downstaging and conversion therapy for patients with locally advanced lung cancer. It can provide surgical opportunities for patients who have no chance of surgery or who have difficulty in surgery, and can increase the rate of radical surgical resection.

Keywords: non-small cell lung cancer, downstaging and conversion therapy, neoadjuvant therapy

EP.08F LOCAL-REGIONAL NON-SMALL CELL LUNG CANCER - UNRESECTABLE NSCLC
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EP.08F.16 Re-Irradiation with Chemotherapy with/without Immunotherapy for In-Field Local Recurrence Among Lung Cancer Patients

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Introduction: Radiotherapy is crucial for non-operative locally advanced lung cancer. Normally, a number of patients with in-field recurrent lung cancer after definitive concurrent chemo-radiotherapy (dCCRT) had the possibility of re-irradiation. For these patients, the salvage radio-chemotherapy or radio-chemotherapy followed by immune checkpoint inhibitors (ICIs) treatment still plays an important role in prolong the overall survival for those patients with good performance status. So far, only a few data had been reported.

Methods: Between Sep 2015 and Nov 2022, 83 patients with in-field recurrent non-small cell lung cancer (NSCLC) who had received highly-palliative re-irradiation (50 Gy/25 fractions) were recruited and retrospectively analyzed. Among these patients, 58 patients received re-irradiation combined with chemotherapy (re-RCT), and another 25 patients received re-radiochemotherapy followed by Durvalumab or other drugs (re-RCIT). The chemotherapy regimens were Paclitaxel and Carboplatin/Cisplatin, repeated every 3 weeks. Two to 6 weeks after the re-irradiation and concomitant thermotherapy, the application of ICIs were started according to the NCCN guidelines. Statistical analyses were performed with SPSS 24.0. The chi-square test was used to compare the treatment-related complications between the two groups. Survival time was performed using the Kaplan-Meier method. Log-rank test was applied to compare survival rates. Potential prognostic variables were estimated using multi-variate Cox regression model. The p value was considered statistically significant if less than 0.05.

Results: Generally, the median progression-free survival (PFS) of re-RCT group and re-RCIT group were 5.6 months and 11.4 months respectively (p=0.031). The median overall survival (OS) was 17.9 and 20.2 months in re-RCT and re-RCIT group respectively (p=0.269). There was no significant difference between the 1, 2 and 3 year survival rates in two groups (67.2%, 29.3%, and 19.0% in re-RCT group vs. 72.0%, 32.0% and 28.0% in re-RCIT group) (p>0.05 respectively). Grade 3-4 treatment-related adverse events (TRAEs) and their incidence rates were: treatment-related pneumonitis, 10.3% vs. 16.0% (p=0.365), neutropenia, 77.6% vs. 76.0% (p=0.872), thrombocytopenia, 15.5% vs. 20.0% (P=0.683) and anemia, 8.6% vs. 12.0% (p=0.774). Incidence rates of fetal bronchial bleeding or fracture were 3.4% vs. 4.0% (p=0.817).

Conclusions: Palliative re-irradiation is an effective treatment for patients with locally recurrent NSCLC after the first-course CCRT. Compared with the radio-chemotherapy, the combination of ICIs may significantly improve the short-term survival, but not the overall survival. The TRAEs were clinically acceptable and manageable, including the pneumonitis (radiation-induced or ICIs-induced), but attention of bronchial fracture or bleeding must be emphasized.

Keywords: Re-irradiation, Lung cancer, Radiotherapy

EP.08F LOCAL-REGIONAL NON-SMALL CELL LUNG CANCER - UNRESECTABLE NSCLC
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EP.08F.18 Survival and Incidence Trends of Non-Small Cell Lung Cancer in Elderly Patients (>75 Years): Insights from SEER Database

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Introduction: Non-small cell lung cancer (NSCLC) is the most common (85-90%) subtype of lung cancer. Approximately 30-40% of all NSCLC cases occur in individuals aged ≥ 75 years. Our study aims to identify survival, incidence rates, and factors impacting overall survival (OS) in patients aged over 75 years diagnosed with NSCLC.

Methods: We conducted a retrospective cohort analysis utilizing the Surveillance, Epidemiology, and End Results database. Cox proportional regression analysis was used to identify the factors that impact the overall survival (OS). Incidence trends are analyzed over different periods, highlighting changes in survival outcomes and demographic factors.

Results: Between 2000 and 2020, a total of 33,040 cases of NSCLC occurred in patients aged ≥ 75 years. Higher incidence rates are observed among males compared to females (54.74% vs. 45.26%). The incidence trends revealed a significant decrease from 2000 to 2020. Additionally, a higher incidence is noted in patients with lower income levels (< $75,000) (56.28% vs. 43.72%). Over the past five years, there has been a marked improvement in survival rates for patients diagnosed with NSCLC. This is evident from the decreasing hazard ratios (HR) and increasing median survival months associated with the years of diagnosis from 2000 to 2020. Specifically, patients diagnosed between 2015-2020 exhibited the most favorable outcomes, with the highest median survival of 8.33 months. These findings highlight the progress made in NSCLC management and underscore the importance of ongoing advancements in treatment strategies to improve patient outcomes. Among the demographic factors, females, urban residents, higher annual income (> 75,000 $), and married status had better OS outcomes than their counterparts. Among disease stages, localized disease had the best, while regional disease had a better OS than distant disease. Chemotherapy generally shows a protective effect, with lower hazard ratios across all stages. Radiation therapy also demonstrates a protective effect, particularly in localized disease. Surgery appears to have the most significant impact on survival, especially in patients with localized NSCLC, where it is associated with the lowest hazard ratio and highest OS. The incidence rates and OS HRs are shown in Table.

Conclusions: Our study highlights significant advancements in NSCLC management for elderly patients over 75 years. Tailored treatments such as chemotherapy, radiation therapy, and surgery have markedly improved survival rates. Key demographic factors also play crucial roles in shaping patient outcomes. These findings provide valuable insights for optimizing care strategies in this population.

Keywords: NSCLC, Elderly Population, Overall Survival

Variable	Group	Incidence Percentage	Hazard Ratio	Survival Months (Median)
Gender	Female	45.3	0.87 (CI: 0.86-0.89)	5.6
	Male (Ref)	54.7		4.6
Years of Diagnosis	2000-2004	30.2	1.43 (CI: 1.37-1.49)	4.5
	2005-2009	38.7	1.35 (CI: 1.30-1.40)	4.7
	2010-2014	17.4	1.25 (CI: 1.20-1.31)	5.5
	2015-2020 (Ref)	13.8		8.3
Income Level	$75,000+	43.7	0.96 (CI: 0.93-0.98)	5.4
	< $75, 000 (Ref)	56.3		5.3
Race	Asian or Natives	6.2	0.98* (CI: 0.94-1.03)*	5.4
	Black	7.0	1.05 (CI: 1.01-1.10)	4.6
	White (Ref)	86.9		5.4
Urban-Rural	Rural	13.5	1.06 (CI: 1.02-1.09)	4.6
	Urban (Ref)	86.5		5.4
Marital Status	Married	49.0	0.97 (CI: 0.94-0.99)	5.4
	Single/Divorced (Ref)	51.0		5.3
Chemotherapy	Yes	27.6	0.76 (CI: 0.74-0.78)	7.5
	No (Ref)	72.4		3.7
Radiation	Yes	40.3	0.69 (CI: 0.67-0.70)	20.3
	No (Ref)	59.7		4.6
Surgery	Yes	5.5	0.42 (CI: 0.40-0.45)	7.3
	No (Ref)	94.5		4.5
Stage	Distant	60.2	2.93 (CI: 2.83-3.03)	3.3
	Regional	22.0	1.56 (CI: 1.50-1.62)	8.4
	Localized (Ref)	17.8		16.3
Distant	Chemotherapy	30.8	0.518 (CI: 0.502-0.535)	6.5
	No Chemotherapy (Ref)	69.2		2.5
	Radiation	36.2	0.781 (CI: 0.758-0.805)	5.5
	No Radiation (Ref)	63.9		1.6
	Surgery	1.8	0.582 (CI: 0.521-0.650)	3.5
	No Surgery (Ref)	98.2		2.4
Regional	Chemotherapy	35.8	0.664 (CI: 0.631-0.699)	20.5
	No Chemotherapy (Ref)	64.2		7.7
	Radiation	49.6	0.668 (CI: 0.636-0.701)	11.7
	No Radiation (Ref)	50.4		7.2
	Surgery	9.3	0.485 (CI: 0.445-0.529)	11.2
	No Surgery (Ref)	90.7		6.5
Localized	Chemotherapy	11.3	1.177 (CI: 1.080-1.282)	37.7
	No Chemotherapy (Ref)	88.7		17.6
	Radiation	52.1	0.747 (CI: 0.705-0.792)	16.6
	No Radiation (Ref)	47.9		20.3
	Surgery	14.0	0.532 (CI: 0.490-0.578)	22.7
	No Surgery (Ref)	86.0		16.4

Notes: "Ref" is reference group for Hazard Ratio Calculation (Denominator), P-value < 0.001 except for *non-significant P value

EP.08F LOCAL-REGIONAL NON-SMALL CELL LUNG CANCER - UNRESECTABLE NSCLC
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EP.08F.19 Dosimetric Benefits in Adaptive Intensity Modulated Radiotherapy with Sib for Lung Cancer: An Indian Regional Cancer Centers' Early Experience

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Introduction: Chemoradiation therapy remains the standard of care for inoperable stage III NSCLC.IMRT based SIB technique can deliver a higher dose to the tumor with a relatively lower dose to the CTV. Individual treatment response can cause anatomical changes or tumor shrinkage which causes significant difference between the planned and actual delivered dose. Adaptive radiotherapy (ART) to the changed tumor volume can decrease these geometric discrepancies, thus preventing the surrounding normal tissues from receiving unnecessary high dose.

Methods: 18 patients with histologically proven unresected stage III NSCLC who were treated with one-time scheduled ART using SIB-IMRT technique between July,2023 to December,2023, were included for dosimetric analysis in the study. They were planned for definitive RT with dose prescription of 66 Gy at 2 Gy per fraction to planning gross tumor volume (PGTV=GTV) AND 59.4 Gy at 1.8 Gy per fraction to planning target volume (PTV) in 33 fractions with concurrent regimen of platinum-based doublet chemotherapy. They initially underwent a planning 3 phase (free breathing, deep inspiration and deep expiration) CT simulation scan of 2.5 mm cuts before initiation of treatment (INITIAL SCAN) and also once after delivery of 44 Gy (ADAPTIVE SCAN). KV CBCT was regularly used to monitor tumor shrinkage pattern as well as to correct interfractional geometric displacement during setup. GTV in pre-treatment scan was defined as visible tumors and metastatic lymph nodes which were delineated in all 3 respiratory phases and joined together to generate individual iGTV. CTV included iGTV with a specific 6-8 mm margin in all directions. PGTV (PTV 66) in our study was defined as iGTV and PTV 59.4 was defined as 5 mm extension from CTV in all directions as per institutional protocol. In adaptive scan, PGTV(PTV66) was generated by delineating the visible shrunken tumors and involved positive lymph nodes in all 3 phases of mid treatment scans and later joining it. But in this study, we keep the CTV and PTV59.4 delineation in the adaptive/mid treatment scan same as the pre-treatment scan.To analyse the dose difference from adaptation, the adaptive CT was coregistered(rigid) with the original pre-treatment planning CT to transfer the entire initial 66 Gy plan on adaptive CT - THIS WAS ASSUMED AS NON-ART PLAN(SIMULATED PLAN). On the other hand, ART plan was calculated by combining 22 fractions of previously treated plan with 11 fractions of the new plan. The dosimetric differences of DVHs between 2 were quantitatively evaluated.

Results: Target volume shrinkage was observed in all patients in the adaptive scan.The median GTV/PGTV before initiation of treatment was 213 cubic cm (range:79.3-454.6).But,after 22nd fraction the median GTV/PGTV was 146 cubic cm (range:69.3-201). The absolute value of (I/L lung-PTV) V20,V30 and mean lung dose (MLD) reduced by an average of 1.2%,2.4% and 67 cGy. Same parameters for C/L lung reduced by 2.44%,1.76% and 123.7 cGy respectively. Mean esophagus was reduced by 215.2 cGy. Mean heart dose(MHD) was reduced by an average 96.2 cGy.

Conclusions: • Adaptative replanning to the shrunk tumor can have significant dosimetric benefits to OARs.

Keywords: ADAPTIVE SCAN, IMRT-SIB, DOSIMETRIC BENEFIT

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SATURDAY, SEPTEMBER 7, 2024 - 11:58 - 11:59

EP.08F.20 Stage IIIA Non-Small Cell Lung Cancer (NSCLC): Outcomes by Treatment Strategy

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Introduction: Current treatment guidelines for Stage IIIA NSCLC from the National Comprehensive Cancer Network (NCCN) are complex and recommend a myriad of options that may or may not include surgery, such as definitive chemoradiation and adjuvant immunotherapy. However, many stage IIIA patients do not undergo definitive chemoradiation and adjuvant immunotherapy as first line therapy due to incomplete mediastinal staging. The purpose of this study was to compare 1, 3, and 5-year overall survival between patients with stage IIIA NSCLC who received definitive chemoradiation +/- immunotherapy versus those who received a multimodal approach involving surgery.

Methods: This is a data-only retrospective multicenter cohort study of patients who were diagnosed with stage IIIA NSCLC at Commission on Cancer (CoC) American College of Surgeons (ACS) accredited hospitals from January 1, 2010 through June 30, 2021. Patients were censored at loss to follow up or study end - 30 June 2023. Overall survival was evaluated as an outcome using Kaplan-Meier analysis between patients received chemoradiotherapy with or without immunotherapy (non-surgical treatment) vs patients received surgery with neoadjuvant or adjuvant chemotherapy/radiation/immunotherapy (surgical treatment). Multivariable Cox proportional hazards regression analyses was conducted to identify independent predictors for overall survival.

Results: A total of 598 patients were identified and included in the study, 281 in the non-surgical treatment group and 317 patients in the surgical group that included neoadjuvant or adjuvant treatment. Age, BMI, CCS, race, and date of diagnosis was similar between group, with a larger proportion of women in the surgical group and higher proportion of tobacco use in the non-surgical treatment group. Shown in Figure 1 is the Kaplan Meier estimate for overall survival. Multivariable Cox Proportional hazards analysis was performed adjusting for age, gender, race, BMI, smoking status and CCS. Overall survival differed significantly between the two groups with average 5-year survival of 52.6% in the surgical treatment group and 30.8% in the non-surgical treatment group. These results are similar to previously published literature and add to the growing body of evidence supporting surgical treatment in appropriate patients with stage IIIAA disease.

Conclusions: There has only been one clinical trial comparing chemoradiation to surgery in stage IIIA NSCLC. The findings included higher progression free survival in the surgical group, as well as improved 5-year overall survival, although these results were published in 2009 before the advent of adjuvant immunotherapy. Our results demonstrate a significant 5-year overall survival of Stage IIIA NSCLC patients who undergo a multimodal treatment approach involving surgery compared to the non-surgical group. This improvement in overall survival provides growing evidence in favor of multimodal surgical treatment in select patients. The treatment plan should come from a multidisciplinary team with an expert thoracic surgeon included who can be a part of the underlying treatment decision for Stage IIIA NSCLC management.

Keywords: IIIA, NSCLC, Stage

EP.09A METASTATIC NON-SMALL CELL LUNG CANCER – LOCAL THERAPIES - RADIATION
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EP.09A.01 Oligoprogression after Local Ablative Treatment for Oligometastatic Non-Small Cell Lung Cancer

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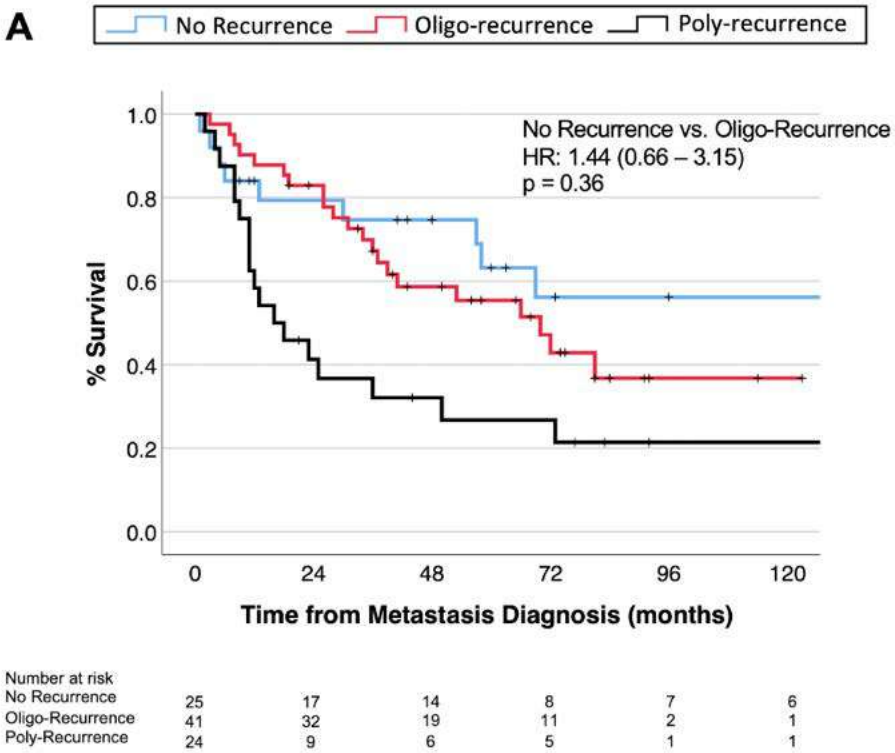
Introduction: At the initial diagnosis of stage IV non-small cell lung cancer (NSCLC), it is estimated that between 25-50% of patients are in an oligometastatic state with few distant metastases and limited systemic tumor burden. Despite the integration of local ablative therapy into the treatment regimen, local and distant recurrences remain a common challenge in these patients. Analogous to the oligometastatic state, an oligoprogression, is defined as the progression of cancer at a limited number of sites with otherwise controlled disease. We aimed to retrospectively assess the outcomes of patients with oligo- and polyprogression after local ablative treatment including surgical resection of the primary tumor for oligometastatic NSCLC.

Methods: We retrospectively identified 90 patients with synchronous or metachronous oligometastatic NSCLC who underwent local ablative treatment including anatomical lung resection between 2009 - 2023. Oligometastatic disease was defined as ≤5 distant metastases in ≤3 organs. Oligoprogression was defined as progression at ≤3 sites, whereas polyprogression was defined as progression at >3 sites.

Results: Oligoprogression occurred in 41 patients with a median latency of 24 months (95% CI: 7.6 - 40.4 months) and polyprogression occurred in 24 patients with a median latency of 8 months (95% CI: 6.9 - 9.7 months). Median follow-up of the entire cohort was 58 months (95% CI 30.4 - 85.6 months) and in 25 patients, no relapse occurred. Of the 41 oligoprogressive patients, 33 (80.5%) underwent local ablative therapy for progression sites. Among these, 23 (69.7%) were treated with radiotherapy, 5 (15.2%) with surgery, and 5 (15.2%) received both treatments. Upon oligoprogression, systemic therapy was changed in 8 (19.5%) of the patients. Overall survival after initial diagnosis of metastases was significantly longer in patients with oligoprogression when compared to patients with polyprogression (70 months, 95% CI: 43-8 - 96.2 versus 16 months, 95% CI: 3.1 - 28.8, p=0.012). A median overall survival of 134 months (0.0 - 289.0 months) was present in non-progressive patients. Notably, the overall survival difference between non-progressive patients and patients with oligoprogression was not significantly different (p=0.36).

Conclusions: Oligoprogression is the most common pattern of relapse after local ablative treatment in oligometastatic NSCLC. In our patient cohort of oligometastatic patients who underwent local ablative treatment including surgical resection of the primary tumor, overall survival is not significantly different in oligoprogressive and non-progressive patients. These findings suggest that the occurrence of oligoprogression is often not a survival-limiting factor.

Keywords: Oligometastatic NSCLC, Local Ablative Treatment, Oligoprogression



EP.09A METASTATIC NON-SMALL CELL LUNG CANCER – LOCAL THERAPIES - RADIATION
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EP.09A.02 Addition of Pulsed Electric Field Ablation to SBRT for Lung Tumors: Effect on Health-related Quality of Life

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Introduction: A close distance to the proximal bronchial tree and/or mediastinum is associated with higher rates of local recurrence and severe toxicity for lung tumors treated with stereotactic body radiation therapy (SBRT). Electric ablation with pulsed electric fields (PEF) is of interest since it does not disrupt extracellular structures and is thought to be a safer ablative approach for tumors adjacent to major blood vessels or cartilaginous airways. We performed a single-arm clinical trial testing the combination of PEF ablation with single-fraction SBRT. Herein we report health-related quality of life (HRQoL) changes associated with the combination treatment.

Methods: In this prospective trial, adult patients with a metastatic lung tumor of any histology were treated with PEF ablation on day 1 and 12 Gy SBRT between days 8-15. Eligibility included those with 1-3 tumors that were ≤6 cm in size. HRQoL data was collected as a secondary endpoint and included the Functional Assessment of Cancer Therapy-Lung Cancer Subscale (FACT-LCS), FACT-Physical Well-Being (FACT-PWB), FACT-Social/Family Well-Being (FACT-SWB), FACT-Emotional Well-Being (FACT-EWB), and FACT-Functional Well-Being (FACT-FWB). Domain subscales were calculated with a range of 0-28 or 0-24 (FACT-EWB), with higher scores indicating more optimal HRQoL. Surveys were collected at initial screening and at 3 months. Exploratory analysis was conducted to test associations between HRQoL domains and pulmonary function testing (PFT).

Results: Six patients with eight tumors were enrolled and treated between March 2023 and September 2023. All patients completed their course of treatment, and there was no missing HRQoL data. Baseline domain scores were: PWB 25.9 (Std Dev 2.3), SWB 21.0 (Std Dev 6.9), EWB 17.3 (Std Dev 4.7), FWB 21.2 (Std Dev 5.8), and LCS 19.4 (Std Dev 5.3). There were no significant changes in HRQoL domains following IRE and SBRT. At 3 months post-treatment, lower FVC was associated with lower EWB (rho = 0.55, beta = 5.3, p = 0.04) and SWB (rho = 0.58, beta = 2.9, p = 0.01), and lower FEV1 was associated with lower EWB (rho = 0.81, beta = 5.6, p = 0.04) and SWB (rho = 70, beta = 3.0, p = 0.01). A larger decrease in DLCO after treatment was associated with lower FWB (rho = 0.79, beta = 1.3, p = 0.006). Other HRQoL domains were not significantly associated with PFT measurements (p>0.05, for all). Only one patient reported worsened dissatisfaction due to side effects (GP5, "I am bothered by side effects of treatment") and was also the only patient to experience a grade 3 or higher toxicity (grade 3 surgical procedure complication, where the patient whose history included chemoradiation for hypopharyngeal carcinoma experienced laryngeal edema preventing extubation until 1 day post-procedure).

Conclusions: In this prospective trial, treatment of lung metastases with combination PEF ablation and SBRT was well-tolerated. Patient-reported responses from standardized instruments showed no significant treatment-related declines in HRQoL. Exploratory analyses identified associations between worse pulmonary function and a larger decrease in DLCO after treatment with poorer well-being scores.

Keywords: Stereotactic body radiation therapy, Pulsed electric field ablation, Quality of life

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EP.09A.03 Safety and Efficacyof Cranial Radiotherapy in Combination with Aumolertinibin EGFR-Mutant NSCLC Patients with Brain Metastases

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Introduction: Third-generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI), such as osimertinib, has a powerful ability to penetrate the blood-brain barrier and a high potency for controlling brain metastases (BMs) from EGFR-mutant non-small cell lung cancer (NSCLC). However, the safety and efficacy of aumolertinib as first-line therapy combined with cranial radiotherapy in EGFR-mutant NSCLC patients with brain metastases has not been fully investigated.

Methods: Patients with EGFR-mutant NSCLC and BMs and receiving aumolertinib and cranial radiotherapy were retrospectively enrolled. The modality of cranial radiotherapy include whole-brain radiotherapy (WBRT), stereotactic radiotherapy (SRT), hypofractionated stereotactic radiotherapy (HSRT) and simultaneously integrated boost whole-brain radiotherapy (SIB-WBRT). All patients received aumolertinib 110mg orally once daily. Central nervous system objective response rate (CNS ORR) were assessed by RECIST v1.1. Overall survival (OS) after BMs were analyzed using the Kaplan-Meier method.

Results: Of the 16 patients enrolled from 2016 to 2023, including SRT in 2, HSRT in 7, WBRT in 4, SIB-WBRT in 3, median age was 63 years (range, 36-76 years), 62.5% were female. 9 patients have 1 to 3 BM lesions,while 7 patients have more than 3 lesions. The median size of the lesions is 1.2cm (range, 0.7-5.1cm). 87.5% of patients have KPS>70. The median OS after BMs and 1-, 2- and 3- OS rates of 16 patients were 31.3 months, 93.3%, 60.0% and 48.0%. The median OS and 1-, 2- and 3- OS rates of 9 patients treated with local hypofractionated radiotherapy (SRT+HSRT) were 33.2 months, 87.5%, 61.2% and 37.5%. And the median OS and 1-, 2- and 3- OS rates of 7 patients treated with WBRT+SIB-WBRT were 29.7 months, 85.7%, 68.6% and 34.3%, respectively. The CNS ORR was 81.3% (13/16; 95% CI: 65.1-97.1). No grade≥3 cerebral radiation necrosis was observed in these patients.

Conclusions: Aumolertinib showed preliminary safety and efficacy at 110mg once daily as first-line therapy in combination with cranial radiotherapy for EGFR-mutant NSCLC patients with brain metastases.

Keywords: Cranial Radiotherapy, Aumolertinib, Brain Metastases

EP.09A METASTATIC NON-SMALL CELL LUNG CANCER – LOCAL THERAPIES - RADIATION
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EP.09A.04 Enhancing Radiotherapy Efficacy for Brain Metastases in Non-Small Cell Lung Cancer Through the Integration of G-CSF and Immunotherapy

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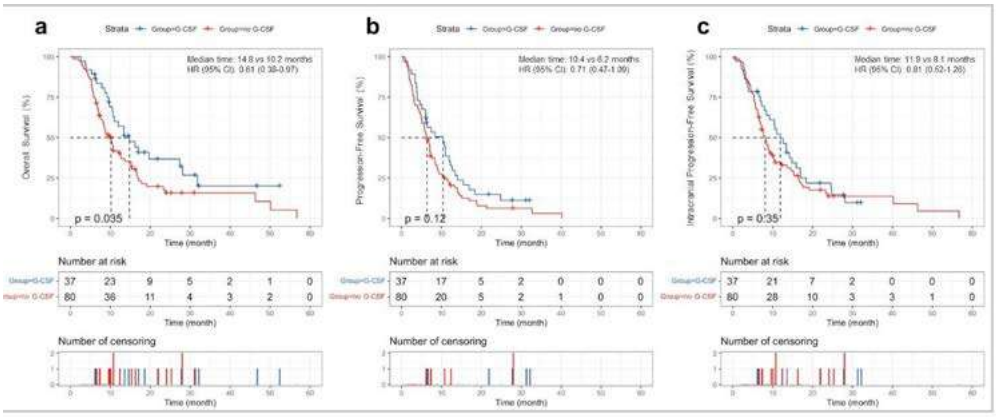
Introduction: Brain metastases (BMs) significantly contribute to the mortality rate among non-small cell lung cancer (NSCLC) patients. This study evaluates the clinical efficacy of combining G-CSF enhanced whole brain radiotherapy (WBRT) with immunotherapy as a primary strategy for treating BMs in NSCLC patients.

Methods: This retrospective analysis enrolled 117 NSCLC patients with 1-10 intracranial metastatic lesions undergoing first-line WBRT combined with immunotherapy. Patients were divided into two groups: those receiving G-CSF (n=37) and those without G-CSF (n=80). We assessed overall survival (OS), intracranial response, progression-free survival (PFS), intracranial progression-free survival (iPFS), and relief from BM-related symptoms.

Results: The G-CSF group demonstrated a significant improvement in OS compared to the non-G-CSF group (median OS: 14.8 vs. 10.2 months; HR: 0.61, 95% CI: 0.38-0.97, p=0.035, Fig.1a). While not statistically significant, trends toward longer PFS (Median time: 10.4 vs 6.2 months; HR: 0.71, 95% CI: 0.47-1.09, p=0.12, Fig.1b) and iPFS (Median time: 11.9 vs 8.1 months; HR: 0.81, 95% CI: 0.52-1.26, p= 0.35, Fig.1c) were observed in the G-CSF group. The analysis of one-year survival rates further demonstrated G-CSF's potential to significantly impact patient outcomes, showing improvements in OS (51.4% vs. 33.8%, p=0.07), PFS (32.4% vs. 18.8%, p=0.10), and iPFS (45.9% vs. 27.5%, p=0.049). This trend continued into the second year, particularly notable in OS (36.7% vs. 15.7%, p=0.04), while PFS (14.8% vs. 6.2%, p=0.18) and iPFS (21.9% vs. 13.6%, p=0.25) displayed improvements that, although suggestive, did not achieve statistical significance. Notwithstanding, there were no significant differences in intracranial responses between the two groups (p> 0.05). Moreover, a significantly higher rate of symptom relief from BM was noted in the G-CSF group (91.7% vs. 59.5%, p=0.037). Cox regression analyses identified post-treatment absolute lymphocyte count (ALC) > 0.9 × 10^9/L (HR 0.57, 95% CI 0.32-0.99, p = 0.046) and hemoglobin (Hb) > 110g/dL (HR 0.41, 95% CI 0.24-0.71, p = 0.001) as factors significantly associated with improved OS.

Conclusions: The integration of G-CSF with WBRT and immunotherapy as a first-line treatment significantly enhances the therapeutic efficacy for NSCLC patients with BMs, particularly in extending overall survival and alleviating BM-related symptoms. These findings underscore the potential of this combined approach in improving clinical outcomes for this patient population.

Keywords: Non-small cell lung cancer; Brain metastases, Whole brain radiotherapy; Immunotherapy, G-CSF; Neutropenia



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EP.09A.05 Consolidative Thoracic Radiotherapy Induced Lymphopenia in Metastatic NSCLC Is Predicted by EDIC and Associated with Poor Clinical Outcomes

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Introduction: Immune checkpoint inhibitors (ICI) have led to significantly improved clinical outcomes in localized and metastatic NSCLC. However, a robust response to ICI is predicated on a viable adaptive immune system. The effective radiation dose to immune cells (EDIC) has been shown to be predictive of lymphopenia. Rates of high-grade lymphopenia after chemoradiation can be upwards of 80% and are correlated with a poorer prognosis. Severe radiation-induced lymphopenia has been demonstrated to attenuate the PFS and OS benefit of consolidative durvalumab. Here, we evaluate whether consolidative thoracic radiotherapy with concurrent maintenance ICI is detrimental in the metastatic setting.

Methods: A retrospective review of patients with metastatic NSCLC treated at our institution from 2022 to 2024 was performed. Six patients with stage IV NSCLC were identified that were treated with upfront chemoimmunotherapy with at least stable disease on early surveillance imaging. Patients subsequently underwent consolidative thoracic radiation (3-4 Gy/fraction to total doses of 45-60 Gy) with continuation of concurrent maintenance ICI. 4 of 6 patients also underwent concurrent SBRT to additional metastatic sites (2 adrenal, 1 lung and 1 thoracic spine). Degree of lymphopenia, EDIC, and oncologic outcomes were evaluated.

Results: Median follow-up was 218 days, with absolute lymphocyte count collected prior to, during and at approximately 1, 4, and 6 weeks after radiotherapy. Four patients had grade 3-4 lymphopenia, three of whom progressed prior to 100 days (the fourth patient had only limited follow-up of less than 1 month). Two patients had grade 1 lymphopenia, one of whom has not progressed and the other who progressed at 494 days and remains alive at greater than 18 months. EDIC was associated with decreased lymphocyte count and higher grade toxicity with lower observed EDIC in patients with G1 lymphopenia (median = 5.1 Gy) compared to those with G3+ lymphopenia (median = 6.2 Gy).

Conclusions: Addition of consolidative radiotherapy to SOC maintenance systemic therapy in patients with limited metastatic NSCLC has previously failed to demonstrate improved outcomes in the phase 2 study NRG LU-002. We postulate that the failure of this larger study could at least be partially explained by the impact of RT on systemic immune function. In this small cohort we demonstrate that lymphopenia from hypofractionated consolidative radiation to the thorax with ICI is associated with poor prognoses in patients with metastatic NSCLC. Short-course, ablative radiation utilizing smaller treatment volumes, lower total radiation doses and more conformal plans may improve outcomes of consolidative radiation by reducing the risk of lymphopenia and preventing immune exhaustion. Further exploration into altered fractionation schedules could lead to improved oncologic outcomes.

Keywords: radiation, immunotherapy, lymphopenia

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EP.09A.06 Assessment of Treatment Outcomes and Chest Wall Toxicity Following Stereotactic Body Radiotherapy for Lung Nodules Adjacent to the Pleura

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Introduction: Stereotactic Body Radiotherapy (SBRT) has emerged as an efficacious approach for early-stage lung cancer and locally effective treatment for oligometastatic-oligoprogressive lung lesions. While SBRT demonstrates a favorable safety profile with minimal toxicity in current literature, its application to lesions proximal to the pleura may lead to chest wall toxicities such as chest wall pain and rib fracture. This study aims to evaluate treatment outcomes and chest wall toxicity following SBRT administered to lung nodules adjacent to the pleura.

Methods: A retrospective analysis was conducted on 70 patients (comprising 74 lesions) who underwent SBRT with 4D respiratory monitoring for lung nodules proximal to the pleura at our center between July 2020 and April 2023. Dose prescription was based on the planning target volume (PTV), excluding volumes intersecting with the ribs. Data collection and analysis were performed using SPSS v23.0, and toxicity rating was assessed in accordance with CTCAE v5.0.

Results: The median age of the patients was 68.5 years (range: 40-86 years). Karnofsky performance score was 80 and above in 81% of patients (n=57). The median volume of the internal Gross Tumor Volume (iGTV) and PTV were 6 cc(range: 1-70 cc) and 22 cc (range: 3-125 cc). Treatment was administered over a median of 5 fractions (range: 4-8) with a total dose of 50 Gy (range: 50-65 Gy). The median Biologically Effective Dose with an alpha/beta ratio of 10 (BED10) was 112.5 Gy (range: 100-150 Gy). The median volume of PTV intersecting with the chest wall was 1.5 cc (range: 1-12 cc). Median chest wall D0.1cc was 55 Gy (range: 22-73 Gy), median V30 was 10 cc (range: 0-61 cc), and median maximum dose to the rib was 40 Gy (range: 22-62 Gy). Following a median follow-up of 21 months (range: 3-43 months) post-treatment, the 2-year local control rate was 92%. While no grade 2 or higher side effects were observed, grade 1 chest wall toxicity was reported in 8% of patients (n=6). One case of grade 1 rib fracture was documented 21 months after SBRT, with a rib maximum dose of 39.8 Gy, treated in 4 fractions. Notably, this patient had a history of breast cancer and prior chest wall irradiation on the same side.

Conclusions: With a dose definition for SBRT in lesions adjacent to the pleura, which subtracts intersecting rib volumes from the PTV, effective treatment outcomes were achieved with minimal toxicity, thereby preserving local control.

Keywords: Radiotherapy, Neoplasms, Neoplasm Metastasis

Table 1: The characteristics of patients and treatment details

	Number/Median (Range)
Age	68.5 (40-86)
Gender	
Male	50
Female	20
Smoking Status	
Never	13
Ever	36
Smoker	21
KPS	90 (70-100)
Lesion	
Early staged lung cancer	42
Metastasis	32
Colorectal	14
Lung	13
Breast	2
Head&neck Tumor	3
BED_{10}	112.5 Gy (100-150 Gy)
SBRT Dose	50 Gy (50-65 Gy)
Fraction	
4	36
5	31
8	7
iGTV (cc)	6 cc (1-70 cc)
PTV (cc)	22 cc (3-125 cc)
Chestwall D0.1 (Gy)	55 Gy (22-73 Gy)
Chestwall V30 (cc)	10 cc (0-61 cc)
Chestwall-PTV intersection volume	1.5 cc (1-12 cc)
Rib D_{max}	40 Gy (22-62 Gy)

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EP.09A.07 Prognostic Factors for Advanced Invasive Mucinous Adenocarcinoma of the Lung with Emphasis on the Treatment Modalities

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Introduction: Invasive mucinous adenocarcinoma (IMA) of the lung represents a rare subtype of lung adenocarcinoma with limited understanding regarding its prognosis, particularly in advanced stages. This study aimed to assess the prognosis of advanced IMA, focusing on treatment modalities.

Methods: A retrospective analysis was conducted on 33 patients diagnosed with advanced-stage IMA or who progressed after curative treatment between 2011 and 2021 at a single center. Overall survival (OS) and progression-free survival (PFS) were the primary and secondary outcomes, respectively, calculated from the date of advanced IMA diagnosis.

Results: The cohort included 13 patients diagnosed at an initial advanced stage and 20 patients who progressed after curative treatment. Treatment modalities included local ablative therapy (LAT) in 13 patients (39.4%), conventional chemotherapy in 24 patients (72.7%), targeted therapy in 7 patients (21.2%), and immunotherapy in 13 patients (39.4%). Median OS was 32.0 months (95% CI, 2.9-61.0), with LAT significantly associated with improved OS compared to non-LAT treatment (not reached vs. 11.3 months, p=0.001). However, OS did not significantly differ based on conventional chemotherapy (p=0.396), targeted therapy (p=0.655), or immunotherapy (p=0.992). On multivariate analysis, LAT remained an independent prognostic factor for OS (HR 0.125; 95% CI, 0.026-0.608; p=0.01). Regarding PFS, there were no significant differences based on treatment modalities. Multivariate analysis identified high body mass index as an independent prognostic factor for progression (HR 0.885; 95% CI, 0.768-0.990; p=0.043).

Conclusions: Our findings suggest that LAT may confer a favorable survival outcome in advanced IMA patients, although it did not significantly impact cancer progression. Further studies are warranted to validate these results and explore additional prognostic factors.

Keywords: lung, mucinous adenocarcinoma, treatment

EP.09A METASTATIC NON-SMALL CELL LUNG CANCER – LOCAL THERAPIES - RADIATION
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EP09A.08 Assessment of MR-Guided Single-Fraction SABR/SBRT of Peripheral Lung Tumors: Dosimetric and Clinical Outcomes - A Prospective Study

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Introduction: The aim of this study was to evaluate the clinical and dosimetric outcomes of online MR-guided single-fraction stereotactic ablative radiotherapy (SABR) and assess acute changes in pulmonary function tests (PFTs), inflammatory markers, and patient-reported quality of life (QoL).

Methods: Patients with inoperable primary lung cancer ≤2 cm or with ≤3 lung metastases ≤3 cm were included in this monocentric prospective study. Patient and treatment characteristics are depicted in the Table. Patients underwent MR-guided single-fraction SABR. Treatement involved delivery of 28 Gy or 30 Gy prescribed to the 80% isodose line, with real-time intrafractional tumor tracking using online 2D cine MRI and respiratory gating. The primary endpoints of the study encompassed local control (LC) and overall survival (OS), while secondary endpoints included acute toxicity (CTCAE v. 5.0), changes in PFTs, inflammatory markers and QoL.

Results: Between October 2020 and October 2022, 29 patients with 33 lung tumors were prospectively enrolled. At a median follow-up of 19.2 months (range: 15.9 - 22.5 months), 1-/2-year LC and OS rates were 96.6% (95% CI: 89.9 - 100.0%)/78.2% (95% CI: 56.8 - 99.6%) and 89.5% (95% CI: 78.3 - 100.0%)/76.1% (95% CI: 59.0 - 93.2%), respectively. Four local failures were observed, three in patients with colorectal carcinoma lung metastases (CRLM) and one in a patient with Ewing sarcoma lung metastasis. Median PTV coverage by the prescribed dose (PTV VPD) was 98.3% (range: 91.9 - 101.7%; compared to PTV VPD of the baseline plans); 4/33 (12.1%) plans were reoptimized, and no CTCAE grade ≥3 side effects were observed. While there was a slight reduction in Forced expiratory volume in 1 second (l) by a median of 4.0% (p = 0.022, range: -23.7 - 66.7%) other PFT parameters remained stable. The neutrophil-to-lymphocyte ratio increased by a median of 8.3% (p = 0.017, range: -100.0 - 207.4%) while serum c-reactive protein and albumin remained stable. Patient-reported QoL did not exhibit significant changes.

Conclusions: MR-guided single-fraction SABR emerges as a safe and effective treatment option for peripheral lung tumors demonstrating encouraging clinical outcomes. This study underscores the potential for dose-escalation in CRLM and offers novel insights into acute changes in lung function, systemic inflammation, and QoL within this context.

Keywords: Single-fraction SBRT, Single-fraction SABR, MR-guided Stereotactic Ablative Radiotherapy

Table 1: Patient and treatment characteristics

All patients	n [%]
Sex	**29 (100)**
Male	18 (62)
Female	11 (38)
Age at time of SABR, median (range) [yrs]	**66 (26 - 86)**
Treatment indication	
Primary lung cancer	**11 (38)**
Early-stage NSCLC (histologically confirmed)	3 (10)
Metastasized NSCLC	7 (24)
Metastasized SCLC	1 (3)
Lung metastases (initial histology)	**18 (62)**
Colorectal cancer	9 (31)
Sarcoma	4 (14)
Skin cancer (non-melanoma)	1 (3)
Pancreatic cancer	2 (7)
Breast cancer	1 (3)
Bile duct cancer	1 (3)
Previous lung radiation therapy	**8 (28)**
Previous pneumectomy	**2 (7)**
Pulmonary comorbidity (i.e. COPD, lung emphysema, or lung fibrosis)	**4 (14)**
ECOG performance status	
0	18 (62)
1	10 (35)
2	1 (4)
Pulmonary function	
FEV_{1s}, median (range) [L]	2.56 (0.78 - 5.19)
(F)VC, median (range) [L]	3.43 (1.99 - 6.19)
$DLCO_{csb}$, median (range) [% predicted]	68 (13 - 102)
CCI (w/o oncological diagnosis), median (range)	**3 (0 - 8)**

All tumors	n (%)
Tumor location	**33 (100)**
Right upper lobe	9 (27)
Right middle lobe	5 (15)
Right lower lobe	12 (36)
Left upper lobe	4 (12)
Left lower lobe	3 (9)
PTV, median (range), cm^3	**6.7 (2.9 – 39.1)**
Fractionation	
1 x 30.0 Gy (prescribed to the 80% IDL)	30 (91)
1 x 28.0 Gy (prescribed to the 80% IDL)	3 (9)

EP.09B METASTATIC NON-SMALL CELL LUNG CANCER – LOCAL THERAPIES - SURGERY
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EP.09B.01 Closing the Gap: Moving Toward Equitable Care in Surgical Management of Stage IV Lung Disease

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Introduction: Despite evolving paradigms in the management of lung cancer, disparities continue to permeate various facets of patient care. We aimed to characterize the relationship between demographic characteristics and likelihood of undergoing lung surgery in stage IV NSCLC. Further, we sought to explore whether any disparities in receipt of surgery changed over time.

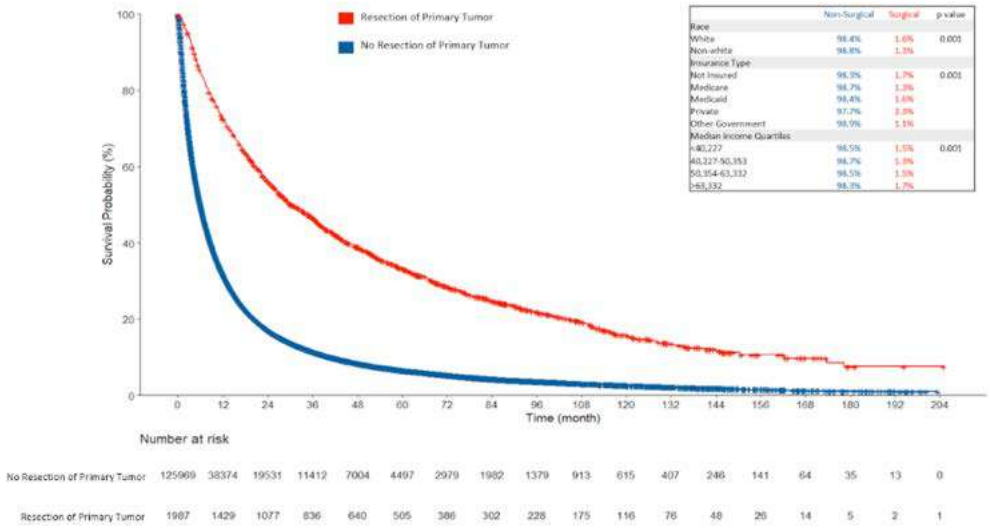
Methods: Using the National Cancer Database, we retrospectively reviewed patients diagnosed with clinical stage IV NSCLC from 2004-2019. Patients were categorized into surgical and nonsurgical groups. Comparisons of demographic, clinical, and outcomes variables were made between groups using Wilcoxon rank-sum test for continuous variables and Fisher's exact test for categorical variables. A multivariable logistic regression model (MVA) was used to assess determinants of receiving surgery. Log-rank test was used to compare overall survival (OS) between groups. Comparative subgroup analyses were performed for patients diagnosed in the years from 2004-2009 versus 2014-2019.

Results: Our cohort was comprised of 137,302 patients, including 2,089 (1.5%) who underwent lung resection as local consolidative therapy (surgical group). Sex distribution within the surgical group was even (1,067 women, 51%). Most patients in the surgical group were between the ages of 61-80 years old (67%, n=1,410), White (89%, n=1864]), and insured (98%, n=2051. Patients who did not receive surgery were more frequently older (p<0.001), non-White (p<0.001), uninsured (p<0.001), and had lower income (p=0.003). After adjusting for clinical T and N, age, and Charleson-Deyo score, we found that non-White, uninsured, and lower income patients remained substantially less likely to receive surgery. Surgical patients had longer OS (median 30.5 months; 95% CI, 28.1-34.3) compared to non-surgical (median 6.0 months; 95% CI 5.9-6.1, p<0.0001, Figure). From 2004 to 2009, the trends mirrored those observed over the entire 15-year span, indicating a lower likelihood of surgery for non-White, uninsured, and lower income patients after adjusting for clinical factors. However, importantly, in subgroup analysis of the last 5 years, no significant differences were observed in terms of race or insurance during this period.

Conclusions: We identified concerning disparities in terms of which patients are offered surgical LCT for stage IV NSCLC. Patients who were non-White, uninsured, and low income were less likely to receive lung surgery, with negative impact on subsequent survival. Notably, comparative data over time suggests that ongoing efforts to address healthcare inequities are making an impact. It is imperative that we persist in addressing inequities in care, thereby ensuring improved outcomes for all patients.

Keywords: Local Consolidative Therapy, Disparities, Stage IV NSCLC

Figure 1. Kaplan-Meier curve representing the overall survival of patients with clinical stage IV non–small cell lung cancer stratified by surgical treatment status.



EP.09B METASTATIC NON-SMALL CELL LUNG CANCER – LOCAL THERAPIES - SURGERY
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EP.09B.02 Performing Lung Resection Simultaneously with Cardiac Valve Surgery is Safe and Economical

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Introduction: A pulmonary tumor is occasionally detected on a chest computed tomography (CT) scan before cardiovascular surgery. In this study we evaluate the safety of performing both lung resection and heart valve surgery simultaneously in one anesthesia, and the advantages of simultaneous surgery from the perspectives of economy and patient experience.

Methods: From January 2018 to January 2023,48 pulmonary tumor is occasionally detected on a chest computed tomography scan before cardiovascular surgery with a median age of 59.8 years. We prioritize recommendation of simultaneous cardiopulmonary surgery, with 31 patients choosing it and 17 patients choosing sequential surgery because the unknown risks. Both groups of patients signed informed consent forms before the surgery. We recorded the patient's intraoperative condition, perioperative data, and total cost for subsequent comparative analysis. The median follow-up time was 3.2 years. The surgical process for the simultaneous cardiopulmonary surgery is as follows: 1. Thoracoscopic wedge resection of the lung and frozen biopsy; 2. Start extracorporeal circulation and perform valve surgery; 3. Resume heartbeat after valve surgery; 4. Confirm pathological malignancy and decide whether to expand to lobectomy 5. Indwelling drainage tubes in the pericardium and chest cavity, completing the chest closure surgery.

Results: No perioperative death occurred in both groups. Pathological examination revealed that in simultaneous surgery group with the clinical stages of 1A in 29 (93.5%) patients, 2A in one patient and 2B in one patient. ALL of the sequential surgery group clinical staging was stage 1A. Among them, 40 patients received the radical pulmonary resection subsequently, whereas 8 patients were unable to receive it due to their poor cardiopulmonary function. Kaplan-Meier analysis of patients with the 3-year survival rate (OS) and lung cancer revealed progression-free survival (PFS) rate were 96.2% and 93.8%, respectively in simultaneous group.94.1% and 94.1% in sequential group. The average hospitalization cost for the simultaneous group is 238,112 RMB, while the average for the sequential group is 307,076 RMB.

Conclusions: Simultaneous pneumonectomy and cardiac valve surgery is a safe and economical method that can reduce anesthesia episodes, accelerate recovery, save costs, shorten waiting time, and reduce patient stress.

Keywords: lung resection, cardiac valve surge, safe and economical

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EP.09B.03 Salvage Surgery Following Inductiontherapy for Advanced ALK-Positive NSCLC: Pathological Response and Surgical Outcomes

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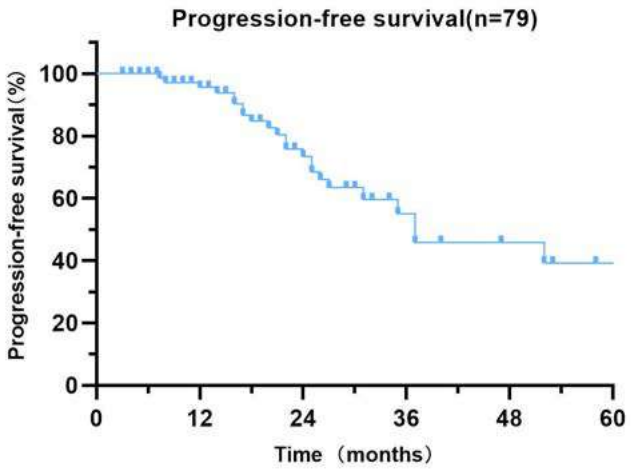
Introduction: ALK-TKIs have dramatically changed clinical outcomes in patients with advanced ALK-positive non-small cell lung cancer (NSCLC). However, the persistent challenge of residual tumor presence remains significant. salvage surgery could be a therapeutic option. We aimed to describe the characteristics and outcomes of patients undergoing salvage surgery after targeted therapy for locally-advanced or metastatic ALK-positive NSCLC.

Methods: We retrospectively collected patients diagnosed with stage IIIA-IVB ALK-positive NSCLC at Guangdong Provincial People's Hospital between January 2016 and March 2024, and those were eligible who underwent pulmonary surgical resection after disease control with targeted therapy. Unidimensional measurements as defined by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 were used in this study. Progress-free survival (PFS) defined as the duration from initial treatment to recurrence or metastasis and were estimated using the Kaplan-Meier method.

Results: A total of 79 patients were consecutively collected, consisting of 51 cases of stage III and 28 cases of stage IV. The median age at diagnosis was 47 years (interquartile range (IQR), 39-55 years), and the majority of patients(n=45,56.9%) were women. The median interval from treatment initiation to surgery was 155 days, with 1 patient achieved complete response (CR), 63 patients achieved partial response (PR) and 15 patients maintained stable disease (SD). Surgical procedures included pneumonectomy in 1.2% of patients, lobectomy in 68.4%, and sublobar resection in 30.4%. 8 patients required conversion to open thoracotomy during surgery. Pathological complete response and major pathological response, defined as 0% and <10% viable tumor cell in the resected tumor bed, respectively, were observed in 29.1% and 69.6% of cases. The median progress-free survival (PFS) time was 37 months. The common recurrence pattern was distant metastases (including 11 intracranial metastases and 2 bone metastases), 5 patients had both intrathoracic recurrence and distant metastases and 5 patients had intrathoracic metastases only.

Conclusions: Target therapy have revolutionized the paradigm of therapy advanced NSCLC with impressive pathological response and promising long-term results. In highly selected ALK-rearranged advanced cases, salvage surgery may have a role.

Keywords: Salvage Surgery, Targeted therapy, ALK-rearrangement



EP.09B METASTATIC NON-SMALL CELL LUNG CANCER – LOCAL THERAPIES - SURGERY
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EP.09B.04 Neoadjuvant Chemo-Immunotherapy Followed by Radical Surgery for Synchronous Oligometastatic Non-Small Cell Lung Cancer

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Introduction: Synchronous oligometastatic NSCLC patients represent a category without a standard therapeutic approach. However, in selected oligometastatic patients, a radical treatment with curative intent seems to offer a good prognosis. Our retrospective analysis aims to analyze the feasibility of the radical multimodality treatment including chemo-immunotherapy in this specific subset of population.

Methods: The study was designed as a single-center, retrospective analysis of patients with synchronous oligometastatic NSCLC undergoing neoadjuvant treatment with platinum-based chemotherapy associated to immunotherapy followed by radical surgery between May 2020 and June 2023. The neoadjuvant treatment included immunotherapy (pembrolizumab or nivolumab) combined with platinum-based chemotherapy. Tumor response was assessed via CT scans, PET-CT and systematic mediastinal minimally invasive staging with EBUS-TBNA.

Results: From January 2020 to June 2023 a total of 11 patients underwent multimodality treatment for synchronous oligometastatic NSCLC. Median age at the diagnosis was 62 (4 - 71). A history of smoking was reported in all patients. Only one patient had a squamous cell histology. A PD-L1 > 50% expression was found in 3 patients. Six patients at the preoperative staging were cN2, of which 4 patients were classified as single-station cN2 after the minimally invasive mediastinal staging. All patients underwent 3 or 4 cycles of chemo-immunotherapy without any III or IV grade of toxicities related to the treatment. All the patients showed a R0 resection after primary tumor surgery. The most frequent site of metastasis was brain (nr=4) and contralateral lung (nr=4). Metastasectomy was performed in 10 patients. One patient with single, 5mm, brain metastasis showed a complete radiological response after neoadjuvant treatment. pCR was reported in 6 patients (54.5%). Five patients underwent adjuvant immunotherapy after surgical resection. After a medium follow up of 16.5 months, all the patients were alive without recurrence.

Conclusions: Neoadjuvant chemo-immunotherapy and radical surgical treatment seems to be safe and feasible in selected synchronous oligometastatic NSCLC with encouraging mid-term outcomes.

Keywords: Oligometastatic NSCLC, Chemo-immunotherapy, pCR

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EP.09B.05 The Role of Pulmonary Metastasectomy (PM) For Non-Primary Lung Cancer: Umbrella Review of Meta-Analyses

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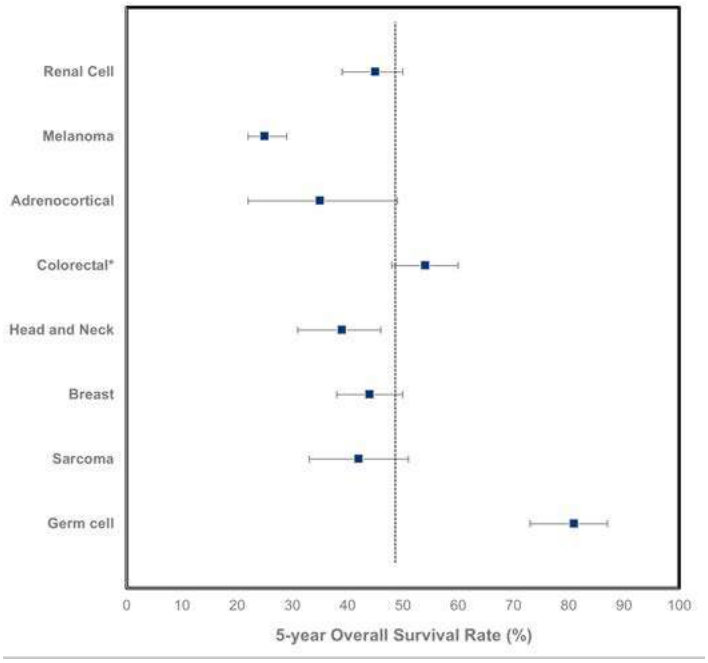
Introduction: The lungs are the most common metastatic area for many cancers. Due to heterogeneous characteristics of primary cancers, the efficacy of pulmonary metastasectomy (PM) in non-primary lung cancers has not been investigated other than colorectal cancers. Furthermore, conducting robust trials in this field are difficult to undertake due to the diverse nature of primary cancers and associated therapeutic approaches. This study aims to investigate the clinical outcomes of PM for non-primary lung cancer by synthesizing existing literature.

Methods: A systematic search for meta-analyses on PM for non-primary lung cancers was conducted, encompassing publications up to January 3, 2024. The analysis included seven primary cancer types: renal cell, breast, adrenocortical, head and neck cancers, melanoma, germ cell tumors, and sarcoma. Primary outcomes, overall survival, and recurrence rates post-PM were assessed using random-effect models to account for study heterogeneity. Subgroup analysis categorized the survival rates based on primary cancer types, and a proportion meta-analysis was performed for comparison.

Results: This study included 16 systematic-review articles and 101 individual studies, involving 10,277 patients who underwent PM for non-primary lung cancer. Patients had a mean age of 48.0 [95% CI 43.9-52.0] years, with 68.4% [95% CI 65.0-71.7] being male. About half of the patients (47.1% [95% CI 40.8-53.5] presented with multiple metastatic lesions, and 26.6% had bilateral involvement of lung. Sublobar resection was mostly performed (82%), and complete R0 resection achieved in 87.2% [95% CI 83.0-90.8]. The pooled 5-year overall survival (OS) rate post-PM was 41.2% [95% CI, 37.1-45.4%], with specific rates for each primary cancer type listed in Table 1. Patients with germ cell tumors demonstrated significantly higher survival rate than other cancers ($p<0.05$), while patients with melanoma exhibited the poorest outcome ($p<0.05$). During follow-up, 57.6% [95% CI 46.4-68.1] had recurrence; 48% of them had intrathoracic-only recurrence and 52% had extra-thoracic recurrence.

Conclusions: This study underscores the survival benefits associated with PM. Overall survival rates following PM do not significantly differ based on primary cancer types, except for germ cell tumors and melanoma. Additionally, the recurrence rates are comparable to those observed in stage 4 advanced cancers. These findings highlight the importance of recognizing and incorporating PM into clinical practice when appropriate.

Keywords: Metastasectomy, lung metastasis, non-primary lung cancer



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EP.11A.01 Evaluation of Six Clinical Prognostic Scores in NSCLC Patients Undergoing First Line Chemoimmunotherapy

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Introduction: Chemoimmunotherapy (CIT) has become the standard of first-line treatment for advanced non-small cell lung cancer (NSCLC) with negative driver genes. The study aimed to evaluate the effectiveness of six prognostic scores for predicting the outcomes to first-line CIT in NSCLC patients.

Methods: NSCLC patients receiving first-line chemoimmunotherapy were included. The prognostic scores evaluated were the Royal Marsden Hospital (RMH), MD Anderson Cancer Center (MDACC), MDACC + Neutrophil-to-Lymphocyte Ratio (NLR), MD Anderson Immune Checkpoint Inhibitor (MDA-ICI) scores, Lung Immune Prognostic Index (LIPI), and Gustave Roussy Immune Score (GRIm). Survival outcomes were estimated using the Kaplan-Meier method, and the prognostic value of these scores was assessed with Cox proportional hazards model.

Results: A cohort of 298 NSCLC patients was analyzed. The median overall survival (mOS) of patients receiving first-line CIT was 36.5 months (95% CI: NR-NR), and the median progression-free survival (mPFS) was 14.5 months (95% CI: 11.9-17.1). nivariate analysis showed that older age (≥ 65), poor performance status (PS≥1), and having more than two metastatic sites were correlated with worse OS (P<0.05). Similarly, the presence of bone, lung, and liver metastases, and more than two metastatic sites were associated with worse PFS(P<0.05). Multivariate analysis showed that PS≥1, bone metastases, and more than two metastatic sites as independent predictors of poor OS (P<0.05). Moreover, having more than two metastatic sites was an poor independent prognostic factor for PFS(P<0.05). Evaluation of the six prognostic scores revealed that the differences in mOS between high- and low-risk groups were statistically significant for RMH, MDACC, MDACC+NLR, and GRIm scores (RMH high- vs. low-risk mOS 20.6 months vs. NR, P=0.026; MDACC 14.0 vs. 34.6 months vs. NR, P=0.003; MDACC+NLR 34.6 vs. 36.5months, P=0.028; GRIm 15.8 vs. 36.5months, P=0.032). Similarly, high-risk patients had significantly shorter mPFS in three of the scoring systems (RMH high-risk vs. low-risk mPFS 8.7 vs. 15.3 months, P = 0.052; MDACC 8.4 vs. 11.2 vs.17.0 months, P = 0.021; MDACC+NLR 11.7 vs. 17.7 months, P = 0.009).

Conclusions: RMH and MDACC scoring systems can more accurately predict the efficacy and prognosis of NSCLC patients treated with first-line chemoimmunotherapy. These findings support the use of these scoring systems by clinicians to inform treatment planning and decision-making.

Keywords: NSCLC, Chemoimmunotherapy, Clinical Prognostic Scores

Evaluation of six clinical prognostic scores in NSCLC patients undergoing first-line chemoimmunotherapy（n=298）

Prognostic Score system		n	(%)	OS（months）		PFS（months）	
				（95%CI）	*P*	（95%CI）	*P*
RMH	0-1	273	91.6	NR（NE-NE）	0.026	15.3（12.5-18.2）	0.052
	2-3	25	8.4	20.6(10.4-30.9)		8.7（3.5-13.9）	
MDACC	0-1	210	70.5	NR（NE-NE）		17.0（12.1-21.9）	
	2	68	22.8	34.6（NE-NE）	0.003	11.2（8.3-14.1）	0.021
	3-5	20	6.7	14.0（4.4-23.6）		8.4（4.3-12.5）	
MDACC+NLR	0-1	192	64.4	36.5（NE-NE）	0.028	17.7（12.9-22.5）	0.009
	>1	106	35.6	34.6（NE-NE）		11.7（9.9-13.4）	
MDA-ICI	0-2	67	22.5	NR（NE-NE）		18.0（12.9-23.0）	
	3	87	29.2	29.4(23.2-35.5)	0.191	16.2（9.1-23.2）	0.400
	4	95	31.9	NR（NE-NE）		12.7（9.8-15.6）	
	5-7	49	16.4	36.5(17.6-55.5)		11.7（9.7-13.6）	
LIPI	0	160	53.7	NR（NE-NE）		16.8（13.2-20.4）	
	1	112	37.6	36.5（NE-NE）	0.684	12.5（9.2-15.7）	0.434
	2	26	8.7	NR（NE-NE）		11.2（8.3-14.1）	
GRIm	0-1	260	87.2	36.5（NE-NE）	0.032	15.3（12.2-18.5）	0.465
	2-3	38	12.8	15.8（NE-NE）		11.9（10.0-13.8）	

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EP.11A.02 Pretreatment Plasma sCD14 as a Prognostic Indicator in aNSLC Patients Undergoing Immunotherapy

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Introduction: CD14+CD16-HLA-DRhi monocytes have been identified as robust prognostic indicators in metastatic melanoma patients undergoing immune-checkpoint blockade. However, the prognostic potential of secretory CD14 (sCD14) in plasma remains unexplored in advanced non-small-cell lung cancer (aNSCLC) patients receiving immunotherapy.

Methods: We collected 149 pretreatment plasma samples from aNSCLC patients undergoing anti-PD1 therapy at Cancer Hospital, Chinese Academy of Medical Sciences (CHCAMS) between 2016 and 2023. Using flow cytometry, we screened 41 cytokines to identify predictive markers distinguishing durable clinical benefit (DCB) from non-durable clinical benefit (NDB) patients (n = 40). An independent cohort (n = 109) validated candidate cytokines, and the prognostic value of sCD14 was confirmed through bulk-RNA sequencing (n = 16 and 27). Single-cell transcriptomic analysis compared signaling pathway enrichment between CD14+ and CD14- monocytes.

Results: Eight predictive cytokines (IL-17A, EGF, TNFR1, GFAP, CCL27, CCL5, CHI3L1, and CD14) were selected and validated, achieving baseline cytokine predictive efficacy with AUCs of 0.865, 0.755, 0.705, 0.726, 0.875, 0.749, 0.749, and 0.84. sCD14 exhibited significant prognostic value in progression-free survival ($p < 0.05$) in the validation cohort, with higher baseline sCD14 levels correlating with superior survival. CD14 expression was further validated in bulk-RNA seq datasets (GSE126044 and GSE135222) showing prognostic significance ($p < 0.05$). Comparative analysis of CD14 expression across 49 cell types revealed its enrichment in monocytes, with CD14-positive monocytes displaying elevated PDL1 (CD274) expression ($p = 0.014$, FC = 1.89) and enrichment in signaling pathways including INFLAMMATORY_RESPONSE, GLYCOLYSIS, and IL6_JAK_STAT3_SIGNALING.

Conclusions: This study identifies sCD14 as a potential biomarker for monitoring aNSCLC patients undergoing immunotherapy, with sCD14 emerging as a potent prognostic indicator. Additionally, CD14+ monocytes demonstrate enhanced PDL1 expression, suggesting their potential role in modulating immunotherapy response.

Keywords: immunotherapy, CD14, prognostic marker

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EP.11A.03 Anti-PD-1 Therapy Plus Denosumab in Advanced Non-Small Cell Lung Cancer with Bone Metastases: A Single-Centre, Retrospective Study in China

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Introduction: Basic studies and clinical studies have demonstrated that bone metastases may affect the efficacy of immunotherapy and concomitant anti-programmed cell death protein 1 (anti-PD-1) therapy and denosumab treatment can improve clinical outcomes of non-small cell lung cancer (NSCLC) patients with bone metastasis. However, limited data are available among Chinese patients, and the effect of this treatment combination on bone metastases has not been adequately studied.

Methods: This single-centre, retrospective study analysed NSCLC patients with bone metastases who received first-line anti-PD1-therapy and concomitant denosumab treatment between March 2021 and June 2022. Bone lesion response was evaluated using a novel quantitative method based on single photon emission computed tomography/computed tomography scans.

Results: 66 patients were included in the final analysis, the median follow-up was 20.08 months (range: 1.00, 46.43). The overall response rate was 36.4% (95% CI: 24.9%-49.1%), with 24 (36.4%) patients having partial response. The median progression-free survival (PFS) was 7.67 months (95%CI:6.20-12.80) and median overall survival(OS) was 20.40 months (95%CI:16.80,28.50). The OS rate (95% CI) was 96.9% (92.7%-100.0%) at 6 months and 79.7% (70.4%-90.2%) at 12 months. Out of 33 bone lesions identified, 28 had improved uptake values between consecutive bone scans (mean change in region-of-interest ratio: -32.7%±19.2%). 16 patients had decreased ROI ratios for all of their focal sites, the ORR of the 16 patients was 50.0% (95% CI: 24.7%-75.4%), the median PFS was 13.28 months (95% CI: 95%CI:7.47,NR), the median OS was 25.8 months (95% CI: 14.30,NR), the OS rate (95% CI) was 93.8 % (82.6%-100.0%) at 12 months.

Conclusions: This study provided further support for the concomitant use of anti-PD-1 therapy and denosumab in NSCLC patients with bone metastases. The novel, quantitative assessment method explored in this study may help inform a new, practical method for bone lesion assessment.

Keywords: NSCLC, denosumab, Anti-PD-1 therapy

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EP.11A.04 Patterns of Failure and Subsequent Treatment after Progression on First-Line Immunotherapy Monotherapy in Advanced NSCLC

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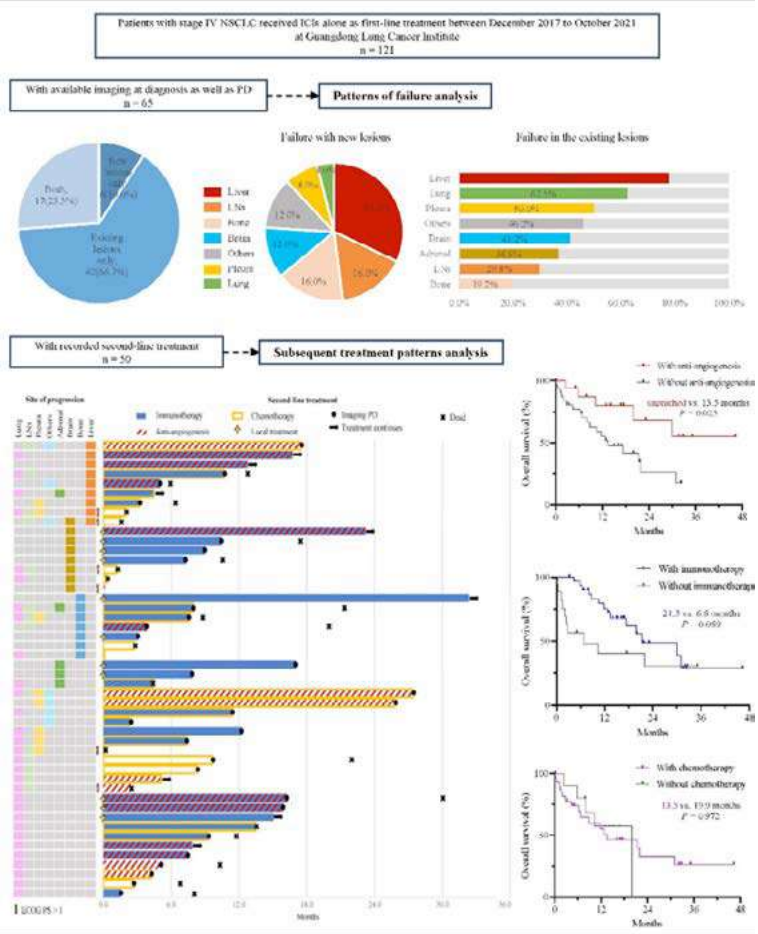
Introduction: Immune checkpoint inhibitors (ICIs) became the recommended first-line therapy for advanced NSCLC without driver gene mutation, but the data about failure pattern of first-line ICIs monotherapy was lacking and the optimal strategy for subsequent treatment remained controversial.

Methods: Patients with advanced NSCLC and receiving first-line ICIs monotherapy at Guangdong Lung Cancer Institute between December 2017 and October 2021 were identified from an electronic database. The progressive sites were recorded to analyze the patterns of failure. Overall survival (OS) was compared between different regimens.

Results: A total of 121 patients receiving first-line ICIs monotherapy were identified, among whom 65 patients with available imaging at diagnosis as well as progressive disease were included in the patterns of failure analysis, and 50 patients with recorded second-line treatment were included in the subsequent treatment patterns analysis. For those with new lesions, progression frequently occurred in the liver (32.0%), LNs (16.0%), and bone (16.0%). As for those with failure in the existing lesions, the most common sites of progression were the liver (77.8%), lung parenchyma (62.5%), and pleura (50%). About 56.9% of patients showed oligoprogression, while the others had progression in more than 3 sites. Isolated oligoprogression occurs most often in the lung parenchyma and intracranial lesions, and more than half of these patients still received immunotherapy after local treatment, with a 2.5-year OS rate of 51.4%. The frequency of anti-angiogenesis therapy, chemotherapy, and immunotherapy used in the second-line therapy was 38.0%, 56%, and 74%, respectively. The application of anti-angiogenesis therapy could significantly prolong the OS (median: unreached vs. 13.5 months, P = 0.025). For those with progression in the liver, the application of anti-angiogenesis therapy could also prolong the OS (unreached vs 6.3 months, P = 0.067). Besides, the median OS of those with immunotherapy in the second-line setting was 21.3 months, which was numerically longer than those without immunotherapy (6.8 months, P = 0.089)

Conclusions: The liver was the most common site of progression on first-line ICIs monotherapy. Anti-angiogenesis-based therapy might be an optimal therapeutic regimen for a second-line setting. Isolated oligoprogressive patients might still benefit from immunotherapy after local treatment.

Keywords: non-small cell lung cancer, PD-1 inhibitor, progression



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EP.11A.05 Use of Immune Checkpoint Inhibitors in Advanced NSCLC Cases with Very Poor ECOG-PS: A Real World Experience.

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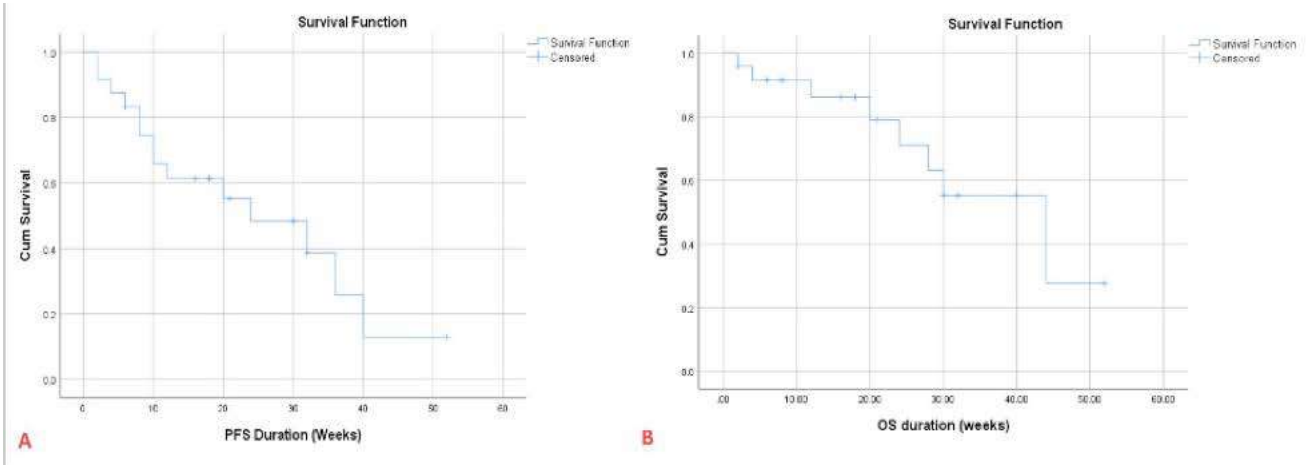
Introduction: Approximately 50% non-small cell lung cancer (NSCLC) patients present with Eastern—cooperative-oncology-group performance status (ECOG-PS) ≥2. Chronic-obstructive-pulmonary-disease (COPD) and coronary-artery-disease (CAD) frequently contribute towards poor PS. Such cases are frequently excluded from the clinical trials, therefore leading to a dearth of safety or effectiveness data for ICI in this specific population. Due to poor PS, chemotherapy is often ruled out, leading to limited management options. Here we are presenting our experience of using immune checkpoint inhibitors (ICI) in patients with PS 3/4.

Methods: Data of all cases treated with ICI from the thoracic oncology clinic was retrieved from September 2022 to March 2024. Inclusion criteria were NSCLC with stage IIIB or higher and ECOG-PS 3 or 4. Demographic and clinical data was collected, coded and analysed. Progression-free survival (PFS) and overall survival (OS) were calculated.

Results: Out of 101 cases, data of 24 patients was retrieved and analysed. Majority subjects were males (83.3%), smokers (79.2%), with COPD (62.5%), squamous histology (66.7%), stage IVA (45.8%), and PDL1 between 1-49% (41.7%). Disease burden contributed to poor PS in majority of subjects (45.8%) followed by comorbidities (37.5%). Mean age was 61.75±10.2 years. ECOG at the time of ICI initiation was 3 in 83.3% and most had previously received one (45.8%) or two (33.3%) lines of therapy. Nivolumab (70.8%) and atezolizumab (29.2%) were the two ICIs used. 20.8% had brain metastasis at the time of ICI initiation and 41.7% had history of prior radiotherapy treatment (any site). Over a median follow-up of 20 weeks, 14 (58.3%) progressed and (33.3%) died. Three patients experienced hypothyroidism, one had pneumonitis and one patient had Grade 3 transaminitis. Median PFS was 24 (IQR 8-40) weeks, whereas median OS was 44 (IQR 24-64) weeks. Best response was Partial Remission in 25%, whereas Stable Disease was achieved in 45.8%. Neither PFS nor OS was significantly different among the groups stratified according to stage, histology, ECOG, type of ICI used, comorbidities, line of therapy or PDL1 Status. Of the 14 progressed, ICI was continued beyond progression in 10. An improvement in ECOG-PS of minimum one unit, was documented in 8 subjects. Quality of life data was not collected.

Conclusions: ICI remain a viable treatment option in patients of advanced NSCLC with very poor ECOG-PS. The relative safety of ICI over chemotherapy may provide an additional tool to Best Supportive Care treatment recommendation for this specific subgroup.

Keywords: Immune Checkpoint Inhibitor, Poor Performance Status, Palliative care



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EP.11A.06 Somatic Gene Changes Associated with Response to Immune Checkpoint Inhibitors in Non-Small Cell Lung Cancer

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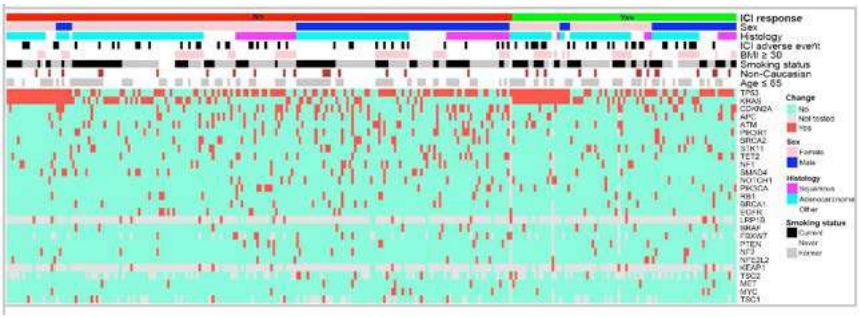
Introduction: While immune checkpoint inhibitors (ICI) have altered the paradigm for treating lung cancer, the long-lasting benefit of ICI therapy remains limited to too few of those who receive it. We examined if somatic changes in genes influence ICI response.

Methods: Response to ICI according to RECIST 1.1 guideline and tumor gene changes were noted from CT imaging, pathology, and other clinical records of 550 primary non-small cell lung cancer patients who received ≥ three doses of ICI within six months at our institution during 2015-23.

Results: Tumors of 277 patients had somatic changes in 1-46 genes (median = 3) as per FoundationOne or OmniSeq tests for 22-368 genes (median = 67) performed before or within 30 days of ICI treatment. Of the total 1,654 changes affecting 340 genes, 1,410 were protein-coding (272 patients), 166 copy loss (72), 35 copy gain (42), 13 fusion (seven), and 1 splicing (one). The fraction of tested genes that had changes was greater in non-Caucasians compared to Caucasians (median 7% vs. 5%, Wilcoxon p=0.041), and in PDL1-low compared to PDL1-high tumors (6% vs. 4%, p = 0.049), but not significantly associated with age, sex, race, smoking status, BMI, cancer histology, or ICI response (partial/complete or not) or adverse events. Among the 72 genes that were tested in > 100 patients, the prevalence of somatic change (0.4%-59%) was highest for TP53 (59%), KRAS (40%), CDKN2A (21%), APC (14%), and ATM (13%). Among the 28 genes (Figure) that were changed in ≥ 10 patients, ICI response was less likely for those with changes in NF1 (21/24 vs. 170/250, p=0.047), SMAD1 (21/24 vs. 170/250, 0.047), and TSC1 (10/10 vs. 146/217, 0.03), but not the other genes, including KRAS (70/111 vs. 121/165, 0.07), STK11 (19/30 vs. 173/247, 0.50), and TP53 (108/163 vs. 84/115, 0.20). In the PDL1-low group (n=138), significant associations with lack of response were noted for NF1 (12/12 vs. 91/125, 0.04) and STK11 (12/21 vs. 91/117, 0.045). For the PDL1-high group (n=118), somatic change in only TSC2 was associated with a lack of response (0/4 vs. 51/79, 0.02). Patients with variation in both KRAS and TP53 were 1.7 times more likely to respond to ICI than others (22/47 vs. 63/229, p=0.009).

Conclusions: KRAS, NF1, STK11, TP53, and TSC1/2 genes may be of high relevance to identify NSCLC patients who are more likely to respond to ICI and to understand the biology of such responsiveness.

Keywords: immunotherapy response, gene mutations, KRAS and TP53



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EP.11A.07 Immunotherapy in Metastatic Pulmonary Lymphoepithelioma-Like Carcinoma

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Introduction: Pulmonary lymphoepithelioma-like carcinoma (pLELC) is a rare subtype of non-small cell lung cancer. With the increasingly dominant role of PD1/PDL-1 checkpoint inhibitor in the treatment landscape of NSCLC, chemotherapy remained the current mainstay approach of systemic treatment for pLELC due to the under-representation of pLELC in major NSCLC IO trials. A body of efficacy data of immunotherapy (IO) in pLELC needs to be accumulated.

Methods: A single tertiary-institution cohort study was conducted to include all patients with recurrent or metastatic pulmonary pLELC in 2010-2023 who received IO in an institutional cancer registry. Patient demographics and clinical characteristics were described and analyzed. Progression-free survival (PFS) and overall survival (OS) were estimated by the Kaplan-Meier method. Comparison of the survival end points were made using the log-rank test.

Results: Two-hundred pLELC patients were identified in database. Twenty-six patients received IO (M=6, F=20), median age was 65 (range 40-80), with 21 (80.3%) were non-smokers. Eight patients underwent IO in 1st line and 18 patients in 2nd line or beyond. PD-L1 tumor proportional score (TPS) were >/= 50% in 23% of patients. None of them had targetable driver mutation of EGFR, ALK and ROS-1. The immunotherapy used in 1st line were mainly pembrolizumab(pembrolizumab =7, atezolizumab = 1). Only 2 patients were given IO-chemotherapy combination. In 2nd line and beyond, 11 patients used nivolumab and 7 used atezolizumab. The response rate was 15.4% and the median PFS for immunotherapy used in 1st line and 2nd line or beyond was 8.63 and 3.50 months respectively. The median OS for immunotherapy used in 1st line and 2nd line or beyond was 26.3 and 8.23 months. An exploratory analysis in subsequent line patients shows trend towards longer median PFS and OS for patients receiving atezolizumab than nivolumab (mPFS 7.73 vs 3.50 months, p=0.231; mOS 22.2 vs 8.00 months, p=0.114). There was 1 patient (3%) complicated with G3 dermatitis.

Conclusions: The observed mPFS and mOS in our cohort of pLELC treated with immunotherapy were numerically similar to those observed in major NSCLC trials, including KEYNOTE-024, Checkmate 057 and OAK. As driver mutation was rarely seen in pLELC, IO monotherapy or combination could become the mainstream treatment as in NSCLC lacking driver mutation.

Keywords: NSCLC, Lymphoepithelioma-like Carcinoma, Immunotherapy

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EP.11A.08 Real-World Comparative Effectiveness in Advanced NSCLC and High PD-L1 with 1L Immune Checkpoint Inhibitors ± Chemotherapy

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Introduction: Immune checkpoint inhibitors (ICIs) ± chemotherapy is currently the recommended treatment for patients with advanced NSCLC (aNSCLC) and programmed cell death-ligand 1 (PD-L1) ≥50%. The objective of the study was to compare real-world clinical outcomes among patients with aNSCLC and PD-L1 ≥50% treated with ICI monotherapy or in combination with chemotherapy in the first-line (1L) setting.

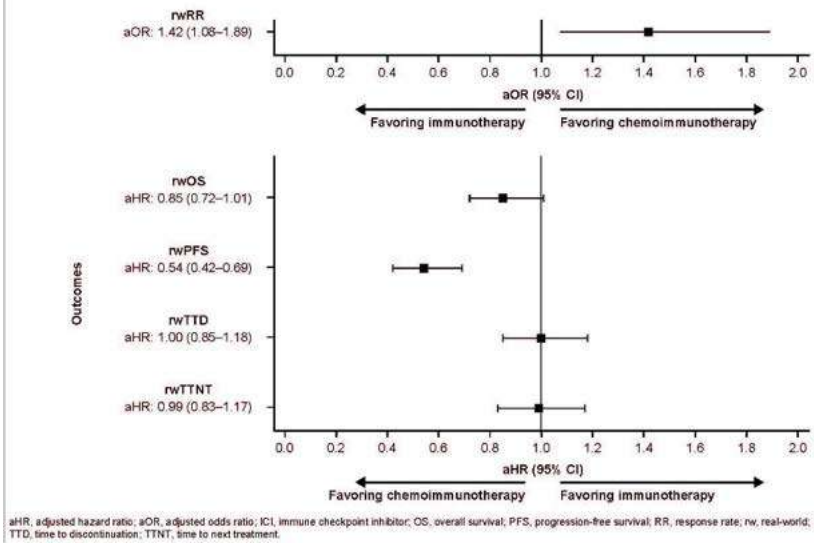
Methods: The ConcertAI Oncology Database was used to identify patients in the United States with aNSCLC with PD-L1 ≥50% prior to initiating 1L ICI+chemotherapy or ICI monotherapy up to 30 days post-treatment between May 2017 and February 2023. We characterized real-world (rw) response rate (rwRR), overall survival (rwOS), progression-free survival (rwPFS), time to discontinuation (rwTTD), and time to next treatment (rwTTNT). Time-to-event outcomes were assessed using Kaplan-Meier methods after applying inverse probability of treatment weighting (IPTW). Differences in outcomes across patients initiating ICI+chemotherapy or ICI monotherapy were assessed using Cox regression with IPTW to adjust for potential key confounders, including clinical and demographic characteristics; unbalanced covariates were added to the Cox model. Statistical significance was interpreted using 95% CIs.

Results: We identified 1,384 eligible patients, of whom 65% initiated ICI monotherapy and 32% started ICI+chemotherapy. The mean age was 70 years (SD: 9.5) and 51.4% of patients were male; most had adenocarcinoma (63.0%) or squamous cell carcinoma (22.5%). After performing IPTW, key confounding variables were generally well balanced between the ICI monotherapy and ICI+chemotherapy groups. The rwRR was 48.1% (95% CI: 42.4-53.8%) and 39.4% (95% CI: 35.7-43.2%) among patients initiating ICI with and without chemotherapy, respectively, yielding an adjusted odds ratio for response of 1.42 (95% CI: 1.08-1.89). The median rwOS was 19.3 months (95% CI: 15.7-24.4) and 15.9 months (95% CI: 13.5-19.1) among patients who received ICI with and without chemotherapy, respectively, yielding an adjusted hazard ratio (aHR) for death of 0.85 (95% CI: 0.72-1.01). Additionally, ICI+chemotherapy was associated with longer rwPFS with an aHR for disease progression or death of 0.54 (95% CI: 0.42-0.69). No differences were observed in rwTTD and rwTTNT across the 2 groups. See Figure 1 for results.

Conclusions: We observed significantly higher rwRR and rwPFS among patients who received ICI+chemotherapy compared with ICI monotherapy. No significant differences in the rwOS, rwTTD, and rwTTNT between patients on ICI+chemotherapy and ICI monotherapy were observed. Further research is needed to understand patient characteristics associated with benefit from each treatment modality.

Keywords: Non-small Cell Lung Cancer, Cemiplimab, Health economics

Figure 1. Real-world outcomes among patients on ICI + chemotherapy and ICI monotherapy



aHR, adjusted hazard ratio; aOR, adjusted odds ratio; ICI, immune checkpoint inhibitor; OS, overall survival; PFS, progression-free survival; RR, response rate; rw, real-world; TTD, time to discontinuation; TTNT, time to next treatment.

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EP.11A.09 Predictive Role of BMI and Inflammation Markers in Immunotherapy (ICI) For HIV Associated Lung Cancer

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Introduction: Historical exclusion of HIV patients(pts) from ICI trials limits data on predictive markers which may differ from HIV negative counterparts due to altered immune activation and inflammation. Inflammation markers are implicated as predictive in ICI treated solid tumors with various optimal cut offs. Here, we study the predictive role of and the optimal cut off for inflammation markers in HIV associated lung cancer treated with ICI.

Methods: Baseline characteristics and survival outcomes for 53 pts with HIV associated advanced lung cancer diagnosed between 2011-2023 treated with ICIs in first or subsequent lines were analyzed. Receiver operator characteristics curve was employed to determine ideal cut offs for systemic inflammation index (SII = neutrophils (N) /lymphocytes (L) x platelets (P)), monocyte-lymphocyte ratio (MLR) and PLR. The optimal cut offs were 874 for SII, 0.6 for MLR, 295 for PLR. Cox regression analysis was conducted to assess the association of body mass index (BMI), NLR, SII, MLR and PLR with overall survival (OS).

Results: 32 pts received ICIs; 21 pts received chemotherapy (CT) exclusively. The baseline characteristics of age, gender, stage, histology, race/ethnicity and ECOG performance status (PS) were balanced. The median age was 57 and 61 years, with 67% and 66% self-identifying as non-Hispanic Black and 29% and 25% as Hispanic in the CT and ICI groups, respectively. The median follow up was 12 months. 84% had HIV viral load < 200 copies/mL, and 86% had median CD4 count > 200 cells/μL. Median PD-L1 TPS (22c3) was 1, the objective response rate was 27% with a disease control rate of 59% in the ICI group. Low BMI and poor ECOG PS were strongly associated with shorter OS and high SII was associated with longer OS in the ICI cohort in univariate and multivariate analyses controlling for age and gender. In comparison, only high MLR and PLR were associated with longer OS in the entire cohort. PD-L1 TPS and CD4 count were not associated with OS in the ICI cohort.

Conclusions: Our study focusing on HIV associated lung cancer reveals that BMI and SII are strongly associated with survival outcomes exclusively in the ICI treated cohort. Given the lack of correlation between PD-L1 expression and clinical outcomes, better predictive biomarkers are necessary. Addition of inflammation markers identified in this study, when validated in larger studies, may assist in refined prediction of survival in ICI treated HIV associated lung cancer.

Keywords: HIV, Immunotherapy, Biomarker

	Total				ICI			
	Univariate		Multivariate		Univariate		Multivariate	
Variable	Hazard ratio (HR)	P value	HR	P value	HR	P value	HR	P value
ECOG PS ≥ 2 vs 0-1	2.13	0.073	1.55	0.345	7.91	<0.001	6.27	0.006
BMI < 18.5 vs ≥ 18.5	1.68	0.263	1.48	0.433	4.27	0.038	4.88	0.045
NLR ≥ 5 vs <5	0.99	0.978	1.00	0.998	1.01	0.986	0.73	0.592
SII ≥ 874 vs <874	0.48	0.065	0.52	0.113	0.32	0.027	0.19	0.011
MLR ≥ 0.6 vs <0.6	0.29	0.024	0.34	0.047	0.30	0.058	0.22	0.049
PLR ≥ 295 vs <295	0.18	0.021	0.20	0.035	0.26	0.074	0.26	0.087

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EP.11A.10 Chronological and Biological Age as a Response Factor to Immune Checkpoint Inhibitors in Advanced Non-Small Cell Lung Cancer

G. Suay[1], A. Ortiz-Gracia[1], C. Rodrigo[2], J. Linares[1], J-C. Garcia-Cañaveras[2], A. Armero[2], F. Aparisi[2], A. Lahoz[1], O. Juan-Vidal[1], [1]University and Polytechnic La Fe Hospital, Valencia/ES,[2]Health Research Institute Hospital La Fe, Valencia/ES

Introduction: Immune checkpoint inhibitors (ICIs) have radically changed the prognosis of patients with non-small cell lung cancer (NSCLC) by increasing the overall survival (OS). However, some doubts exist regarding special populations such as elder patients, which show less benefit to different ICIs in different subgroup analyses of approbatory trials. It has been suggested that this may be a consequence of immunosenescence. However, the elder population was underrepresented in those trials, and there is scarce real-world data.

Methods: Our study aimed to retrospectively analyze the baseline characteristics and overall survival (OS) according to age in patients with advanced NSCLC who received first-line ICIs. Patients were treated in a tertiary reference Hospital in Spain from January 2016 to December 2024. The cohort was also stratified based on the number of comorbidities as a surrogate marker of biological age.

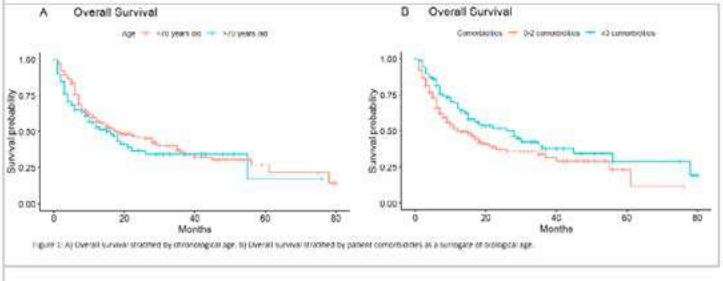
Results: 247 patients with advanced NSCLC, candidates to ICIs, were included into the study (Table 1). No statistically significant difference in median OS was observed when comparing patients with <70 years old and patients with ≥70 years old (18 vs 15 months; p=0.270) (Figure 1A). The analysis of median OS stratified by comorbidities (as a surrogate of biological age) showed statistically significant differences in patients who had 0-2 comorbidities, compared with patients who had ≥3 comorbidities (28 months vs 13 months; HR= 0.697; p=0,04) (Figure 1B).

Conclusions: Our study shows that there are no statistically significant differences in OS stratified by chronological age. However, when considering the number of comorbidities as a surrogate of biological age, median OS was worse in patients who had ≥3 comorbidities. Biological age might be a key factor regarding response to ICIs treatment. Further research should be done to better understand the immunosenescence process, and to personalize treatments to each patient.

Keywords: non-small cell lung cancer, immune checkpoint inhibitors, immunosenescence

Table 1. Patient Baseline Characteristics (N=247)

Sex	Male: 173 (70%) Female: 74 (30%)
Age (Median)	65 (Range 39-85)
Smoking History	Yes: 232 (93.9%) No: 15 (6.1%)
Histology	Adenocarcinoma: 170 (68.8%) Squamous: 59 (23.9%) Other histology (NOS, undifferentiated…): 18 (7.3%)
Brain Metastases	Yes: 65 (26.3%) No: 182 (73.7%)
PD-L1 expression	<1%: 86 (34.8%) 1-49%: 68 (27.5%) =50%: 86 (34.8%) Unknown: 7 (2.8%)
First-line Treatment Protocols	Immune Checkpoint Inhibitor Monotherapy: 86 (34.8%) Atezolizumab: 8 (3.2%) Cemiplimab: 4 (1.6%) Pembrolizumab: 74 (30%) Immune Checkpoint Inhibitor Combination: 161 (65.2%) Carboplatin-Paclitaxel-Bevacizumab-Atezolizumab: 5 (2%) Carboplatin-Paclitaxel-Pembrolizumab: 43 (17.4%) Carboplatin-Pemetrexed-Nivolumab-Ipilimumab: 12 (4.9%) Carboplatin-Pemetrexed-Pembrolizumab: 53 (21.5%) Cisplatin-Pemetrexed-Nivolumab-Ipilimumab: 7 (16.2%) Cisplatin-Pemetrexed-Pembrolizumab: 40 (16.2%) Carboplatin-Paclitaxel-Nivolumab-Ipilimumab: 1 (0.4%)
Performance Status	0: 55 (23%) 1: 157 (65.7%) 2: 23 (9.6%) 3/4: 4 (1.7%)
Number of Comorbidities (Median)	3 (Range 0-13)
Number of Drugs (Median)	5 (Range 0-21)



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EP.11A.11 Application of Circulating Tumor Cell (CTC) PD-L1 Detection in the Evaluation of Therapeutic Efficacy in Advanced NSCLC: A Retrospective Study

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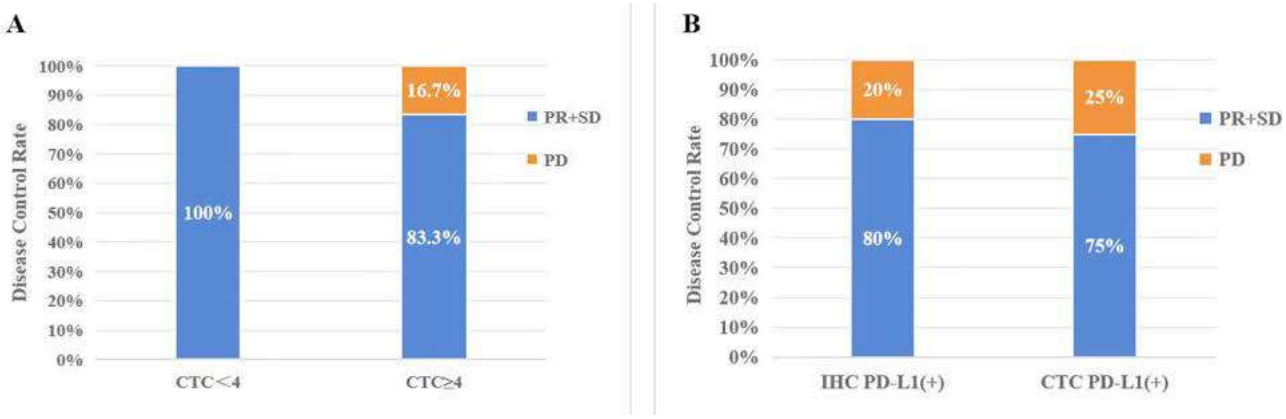
Introduction: PD-L1 shows a dynamic expression profile during therapies. It is affected by intratumoral heterogeneity, leading to different responses to immune checkpoint inhibitors (ICIs), but the invasiveness and risks of tissue biopsy make longitudinal sampling challenging and almost unfeasible. Our study aims to analyze the consistency between CTC PD-L1 liquid biopsy and pathological tissue PD-L1, to explore whether the CTC PD-L1 can screen the beneficiaries of immunotherapy, and to assess the predictive value of CTC on treatment response and prognosis.

Methods: Sixty-four patients newly diagnosed with advanced-stage NSCLC who undergo PD-L1 immunohistochemical detection were recruited in our institute from February 2022 to April 2024. CTCs were captured and identified from the peripheral blood of enrolled patients through the microfluidic chip-based CTC screening platform CTC100. CTC and CTC PD-L1 expression were dynamically evaluated at baseline, on treatment, and disease progression.

Results: CTCs and PD-L1(+) CTCs were detected in 57/64 (89%) and 44/57 (77.2%) patients at baseline. The mean and median values of baseline CTCs were 10 and 7, respectively. Thirty-one of 51 patients (60.8%) with available immunohistochemistry (IHC) PD-L1 results presented positive PD-L1 expression (TPS>1%). Among the 47 comparable samples, the overall coincidence rate of PD-L1 status between the tissue sample and CTC was 70.2%, with a positive concordance rate of 93.1% and a negative concordance rate of 33.3%. The positive predictive value (PPV) and negative predictive value (NPV) of CTC PD-L1 were 69.2% and 75%, respectively. In the current incomplete clinical follow-up, we obtained preliminary results worth further exploration. We found that the disease control rate was lower for patients with high CTC levels (Figure1A), and patients with CTC PD-L1 positive expression at baseline have no less response to immunotherapy than those with tissue PD-L1 positive expression (Figure1B).

Conclusions: CTC PD-L1 has a high consistency with immunohistochemical PD-L1. Detection of PD-L1 expression on CTC before treatment is an alternative approach to help therapy decisions. Serial biopsies of CTC may enable treatment response monitoring on immunotherapy.

Keywords: NSCLC, circulating tumor cell, immunotherapy



EP.11A.12 Real-World Treatment Patterns and Clinical Outcomes Following Chemotherapy and Anti-PD-(L)1 In Non-Small Cell Lung Cancer

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Introduction: Effective treatment options for advanced/metastatic non-small cell lung cancer (NSCLC) are limited, especially for those with progression after platinum-based chemotherapy (PBC) and an anti-programmed cell death 1 protein (PD-1) or ligand 1 (PD-L1) regimen. We report real-world treatment options and associated outcomes, including time to treatment discontinuation (TTD), progression-free survival (PFS), and overall survival (OS) in US patients who previously received PBC and anti-PD-(L)1 regimens.

Methods: This study used data from the nationwide Flatiron Health electronic health record-derived deidentified database. Patients were aged ≥18 years with an initial diagnosis of advanced/metastatic NSCLC and an ECOG performance status of 0 or 1 who had received PBC and anti-PD-(L)1 therapy in 1 (in combination) or 2 (in sequence) lines and initiated ≥1 subsequent treatment between 2018 and 2023. The index date was the start date of subsequent treatment (defined as the index regimen). Patients were followed up until death or last available data through June 30, 2023. Patient characteristics, treatment patterns, and outcomes were analyzed in the overall patient group and according to initial treatment (cohort 1: first-line PBC + anti-PD-(L)1; cohort 2a: first-line PBC and second-line anti-PD-(L)1; or cohort 2b: first-line anti-PD-(L)1 and second-line PBC). Subgroup analyses were stratified by index regimen, without adjustment for differences between groups. TTD, PFS, and OS were estimated using Kaplan-Meier methods.

Results: A total of 1793 patients were included: 73.5% in cohort 1, 22.5% in cohort 2a, and 4.1% in cohort 2b. Median follow-up from index date was 7.8 (range, 0.0-65.0) months. A broad range of treatments were used after PBC and anti-PD-(L)1 regimens; among all patients, the most common were docetaxel + ramucirumab and docetaxel monotherapy (Table 1). Median TTD, PFS, and OS were similar across cohorts. Compared with outcomes in the overall population, median TTD (2.63 [95% CI, 2.10-3.02] months), PFS (4.17 [3.61-4.57] months), and OS (7.89 [7.10-8.71] months) were shorter in patients who received chemotherapy monotherapy as index therapy, including docetaxel and gemcitabine monotherapies. Median TTD (5.59 [4.40-8.77] months), PFS (8.71 [5.88-12.85] months), and OS (26.97 [20.37-31.74] months) were longer in those receiving index immuno-oncology monotherapy.

Conclusions: Short median TTD, PFS, and OS underscore a significant unmet need among patients previously treated with PBC and anti-PD-(L)1, particularly among those subsequently treated with chemotherapy monotherapy. Further investigation of novel modalities to extend survival, including immuno-oncology combinations, is warranted in this patient population.

Keywords: Real-world, Advanced NSCLC, Treatment Patterns

	All patients (n=1793)	**Cohort 1 (n=1317)**	**Cohort 2a (n=403)**	**Cohort 2b (n=73)**
Top 2 index regimens, n (%)				
Most frequent	Docetaxel + ramucirumab 314 (17.5)	Docetaxel + ramucirumab 256 (19.4)	Docetaxel + ramucirumab 51 (12.7)	Gemcitabine 11 (15.1)
Second-most frequent	Docetaxel 158 (8.8)	Docetaxel 115 (8.7)	Gemcitabine 45 (11.2)	Docetaxel + ramucirumab 7 (9.6)
TTD, median (95% CI), months	3.71 (3.48-3.94)	3.71 (3.48-4.17)	3.48 (3.02-3.91)	4.17 (2.33-6.01)
PFS, median (95% CI), months	5.29 (5.03-5.52)	5.19 (4.83-5.52)	5.49 (5.09-6.18)	5.03 (3.65-6.64)
OS, median (95% CI), months	11.20 (10.48-11.93)	11.27 (10.32-12.39)	11.01 (9.79-12.19)	11.76 (8.54-15.64)

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EP.11A.13 Efficacy and Safety of Immune-Checkpoint Inhibitors in Advanced NSCLC Patients with Rare Mutation after Developing Targeted Therapy Resistance

W. Zhang[1], Y. Li[1], H. Jiang[1], D. Wang[1], B. Liu[1], F. Qian[1], B. Zhang[1], Y. Zhang[1], R. Li[2], W. Ma[2], B. Han[1], Y. Lou[1], [1]Shanghai Chest Hospital, Shanghai Jiao Tong University, Shanghai/CN,[2]Department of Clinical Research Center, Shanghai Chest Hospital, Shanghai/CN

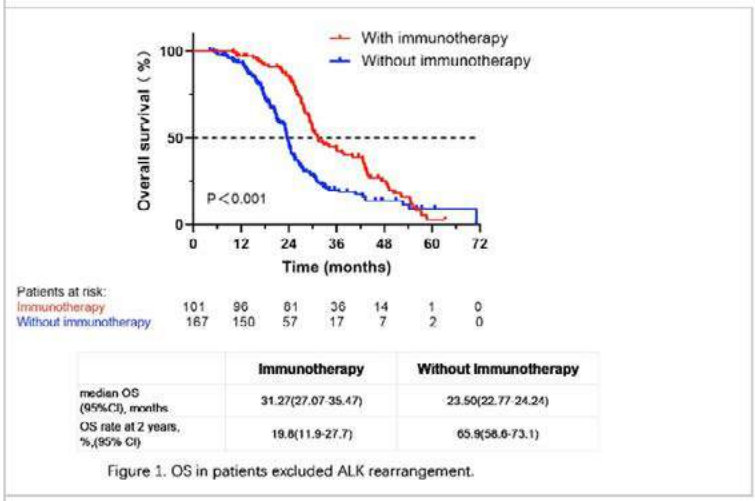
Introduction: Efficacy and safety of Immune-checkpoint inhibitor (ICI) in patients with non-small cell lung cancer (NSCLC) harboring rare molecular alterations after developing targeted therapy resistance remain poorly elucidated.

Methods: We retrospectively collected the statistics of NSCLC patients carrying rare oncogenic driver mutations who treated at Shanghai Chest Hospital between June 1st, 2018 and December 31th 2022. Progression-free survival (PFS) and overall survival (OS) were utilized to evaluate the outcomes of this study.

Results: A total of 375 patients were included. Up to July 15th 2023,the median follow-up time was 25.1 months (IQR, 6.2-63.6 months). The molecular alterations involved EGFR rare mutation (n=141, 37.6%), ALK rearrangement (n=107, 28.5%), ROS1 rearrangement (n=86, 22.9%), MET amplification or exon 14 mutation (n=27, 7.2%), BRAF V600E mutation (n=14, 3.7%). Survival analysis indicated that when exclude patients with ALK rearrangement, patients treated with immunotherapy in the post-line had better overall survival (OS) and Progression-free survival (PFS) compared with those treated with other treatments (median OS, 31.3 vs. 23.5 months, P<0.001; median PFS, 4.9 vs. 9.2 months, P<0.001)(Figure 1 and Figure 2). What's more, high level PD-L1 expression status can not demonstrate better PFS in patients received immunotherapy after developing targeted therapy acquired resistance. From 375 patients with available data, 33 (8.8%) had grade 3-5 irAEs, including 21 (5.6%) of grade 3,11(2.9%) of grade 4, and 1 of grade 5 (0.3%, endocrine di-sorder).

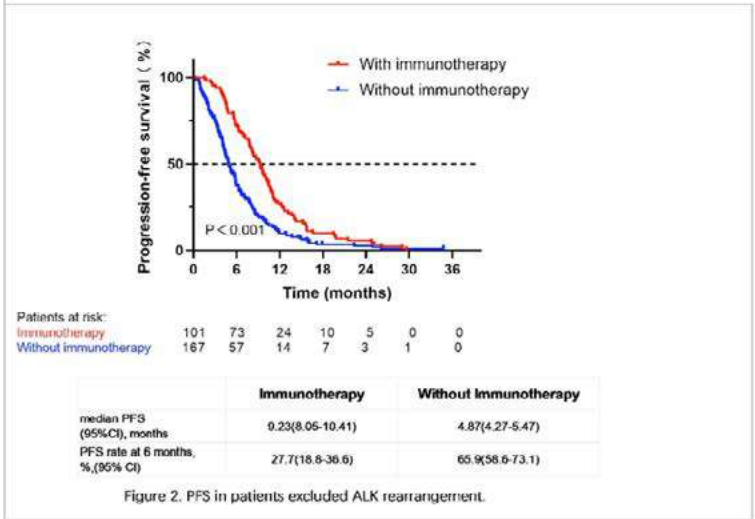
Conclusions: Our study implies that immune checkpoint inhibitor-based treatment may provide more favorable survival for these patients than other treatments, while patients with ALK rearrangement seems to benefit more from targeted therapy in post-line. The recording of significant (grades3 and 4) irAE was optional. What's more, PD-L1 expression status was not associated with the prognosis of these patients.

Keywords: Non-small-cell lung cancer, Immunotherapy, Rare molecular alterations



	Immunotherapy	Without Immunotherapy
median OS (95%CI), months	31.27(27.07-35.47)	23.50(22.77-24.24)
OS rate at 2 years, %,(95% CI)	19.8(11.9-27.7)	65.9(58.6-73.1)

Figure 1. OS in patients excluded ALK rearrangement.



	Immunotherapy	Without Immunotherapy
median PFS (95%CI), months	9.23(8.05-10.41)	4.87(4.27-5.47)
PFS rate at 6 months, %,(95% CI)	27.7(18.8-36.6)	65.9(58.6-73.1)

Figure 2. PFS in patients excluded ALK rearrangement.

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EP.11A.14 Impact of Immune-Related Adverse Event Severity on Overall Survival in Patients Receiving PD-1/L1 Therapy, with a Focus on Combination Regimens

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Introduction: Anti-PD-1/L1 antibody (PD-1/L1) plays a crucial role in the treatment of non-small cell lung cancer (NSCLC) lacking driver mutations, with combination therapies involving chemotherapy (CT) and/or anti-CTLA4 antibody (CTLA) becoming standard. While these treatments may lead to immune-related adverse events (irAEs), studies have demonstrated a link between irAEs and treatment efficacy. However, the impact of severe irAEs on the overall survival (OS) of patients undergoing PD-1/L1 therapy, particularly in combination regimens, remains underexplored.

Methods: We conducted a retrospective analysis of patients diagnosed with advanced or recurrent NSCLC who received PD-1/L1 therapy, including PD-1/L1 alone, PD-1/L1 with CT, and PD-1/L1 with CTLA ± CT between January 2018 and December 2022. Toxicity was assessed using CTCAE version 5.0, categorizing irAE severity into two groups: severe (Grade 3-5) and mild (Grade 1-2). We assessed the association between irAEs and OS using Kaplan-Meier analysis and the log-rank test was used to compare survival curves. Significant differences were defined by p values < 0.05.

Results: Of the 256 enrolled patients, 59 (23%) experienced severe irAEs, 88 (34%) had mild irAEs, and 109 (43%) had no irAEs. The median OS for patients with mild irAEs was significantly longer than for those with no irAEs (33.6 months; 95% CI, 24.6-40.3 vs. 16.6 months; 95% CI, 12.3-23.6, P=0.0146). Conversely, patients with severe irAEs had a shorter median OS (13.3 months; 95% CI, 9.0-21.4) compared to those with no irAEs. The relationship between irAE severity and OS by regimen is presented in the table.

Conclusions: Whether in PD-1/L1 monotherapy or combination therapy, patients with mild irAEs exhibited longer OS, while patients with severe irAEs showed either no significant difference or shorter OS compared to those with no irAEs.

Keywords: non-small cell lung cancer, irAE, Overall Survival

	PD-1/L1 monotherapy	PD-1/L1 with CT	PD-1/L1 with CTLA-4 ± CT
	n=55	n=116	n=85
severe irAEs	8 (14%)	19 (16%)	32 (38%)
mild irAEs	18 (33%)	40 (35%)	30 (35%)
no irAE	29 (53%)	57 (49%)	23 (27%)
Median OS (95% CI), months			
severe irAEs	16.1 (5.2-28.6)	16 (1.84-NR)	10.9 (7.0-19.6)
mild irAEs	38.3 (17.0-42.5)	33.6 (14.2-40.3)	28.0 (21.8-NR)
no irAE	9.6 (12.3-37.1)	17.7 (3.8-23.4)	16.3 (8.7-23.4)

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EP.11A.15 NSCLC-ClustOpt: A Semi-Supervised Optimized Clustering to Stratify Patients with NSCLC on Immune Checkpoint Blockers Therapy

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Introduction: Immune checkpoint inhibitors (ICIs) have improved the clinical outcomes of patients affected by advanced non-oncogene addicted non-small cell lung cancer (NSCLC). The aim of our study is to develop a semi-supervised optimized K-means clustering algorithm (ClustOpt) to prognostically stratify patients with advanced NSCLC treated with ICIs based on baseline features.

Methods: Data extraction involved, retrospectively, patients with advanced NSCLC treated with ICIs at Department of Medical Oncology, Ancona. Baseline body mass composition (BC) was assessed through computed tomography (CT) scan at L3 level, abstracting subcutaneous and visceral fat and muscle mass indicators. Moreover, baseline clinicopathologic features, nutritional status through The Controlling Nutritional Status (CONUT) score, and comorbidities were collected. A semi-supervised clustering analysis (ClustOpt) was employed to identify two groups of patients with different outcomes in terms of progression-free survival (PFS) and overall survival (OS). Then, we assessed whether these two groups had different BC phenotype. ClustOpt was implemented by optimizing the initial centroid's position with Particle Swarm Optimization algorithm. The cost function used for optimization is the time warp distance between the survival curves associated to the 2 generated clusters. The model was developed in Python on-cloud using the Google Colab service.

Results: A total of 50 patients with complete baseline data available were included in the final analysis. The two generated clusters of patients were cluster 1 (n=22) and cluster 2 (n=28) (Table).

The two clusters detained different clinical outcomes: median PFS was 24.4 months for cluster 1 and 7.1 months for cluster 2 (HR 0.38, 95%CI 0.18-0.75, p=0.01), and median OS was 41.8 months for cluster 1 and 13.3 months for cluster 2 (HR 0.43, 95%CI 0.21-0.89, p=0.02). After that, we investigated whether these two prognostically different clusters had differences in terms of BC phenotype assessed by CT scan at baseline. Compared to patients in cluster 2, patients in cluster 1 showed higher median lean psoas muscle area (1449.2 versus 1025, p=0.003), higher median psoas muscle index (7.2 versus 5.2, p=0.004) and lower median intramuscular adipose tissue content (-0.2 versus -0.1, p=0.04).

Conclusions: By using easy to obtain and reproducible baseline clinicopathologic features, employing semi-supervised clustering, we were able to stratify patients with advanced NSCLC in two groups with different prognosis in terms of PFS and OS, under ICIs. Moreover, we showed that also BC phenotype was different in the two groups, with better muscle mass indicators in the group with longer survival.

	Cluster 1 (N=22)	Cluster 2 (N=28)	p-value
Age			
Median (range)	62 (59-64)	74 (72-79)	< 0.001*
NLR			
Median (range)	4.2 (3.3-8.3)	6.1 (4.2-8.7)	0.2
Sex			
Male	16 (73%)	20 (71%)	0.9
Female	6 (27%)	8 (29%)	
Histology			
Adenocarcinoma	19 (86%)	19 (68%)	0.09
Squamous	2 (9%)	9 (32%)	
Others	1 (5%)	0 (0%)	
ICI Treatment			
Monotherapy	15 (68%)	24 (86%)	0.1
Combination	7 (32%)	4 (14%)	
Therapy line			
1st	20 (91%)	26 (93%)	0.8
≥ 2	2 (9%)	2 (7%)	
ECOG PS			
0-1	21 (95%)	26 (93%)	0.7
≥ 2	1 (5%)	2 (7%)	
Smoking			
No	4 (18%)	6 (21%)	0.8
Yes	18 (82%)	22 (79%)	
Cardiovascular disease			
No	17 (77%)	18 (64%)	0.3
Yes	5 (23%)	10 (36%)	
Diabetes Mellitus			
No	19 (86%)	21 (75%)	0.3
Yes	3 (14%)	7 (25%)	
Hypertension			
No	14 (64%)	9 (32%)	0.03*
Yes	8 (36%)	19 (68%)	
Statin use			
No	16 (73%)	15 (54%)	0.2
Yes	6 (27%)	13 (46%)	
CONUT score			
Low	19 (86%)	14 (50%)	0.01*
High	3 (14%)	14 (50%)	
Metastatic sites			
0-1	11 (50%)	13 (46%)	0.6
≥ 2	11 (50%)	15 (54%)	
PD-L1			
0%	4 (18%)	1 (3%)	0.2
1 - 49%	5 (23%)	5 (18%)	
≥ 50%	13 (59%)	22 (79%)	

Abbreviations: NLR, neutrophil-to-lymphocyte ratio; ECOG PS, Eastern Cooperative Oncology Group Performance Status; CONUT Score, Controlling Nutritional Status Score.
***p-value < 0.05**

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EP.11A.16 Infusion Timing of ICI Monotherapy in Patients with Advanced NSCLC: A Single Institution-Retrospective Study

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Introduction: The prognosis of non-small cell lung cancer (NSCLC) patients is still reported to be poor. Immune checkpoint inhibitors (ICIs) has caused a paradigm shift in the treatment of NSCLC, but its efficacy is limited. It is necessary to enhance the efficacy of ICI treatment. Recently, several studies suggested that infusion timing of ICI affected the efficacy. In this study, we investigated the association between clinical outcomes and infusion timing of immune checkpoint inhibitor monotherapy in patients with advanced NSCLC.

Methods: Patients who received at least 4 ICI monotherapy in any line between 2016 and 2022. The study population was split into two groups according to the timing of the initial 4 ICI infusions. Early group was defined as patients received 2 to 4 infusions starting before 11:45am and non-early group was defined as except for early group. Progression-free survival (PFS) and overall survival (OS) were analyzed according to each group.

Results: Eighty-five consecutive patients who received ICI monotherapy were screened and 50 patients were received at least 4 ICI monotherapy. Non-early group included 17 patients and early group included 33 patients. Although there was no significant difference about characteristics in the two groups, early group tended to contain more PS 0, more pretreatment, more adenocarcinoma and more women. PFS tended to be better in early group than non-early group (median PFS: 11 months vs 6.5 months, HR: 0.74(95%CI, 0.32-1.33). OS tended to be also better in early group than non-early group (median OS: 39.3 months vs 15.9 months, HR: 0.62(95%CI, 0.24-1.41).

Conclusions: Although there was no significant difference due to lack of power, there was a trend toward better PFS and OS in early group. It was suggested that ICI should be administered in the morning. Prospective intervention study is needed.

Keywords: Non-small cell lung cancer, immune checkpoint inhibitor, Infusion timing

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EP.11A.17 Efficacy and Influencing Clinical Factors of Tislelizumab Combined with Chemotherapy Plus Bone-Targeted Agents for NSCLC Bone Metastasis

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Introduction: About one-third of advanced non-small cell lung cancer patients still experience bone metastasis. Bone-related events can affect quality of life and the efficacy of metastatic NSCLC patients remained to be improved according to bone metastatic status. This study was aimed to evaluate the efficacy and influencing clinical factors of tislelizumab combined with chemotherapy plus bone-targeted agents as first-line therapy for NSCLC patients with bone metastasis.

Methods: This study prospectively recruited 29 eligible untreated NSCLC patients with bone metastasis. These patients received 4-6 cycles of tislelizumab combined with chemotherapy plus one of bone-targeted agents like denosumab, Ibandronate, followed by tislelizumab plus bone-targeted agents maintenance therapy until progression. The primary endpoints include progression free survival, object response rate, disease control rate by RECIST1.1. The secondary endpoints include overall survival, safety outcomes and influencing clinical factors etc.

Results: As of Mar 2024, 29 pts with stage IV NSCLC with bone metastasis were included by a median age of 65 (range 55-78) years, and 80% males. The median PFS of total population was 9.6 months, the overall ORR and DCR were 65.5 %, and 86.2%, respectively. For the influencing clinical factors, we found that PLR(the ratio of platelet -to-lymphocyte)≥200 was associated with significantly lower PFS(p=0.086), however, the NLR(the ratio of neutrophil-to-lymphocyte)≤5 was associated with a trend for longer PFS(p = 0.240). For the safety outcomes, mild immune-related AEs such as rash, pruritus,hypothyroidism, pneumonitis were experienced and none ≥3irAE occurred.

Conclusions: This study demonstrated that tislelizumab combined with platinum-based chemotherapy plus bone-targeted agents is a promising option in the first line therapy for advanced NSCLC patients with bone metastasis and baseline levels of NLR and PLR were important and associated with PFS outcomes of immunotherapy.

Keywords: immunotherapy, bone metastasis, NLR,PLR

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EP.11A.18 LUMINATE 101-Maccabi: Real-World Study of Treatment Patterns and Clinical Outcomes in Patients with Mnsclc in an Israeli HMO

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Introduction: Most patients with non-small cell lung cancer (NSCLC) progress on first-line (1L) treatment, including those treated with immunotherapy (e.g., programmed death receptor 1 and programmed death-ligand 1 [PD(L)1] inhibitors). Limited effective therapies are available in second-line (2L)+, presenting an unmet need. The LUMINATE-101-Maccabi study assessed the treatment landscape and outcomes in patients with epidermal growth factor receptor wild-type (EGFR-WT), nonsquamous metastatic NSCLC (mNSCLC) in an Israeli Health Maintenance Organization (HMO).

Methods: This retrospective cohort study used the de-identified Maccabi Healthcare Services Israel electronic database to assess adult patients with EGFR-WT or unknown type, nonsquamous mNSCLC (≥2 NSCLC diagnosis codes) who initiated 1L treatment between 01 January 2017 and 31 December 2020. Patient characteristics and treatment patterns from 1L to 2L were evaluated using descriptive statistics. Time-to-event analysis for time on treatment (ToT), time to next treatment or death (TTNTD), progression-free survival (PFS), and overall survival (OS) from 2L treatment initiation were assessed using Kaplan-Meier analysis. Data were collected until December 2022 to allow ≥24 months follow-up.

Results: Of 886 patients with EGFR-WT nonsquamous mNSCLC who initiated 1L treatment, 176 (20%) subsequently received 2L treatment. At 2L treatment initiation, median age was 67 (61-74) years, 34% were female, and 93% had adenocarcinoma. ECOG performance status at 1L treatment initiation was 0-1 in 52% of patients. Demographics stratified by 1L and 2L treatment were similar, except patients who received 1L platinum-doublet chemotherapy and 2L PD(L)1 combination were younger (median age: 60 [52-61] years). Median ToT, TTNTD, PFS, and OS from 2L treatment initiation for the various 1L to 2L treatment sequences are shown in the Table. The most common 1L to 2L treatment sequences were platinum-doublet chemotherapy to PD(L)1 monotherapy, and PD(L)1 monotherapy to pemetrexed. Most 1L to 2L sequence subgroups demonstrated poor outcomes, except for two groups (platinum-doublet chemotherapy to chemotherapy, and PD(L)1 monotherapy to PD(L)1 combination), which were relatively small (N=8 and N=5, respectively). Among subgroups with >20 patients, PD(L)1 monotherapy to pemetrexed demonstrated numerically better outcomes than platinum-doublet chemotherapy to PD(L)1 monotherapy. Third-line treatment was initiated in 31% of patients.

Conclusions: In this real-world study, almost half of patients received 1L platinum-doublet chemotherapy and switched to PD(L)1 monotherapy in 2L. Docetaxel, the currently recommended 2L treatment and standard-of-care in clinical trials was not commonly used in this cohort. Clinical outcomes were generally poor at 2L treatment, highlighting the unmet need for more effective treatment options following progression on 1L.

Keywords: mNSCLC, Real-World, Clinical Outcomes

Table: Clinical outcomes from 2L treatment initiation for the various 1L to 2L treatment sequences

1L (N)	2L[a]	2L N (% of each 1L group)	Median ToT, months (95% CI)	Median TTNTD, months (95% CI)	Median PFS, months (95% CI)	Median OS, months (95% CI)[d]
Platinum-doublet chemotherapy, N=90	Chemotherapy	8 (9%)	2.5 (1.0, NR)	4.0 (2.3, NR)	3.5 (2.2, NR)	28.8 (8.7, NR)
	PD(L)1 monotherapy	74 (82%)	1.5 (1.0, 2.2)	3.6 (2.9, 5.1)	2.5 (2.1, 3.4)	4.6 (3.5, 7.1)
	PD(L)1 combination therapy	8 (9%)	3.3 (2.1, NR)	5.6 (3.4, NR)	4.7 (2.0, NR)	7.1 (5.6, NR)
PD(L)1 monotherapy, N=48	Pemetrexed	31 (65%)	3.5 (1.7, 6.1)	6.7 (4.0, 10.1)	3.4 (2.7, 6.7)	7.7 (5.4, 11.2)
	Other chemotherapy[b]	12 (25%)	1.6 (0.3, NR)	2.9 (2.0, NR)	2.1 (0.9, NR)	3.5 (2.0, NR)
	PD(L)1 combination therapy	5 (10%)	5.8 (4.0, NR)	8.6 (7.6, NR)	7.3 (4.4, NR)	12.4 (10.7, NR)
PD(L)1 combination therapy, N=38	Docetaxel	14 (37%)	1.1 (0.7, 3.8)	1.9 (1.4, 5.6)	1.8 (1.3, 4.7)	2.8 (1.4, 13.7)
	Other chemotherapy[c]	17 (45%)	1.0 (0.6, 2.2)	2.3 (1.9, 6.0)	1.9 (1.4, 4.8)	2.5 (1.9, 21.8)
	PD(L)1 combination therapy	7 (18%)	1.4 (0.7, NR)	2.6 (2.4, NR)	2.1 (1.1, NR)	4.7 (2.5, NR)

[a]All 2L chemotherapy treatments were switches and not re-challenges. [b]Any chemotherapy besides pemetrexed. [c]Any chemotherapy besides docetaxel. [d]Variability in the OS estimate may be due to small sample size of some subgroups.

1L, first-line; 2L, second-line; CI, confidence interval; N, number; NR, not reached; OS, overall survival; PD(L)1, programmed death receptor-1 and programmed death receptor-ligand 1; PFS, progression-free survival; ToT, time on treatment; TTNTD, time to next treatment or death.

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EP.11A.19 Efficacy and Outcomes of Immunotherapy-Based Treatments in EGFR-Mutant Non-Small Cell Lung Cancer

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Introduction: Epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) are approved for first-line treatment for EGFR-mutant metastatic non-small cell lung cancer (NSCLC); however, most patients ultimately experience tumor progression. The optimal immunotherapy (IO)-based treatment strategies to improve survival outcomes, along with the optimal timing for such an approach in EGFR-mutant NSCLC after failure of EGFR-TKIs, continues to be a subject of ongoing debate.

Methods: A retrospective analysis of outcomes for patients with EGFR-mutant NSCLC who underwent IO alone or IO combined with chemotherapy (C/T) as subsequent treatment after disease progression was conducted. Data were collected from January 2014 to December 2022 at Taipei Veterans General Hospital. The Kaplan-Meier method was utilized to evaluate overall survival (OS) and time to treatment failure (TTF). The Cox proportional hazard model was employed to examine the relationship between clinical characteristics and survival outcomes.

Results: This study enrolled a total 107 patients with advanced EGFR-mutant NSCLC, all of whom had received treatment with first- or second-generation EGFR-TKIs. The IO alone group comprised 33 cases, while the group receiving IO combined with C/T (IO+C/T) included 74 cases. The median number of prior treatment lines before starting immunotherapy was 2. The IO+C/T group exhibited a trend toward longer OS and TTF than IO alone group (OS: 20 vs. 16 months, p=0.74; TTF: 4 vs. 2 months, p=0.71). The multivariate analysis showed that patients who underwent more than 4 lines of treatment before IO-based treatment demonstrated poorer OS (hazard ratio [HR] 2.26, 95% confidence interval [CI] 1.17-4.37, p=0.01) and TTF (HR 1.89, 95% CI 1.12-3.21, p=0.02) compared to those with fewer than 4 lines of treatment .The HRs for OS were 4.91 (95% CI 2.11-11.46) for patients receiving more than 4 lines of treatment and 2.04 (95% CI 0.99-4.19) for those undergoing 2-4 lines of treatment before IO-based therapy, in comparison to patients who received 0-1 lines of treatment (p<0.01), suggesting that initiating IO-based treatment earlier can significantly reduce the risk of death. In patients with EGFR L858R mutation, the multivariate also showed that patients receiving more than 4 lines of treatment before IO-based treatment had higher risk of treatment failure (HR 2.52, 95% CI 1.01-6.26).

Conclusions: This study highlights the advantages of incorporating IO-based therapies early in the treatment regimen for patients with advanced EGFR-mutant NSCLC after failure of EGFR-TKIs. IO+C/T tended to yield better survival than IO alone. Furthermore, the detrimental effects of undergoing numerous prior treatments before starting IO-based therapy emphasize the critical need to commence such treatments early.

Keywords: Epidermal growth factor receptor, non-small cell lung cancer, immunotherapy

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EP.11A.20 Incidence and Outcomes of Adrenal Oligoprogression in Metastatic Lung Cancer During Immunotherapy

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Introduction: Lung cancer presents as stage IV disease at diagnosis in around 70% of patients with small cell lung carcinoma and 30-40% with non-small cell lung carcinoma. One of the most common sites of metastasis is the adrenal gland. Significant advances in treatment have occurred with the use of immunotherapy when there are not actionable mutations. However, treatment response can be heterogeneous in different metastatic sites, which may be related to tumor microenvironment. Some studies have demonstrated response heterogeneity in the adrenal gland, suggesting that it may serve as a sanctuary for metastasis after immunotherapy use, possibly related to the glandular microenvironment, corticosteroid production, and T-lymphocyte inactivation. This study aims to evaluate the incidence of adrenal oligoprogression in metastatic lung cancer after immunotherapy treatment and its impact on overall survival.

Methods: A retrospective analysis of medical record data from Hospital Israelita Albert Einstein and Hospital Municipal Vila Santa Catarina was conducted from 2017 to 2022 to evaluate patients diagnosed with lung cancer who received immune checkpoint inhibitors. The primary objective of the study was to assess the incidence of adrenal oligoprogression during immunotherapy. Secondary objectives included overall survival (OS) of patients with adrenal oligoprogression and association with baseline characteristic by Cox regression method. Imaging examinations were assessed before the start and after the completion of immunotherapy. Survival curves were plotted utilizing the Kaplan-Meyer method.

Results: We queried data from 159 patients with metastatic NSCLC and SCLC who received anti-PD-1 either as monotherapy or in combination with chemotherapy. We included 37 patients with adrenal metastasis either before and/or during immunotherapy treatment. Mean age was 65 years and 70% were male. The median OS of the entire cohort was 36.1 months (95% CI 18.1 - 54.1). Twenty-nine patients (78%) had any disease progression, with 24 (65%) of patients having adrenal progression (with or without progression at other sites). Adrenal oligoprogression was observed in 9 patients (24.3%), of whom 7 underwent stereotactic body radiation therapy. In the 37-patient cohort, there was no other site of oligoprogression besides the adrenal gland. The OS was numerically longer in patients with adrenal oligoprogression, but statistical significance was not achieved due to the small sample size.

Conclusions: Adrenal oligoprogression may occur in a significant portion of patient with metastatic lung cancer. The adrenal gland may represent a sanctuary site of disease resistance to immunotherapy and deserves further research to validate our finding and elucidate the underlying mechanisms involved.

Keywords: metastatic lung cancer, immunotherapy, adrenal gland

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EP.11A.21 Target Switching as an Effective Second-Line Strategy for Refractory Metastatic NSCLC

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Introduction: Immune checkpoint inhibitors (ICIs) have revolutionized the treatment of metastatic non-small cell lung cancer (NSCLC) without actionable mutations, providing durable response in certain patients. Nonetheless, patients who progress on ICI face limited second-line treatment options, primarily cytotoxic chemotherapy or investigational treatments. Often, factors such as performance status or personal preference preclude these options. The strategy of switching the checkpoint target from the receptor to ligand (or vice-versa) following disease progression or adverse events has not been explored in clinical trials. This study evaluated the efficacy of this strategy, with or without chemotherapy, in NSCLC patients who experienced disease progression or adverse events on 1st ICI.

Methods: In this single-center, IRB-approved retrospective study, we analyzed outcomes of NSCLC patients from June 2015 to December 2022 who were treated with PD-1 followed by PD-L1 inhibitor (or vice-versa) after disease progression or adverse events. We evaluated progression free survival (PFS) from start of the initial ICI and subsequent ICI to disease progression or death. Patients who were alive without disease progression or had an adverse event before disease progression were censored at their last follow-up or at time of adverse event, respectively. Multivariable cox-proportional hazard model examined factors associated with PFS on 2nd ICI.

Results: In our cohort of 45 patients (49% female and 51% male), the majority of 87% (39/45) switched to a 2nd ICI after disease progression on 1st ICI. The remaining 13% (6/45) switched due to adverse event on 1st ICI. Median PFS on 1st ICI was 5.6 months (95% CI: 4.7-12.1). Median PFS on 2nd ICI was 4.9 months (95% CI: 2.5-10.8) which extended to 8.9 months (95% CI: 4.9-25) in patients who tolerated the 1st ICI beyond the first 8 months without disease progression (n=16). The median overall survival was 24.4 months (95% CI: 16.9-33.6). Among 34 patients who received a PD-1 inhibitor followed by PD-L1 inhibitor, the median PFS was 5.0 months (95% CI: 2.5-8.9). Conversely, in 11 patients who received a PD-L1 inhibitor followed by a PD-1 inhibitor, the median PFS was 2.6 months (95% CI: 2.4-11). In the multivariable cox proportional hazards model, no significant difference was observed in PFS based on PFS on 1st ICI (p=0.09), PD-L1 tumor proportion score (p=0.27), or target of 2nd ICI (p=0.43). However, combination therapy with chemotherapy was associated with a worse PFS (HR 3.31, 95% CI: 1.54-7.13).

Conclusions: Switching the ICI target from PD-1 to PD-L1 (or vice-versa) following disease progression offers benefit in refractory metastatic NSCLC, with a median PFS comparable to that of single agent chemotherapy. Although PFS on initial ICI or target of 2nd ICI did not significantly impact outcomes, adding chemotherapy to second-line ICI was associated with worse outcome. These findings highlight the potential benefits of switching target as a viable strategy for those with disease progression or adverse events while cautioning against use of chemotherapy in this context.

Keywords: Refractory metastatic NSCLC, PD-1/PD-L1 axis, Immune checkpoint inhibitor

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EP.11A.22 Comparing Outcomes and Adverse Events in Lung Cancer Immunotherapy: The Impact of Smoking Status

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Introduction: Lung cancer remains the leading cause of cancer-related death worldwide. Despite advances in early detection and treatment, the prognosis for patients with advanced-stage lung cancer continues to be poor. Checkpoint inhibitor therapy commonly termed immunotherapy is the corner stone of treatment in patients with early and advanced lung cancer patients. In some studies immunotherapy was found to have a better outcome in NSCLC patients with a smoking history compared to non-smokers. We conducted a retrospective analysis in our patients to identify the correlation between smoking and patient outcomes and adverse events.

Methods: We reviewed and analyzed data on all patients with lung cancer diagnoses who were treated with immunotherapy from January 2020 to December 2022 (approximately two years). We performed a retrospective chart analysis on patients who received immunotherapy for lung cancer. Data collected included age, race, smoking status, causes for early discontinuation, immunotherapy-related adverse events (not including thyroid dysfunction), and corticosteroid use.

Results: During our study timeline, a total of 122 eligible patients were included in the analysis. The average age of the patients is approximately 72 years (38 to 94 years old). Most patients were Caucasian (n=113), three patients were African American, and six patients belonged to other races. With regards to immunotherapy drugs, most patients were on pembrolizumab (n=59), followed by atezolizumab (n=30), durvalumab (n=29), and nivolumab (n=4). A total of 81 patients (66%) had discontinued treatment earlier than planned, and early discontinuation rates for immunotherapy were significantly higher in current smokers compared to former or never smokers (60 % vs. 49%), with the most common reason for early discontinuation being progression of disease or hospice transition (56%). Other reasons for early discontinuation included immunotherapy adverse effects, death, and non-compliance. A total of 31 patients had adverse effects documented explicitly as related to immunotherapy, and the most common was severe fatigue (6 patients), followed by dermatitis (5 patients). Other adverse events included anemia, nausea, colitis, cytopenia, pneumonitis, hepatitis, arthralgia, and neuropathy in the order of their frequency. Systemic corticosteroids were used in 16 patients for immunotherapy-related adverse effects, and the remaining patients either received topical steroids or drug discontinuation alone. An additional eight patients were identified to be using topical steroids without any documentation of dermatological adverse effects. In our analysis, we also observed that a significantly higher percentage of patients (77 %) with immunotherapy adverse effects were former, or non-smokers compared to current smokers.

Conclusions: From our retrospective study, we observed that a significant proportion of patients on immunotherapy for lung cancer discontinue treatment due to disease progression, and the rates of disease progression are much higher in current smokers. This observation argues against previous reports of better clinical responses in smokers receiving immunotherapy. The interesting observation in our study is that patients who are active smokers tend to have a lesser number of immunotherapy-related adverse events compared to past smokers and non-smokers. We also identified a proportion of patients using topical steroids without any documentation of dermatitis, likely underreporting dermatological immune-related side effects.

Keywords: immunotherapy, advanced lung cancer, smokers

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EP.11A.23 REAL-IMPACT: Real-World Effectiveness of Immunotherapy in PD-L1 Negative Advanced NSCLC - A Multicenter Cohort Study in Argentina

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Introduction: Schemes involving immune checkpoint inhibitors (ICI) have revolutionized first-line treatment for Advanced NSCLC without driver mutations regardless of PD-L1 expression. However, selecting the optimal treatment for the subgroup of patients without PD-L1 expression poses a challenge due to the heterogeneity of benefits observed in clinical trials and the lack of real-world data in this subgroup. In turn, due to the high cost of these therapies, their indication is not authorized by some health providers in developing countries. This study aims to demonstrate the effectiveness of different approved ICI schemes versus chemotherapy (CT) alone in the subgroup PD-L1 negative patients in the real-world context in Argentina.

Methods: Retrospective cohort study including patients with advanced NSCLC PD-L1 negative (<1% by IHC), without driver mutations (negative test for EGFR and ALK), treated at the first line with ICI or CT from 2017 to December 2023 from 22 Argentinian centers. Progression-free survival (PFS), overall survival (OS), and overall response rate (ORR) outcomes were compared between those treated with ICI schemes versus CT in the first line.

Results: 218 patients were analyzed. Median age 65 (59-74), male gender 126 (57%), previous or active tobacco use 187 (88%), adenocarcinomas 181 (82%). Treated with ICI 151 (69%) and 67 (31%) with CT.IO schemes: CT + Pembrolizumab 125 (82%), Ipilimumab + Nivolumab 12 (7.9%), CT + Ipilimumab + Nivolumab 11 (7.3%), CT + Atezolizumab + Bevacizumab 3 (2%). At the data cut/off, the median follow-up was 20.8 months. The median PFS was 10 in the ICI group vs 7.2 months in the CT group log-rank P: 0.003 Cox Regression HR 0.61 (0.43-0.85) P: 0.004 . The 12-month OS was 71% in the ICI group vs 69% in the CT group. The ORR was 47% in the ICI group vs 25% in CT P: 0.04. Grade 3 immune-related adverse events occurred in 8.7% of patients.

Conclusions: Our study in advanced PD-L1 negative NSCLC patients demonstrated the effectiveness of ICI in the real-world context. The results showed statistically significant improvements in PFS and ORR. The frequency of grade 3 adverse events were similar to those reported in clinical trials. Longer follow-up is needed to evaluate the benefits of OS.

Keywords: NSCLC, IMMUNOTHERAPY, REAL WORLD

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EP.11A.24 Clinical Prognostic Index for Immunochemiotherapy in Lung Cancer (CLIPI-LC)- A Prognostic Score for Advanced Non-Small-Cell Lung Cancer

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Introduction: Immunochemotherapy is the standard of care for NSCLC patients with PD-L1 expression < 50%. However, early disease progression is observed in some cases. Prediction of this scenario would be useful.

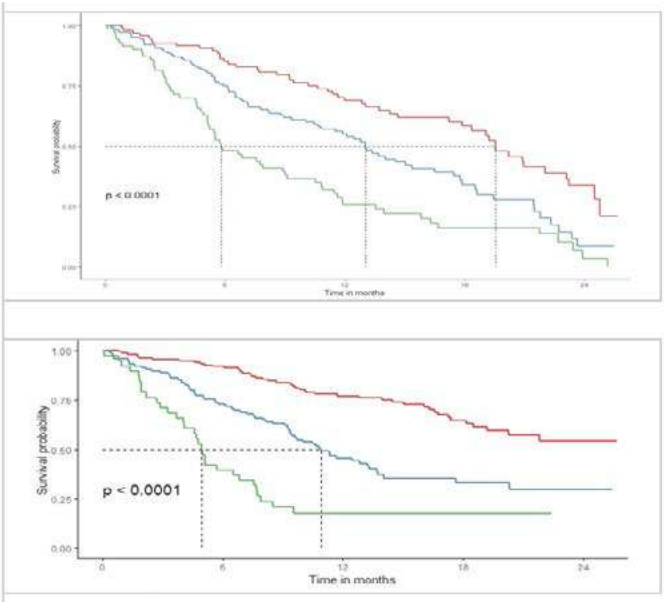
Methods: We analysed a group of 303 patients with NSCLC (CS IV). OS and PFS were estimated using Kaplan-Meier estimator and Cox model. For morphological parameters, we explored functional forms and cut-off points to optimize concordance in exploratory OS analysis. The final model including factors significant in univariate analysis was used to develop predictive scoring (Table 1).

Results: After the median of follow-up 10.52 months in the entire cohort mPFS was 13.1 months (95%CI 11.4-15.3) and mOS - 16.3 months (95%CI 1.3-20.3). The mPFS within the prognostic groups groups were - respectively- 19.5, 13 and 5.8 months (p<0.001; Fig.1), with the percentage of patients without disease progression after 12 months estimated at 69%, 45.1% and 25.8% (p<0.001). The mOS were NR, 14.5 and 5.8 months (p<0.001;Fig.2), with the percentage of patients alive after 12 months - 81.2%, 60.2% and 20.4% (p<0.001).

Conclusions: The efficacy of immunochemotherapy in the real-world population is variable. CLIPI-LC is a useful tool to stratify patients according to their baseline clinical parameters.

Keywords: Prognostic index, NSCLC, Immunochemotherapy

Co-efficient	Value	Points
Weight loss >10% of baseline	Yes	1
ECOG	1	1
Sum of tumour diameter (mm)	≥125mm	1
Liver metastases	Yes	1
Bone metastases	Yes	1
Monocytes*NLR	>2.3	2
SCORE		Sum of points Prognostic group:Good (1-3 points), Intermediate (4-5 points);Poor (6-7 points).



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EP.11A.25 Consensus on Maintenance Therapy after a First-Line Pembrolizumab-Containing Regimen in Advanced/metastatic NSCLC

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Introduction: First-line (1L) maintenance therapy (1LMT) treatment guidelines are inconsistent for patients with advanced/metastatic non-small cell lung cancer (a/mNSCLC) who have completed a 1L induction pembrolizumab-containing regimen. This study used a Delphi method to reach consensus on 1LMT recommendations for patients with a/mNSCLC without actionable genomic alterations.

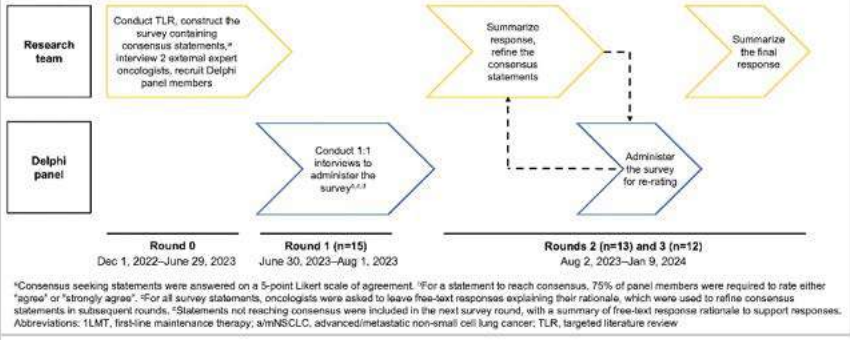
Methods: A literature review and input from two clinical experts (UT, NR) were used to develop consensus statements related to 1LMT. Using an iterative Delphi method, the survey was administered over three rounds between June 30, 2023, and January 9, 2024, (Figure) to a panel of oncologists actively treating patients with a/mNSCLC in France, Germany, the UK, and the US. In each round, updates to the survey were based on aggregated results from the prior round.

Results: Participating oncologists (round 1, n=15; round 2, n=13; round 3, n=12) concurred that 1LMT should be considered for patients with a/mNSCLC who achieved a response or stable disease after 4-6 cycles of 1L pembrolizumab-containing induction. The panel's recommended 1LMT varied by 1L induction treatment, programmed death-ligand 1 (PD-L1) level, and Eastern Cooperative Oncology Group performance status (ECOG PS; Table). When considering 1LMT duration, the panel agreed on factors to consider (toxicity/side effects, patient preference, ECOG PS, and disease progression). If 1LMT pembrolizumab was used (as monotherapy or with pemetrexed), oncologists agreed it should be used for up to 2 years, as long as it was tolerated (including induction and 1LMT duration); the panel did not agree on a preferred pemetrexed duration.

Conclusions: In this study, panel oncologists concurred on a 1LMT strategy, but differed on recommended 1LMT when PD-L1 levels were <50% and on preferred pemetrexed duration. Given a lack of 1LMT treatment guidelines for patients with a/mNSCLC without actionable genomic alterations, these results provide useful recommendations for treating physicians.

Keywords: first-line maintenance therapy, metastatic NSCLC, treatment recommendations

Figure. Delphi method used to reach consensus on 1LMT recommendations for a/mNSCLC



[a]Consensus seeking statements were answered on a 5-point Likert scale of agreement. [b]For a statement to reach consensus, 75% of panel members were required to rate either "agree" or "strongly agree". [c]For all survey statements, oncologists were asked to leave free-text responses explaining their rationale, which were used to refine consensus statements in subsequent rounds. [d]Statements not reaching consensus were included in the next survey round, with a summary of free-text response rationale to support responses.
Abbreviations: 1LMT, first-line maintenance therapy; a/mNSCLC, advanced/metastatic non-small cell lung cancer; TLR, targeted literature review

Table. Consensus status on 1LMT in nonsquamous and squamous a/mNSCLC

Nonsquamous histology				
1L induction therapy	**ECOG PS score**	**PD-L1 level**	**1LMT should be considered**	**1LMT**
Pembrolizumab-platinum–pemetrexed	0/1	≥50%	Yes	Pembrolizumab–pemetrexed or pembrolizumab monotherapy
Pembrolizumab-platinum–pemetrexed	0/1	<50%	Yes	No consensus reached[a]
Pembrolizumab-platinum–pemetrexed	2	Any	Yes	No consensus reached[a]
Pembrolizumab-platinum–pemetrexed	3/4	Any	No	–
Pembrolizumab- platinum +/– non-pemetrexed	0/1	≥50%	Yes	Pembrolizumab monotherapy
Pembrolizumab- platinum +/– non-pemetrexed	0/1	<50%	Yes	No consensus reached[b]
Pembrolizumab- platinum +/– non-pemetrexed	2	Any	Yes	Pembrolizumab monotherapy
Pembrolizumab- platinum +/– non-pemetrexed	3/4	Any	No	–
Squamous histology				
1L induction therapy	**ECOG PS score**	**PD-L1 level**	**1LMT should be considered**	**1LMT**
Pembrolizumab-platinum + non-pemetrexed	0–2	Any	Yes	Pembrolizumab monotherapy
Pembrolizumab-platinum + non-pemetrexed	3/4	Any	No	–

[a]>90% selected pembrolizumab-based, but did not reach a consensus on whether to recommend pembrolizumab–pemetrexed, pembrolizumab monotherapy, or both. [b]All selected pembrolizumab-based, but did not reach a consensus on whether to recommend pembrolizumab–pemetrexed, pembrolizumab monotherapy, or both.
Abbreviations: 1L, first-line induction; 1LMT, first-line maintenance therapy; ECOG PS, Eastern Cooperative Oncology performance status; PD-L1, programmed death-ligand 1

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EP.11A.26 Evaluating Efficacy and Safety of Nivolumab in Pretreated NSCLC Patients: Insights from Real-World Data

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Introduction: Over the past years, the treatment strategies for metastatic NSCLC have changed. Three anti-PD-(L)1 agents, nivolumab, pembrolizumab, and atezolizumab, have been approved as a second-line treatment. Since the introduction of the first immunotherapy as a second-line treatment for non-small cell lung cancer (NSCLC) in 2014, nivolumab has demonstrated superior efficacy compared to docetaxel, particularly in advanced squamous and nonsquamous NSCLC with a median overall survival (mOS) of 12.2 months for nonsquamous and 9.2 months for squamous NSCLC.

Methods: We performed a retrospective, real-world, non-interventional cohort study of all patients with metastatic or recurrent non-small cell lung cancer treated with nivolumab monotherapy for second-line or later-line treatments in University Hospital Center Zagreb, Department for Pulmonary Diseases. In total, 105 patients diagnosed with non-small-cell lung cancer after progression on standard chemotherapy were included. The program started in March 2017 and the last patient was enrolled in October 2017. The patients were observed for disease progression and death until November 1st 2023. The primary objective of this study was to evaluate the safety and effectiveness of nivolumab.

Results: Median follow-up time was 79.9 months (35.8-87.6) for PFS and 82.4 months (81.6-87.6) for OS. Despite previous treatment modalities, mOS was 15.9 months (95% CI 10.6-20.3). The median PFS was 7.07 months (95% CI 5.57-9.9). Therapy was primarily applied in the second and third lines (n=67; 64.4%), but even up to the seventh line (n=2; 1.9%). Mean number of applied nivolumab doses was 17 (1-69). Side effects were observed in 22 patients (20.9%), leading to treatment discontinuation in 16 patients (15.2%). The most common side-effect was pneumonitis in 7 patients (6.7%), followed by endocrine disorders (n=4; 3.8%) and rash (n=4; 3.8%), then gastrointestinal (n=3; 2.9%), myositis (n=3, 2.9%) and hepatitis (n=1; 0.9%). Patients who developed side effects had significantly longer mPFS than the ones who didn't (13.2 vs 6.1 months; 95% CI 4.77-9.07 vs 9-35.83; p=0.007).

Conclusions: This study represents the real-world experience with nivolumab. Although our patients were heavily pretreated, there was a clear survival benefit of nivolumab treatment compared to available extensive clinical trial data. We observed that the development of side effects was a significant factor in better overall survival and progression-free survival.

Keywords: nivolumab, Real-world outcomes, immunotherapy

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EP.11A.27 Real-Life Study of Patients with Unresectable Stage III Non-Small Cell Lung Cancer Treated with Chemoradiotherapy Followed by Durvalumab.

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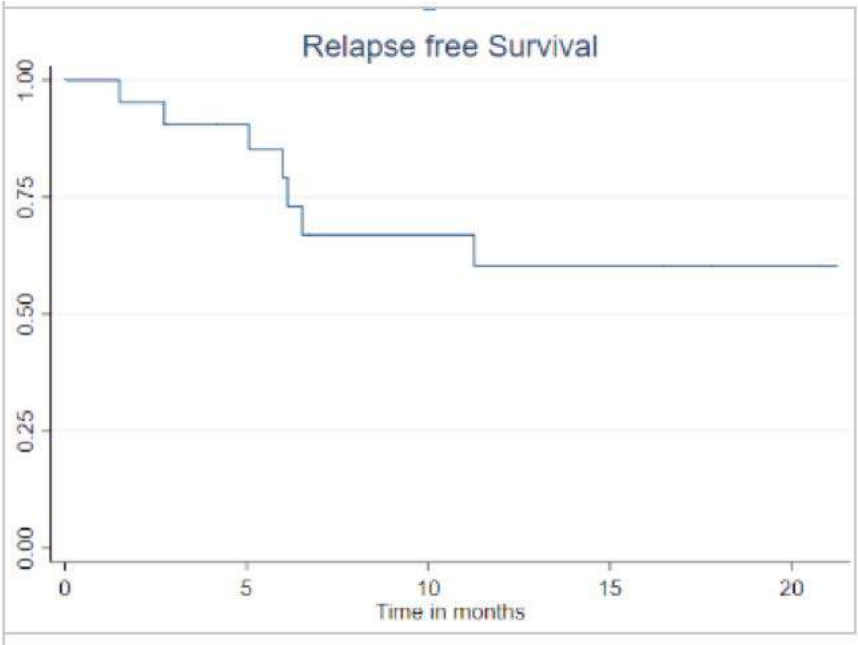
Introduction: There is limited evidence in our setting regarding durvalumab in patients with unresectable stage III non-small cell lung cancer (NSCLC)

Methods: Retrospective cohort study of NSCLC patients who underwent durvalumab within a closed cohort of affiliates to the private healthcare system of the Hospital Italiano de Buenos Aires. Relapse-free survival (DFS) and overall survival (OS) were evaluated.

Results: Twenty-two patients were analyzed, median age 66 years IQR 63 to 71, 95% (21) PS 0 - 1. Eighty-two percent (18) were smokers, 82% (18) had adenocarcinomas, with a prevalence of molecular testing of 82% (18), of which 44% (8) were PD-L1 negative, and 33% (6) had PD-L1 greater than 50%. Ten percent (2) experienced serious immune-mediated toxicities, one patient developed G4 pneumonitis and another Guillain-Barre syndrome. With a median follow-up of 22 months, 36% (8) of patients experienced relapse, while 76% were disease-free at 12 months after completing durvalumab treatment. The value of PD-L1 was not associated with the probability of recurrence or relapse-free survival (HR 1,1 IC95 0,99-1,02 p= 0,3 Cox Regression Model). The median relapse-free survival was not reached; of the 8 relapsed patients, 50% (4) received second-line treatment with docetaxel-based chemotherapy regimens, and 5 died, with median post-relapse overall survival of less than 6 months.

Conclusions: Encouraging results are observed in terms of relapse-free survival and treatment response. Despite limited evidence in our region, the majority of patients treated with durvalumab experienced prolonged relapse-free survival.

Keywords: Durvalumab, PACIFIC, Real World



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EP.11A.28 Efficacy and Safety of Penpulimab-Containing Regimens for Advanced Malignant Solid Tumors That Have Failed Immunotherapy: A Real World Study.

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Introduction: Immuno-checkpoint inhibitors(ICI) have shown good anti-tumor efficacy and survival benefits in a variety of solid tumors, such lung cancer, gastric cancer(GC), esophageal cancer (EC), head and neck squamous carcinoma (HNSCC) and nasopharyngeal cancer(NPC). ICI have rewritten the guidelines for multiple tumor types. However, there are still a large number of patients who are ineffective or initially effective after use ICI, and subsequently develop ICI resistance. For this patients, how we choose further treatment is currently uncertain clinically. Some studies suggest that even if the treatment of PD - (L) 1 is ineffective or progresses, it can still bring a certain degree of benefit to re-challenge with other target ICI. This study was to evaluate the efficacy and safety of the patients with advanced malignant solid tumors with the regimen of penpulimab (PD1 antibody).

Methods: This is a non-interventive registration study. Eligible participants must be ≥ 18 years old and have proven malignant tumors that are ineffective, fail for immunotherapy and have no other standard treatment. Patients were treated with penpulimab alone or in combination with chemotherapy or anti-angiogenic agents until progression or unacceptable toxicity. The primary endpoint is objective response rate (ORR). Secondary endpoints were disease control rate (DCR), progression free survival (PFS), overall survival (OS) and safety.

Results: Form Sep 2021 to Feb 2024, 26 patients(median age 59.9 years, male 65.4%)were recruited, including 7 pts with NSCLC, 4 pts with HNSCC, 3 pts with NPC, 3 pts with Intestinal cancer, 3 pts with GC and 6 with other tumor types. Among all, 1 chieved PR and 22 achieved SD, the DCR was 88.5% (23/26). The median treatment duration was 9.5 cycles and the median PFS was 9.1 months. Among the 7 pts with NSCLC, the DCR was 85.7% (6/7) (See the table below for details). Treatment-related adverse events (TRAEs) of grade 3 were observed in 5 (17.9%) of the 28 patients. The most common TRAEs were decreasedanemia (57.7%, 15/26), lymphocyte count(53.4%, 14/26), hypoalbuminemia (42.3%, 11/26), increased thyrotropin (34.6%, 9/26), hypercholesterolemia (26.9%, 7/26), albuminuria(19.2%, 5/26).

Conclusions: Penpulimab-containing regimens for advanced malignant solid tumors that have failed ICI have shown significant efficacy and a favorable safety profile. More specific studies are needed to confirm these results.

Keywords: Immune rechallenge, NSCLC, immunotherapy

No.	PD-L1 expression	ECOG PS	PFS-months	PFS status	Best objective response
1	50%	1	25.9	0	SD
2	<1%	1	21.9	0	SD
3	≥1%	1	2.4	1	PD
4	NE	1	18.1	1	SD
5	1%-49%	1	17.1	1	SD
6	≥1%	1	2.6	0	SD
7	NE	0	5.3	1	SD

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EP.11A.29 C-Reactive Protein's Impact on Immune Adverse Events in Non Small Cell Lung Cancer Patients Undergoing Immunotherapy: Meta-Analysis

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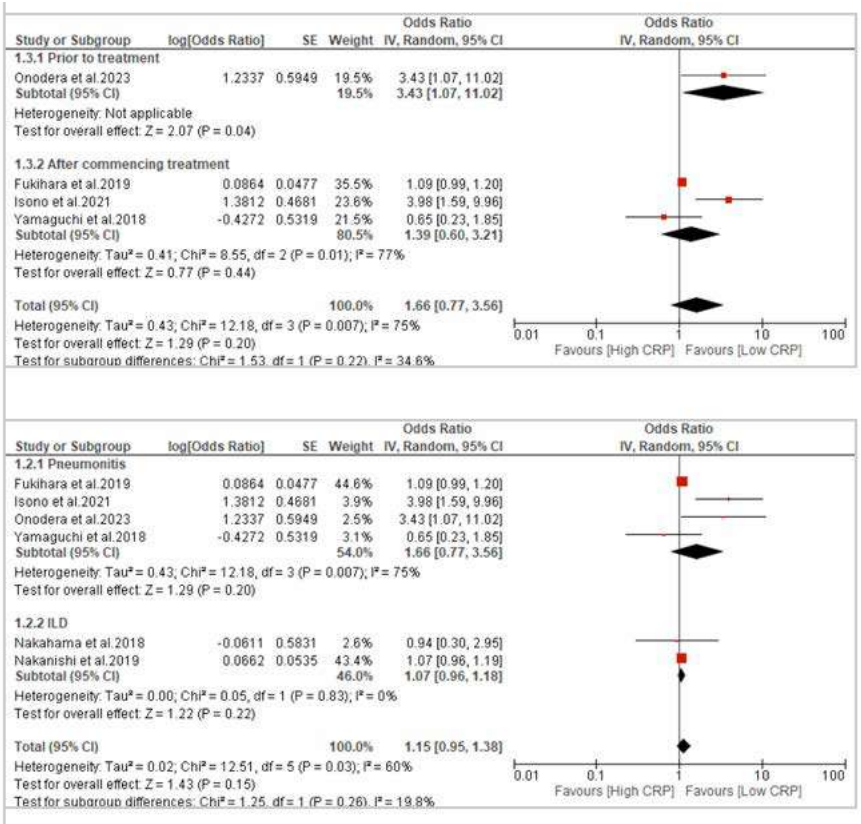
Introduction: Immune checkpoint inhibitors (ICIs) have transformed the management of advanced malignancies, notably non-small cell lung cancer (NSCLC). However, ICIs can induce immune-related adverse events (irAEs) necessitating biomarker identification for irAE detection and monitoring.

Methods: A comprehensive search of PubMed, Embase, Web of Science, and Google Scholar until April 2024 was conducted. English-language studies relevant to the research objective were included while excluding case reports, editorials, conference abstracts, reviews, and studies combining ICIs with other therapies. Statistical analyses were performed using Review Manager software, and bias assessment was conducted using the Newcastle Ottawa Scale. Subgroup analyses were performed for CRP and pneumonitis/interstitial lung disease (ILD) association, as well as pretreatment and post-treatment CRP levels and pneumonitis risk

Results: Six eligible studies were identified. Subgroup analysis indicated no significant difference in pneumonitis risk between high and low CRP levels (OR: 1.66; 95% CI: 0.77-3.56; p = 0.20). However, high pretreatment CRP was associated with increased pneumonitis risk (OR: 3.43; 95% CI: 1.07-11.02; p = 0.04). Conversely, no significant ILD risk increment was observed with higher pretreatment CRP levels (OR: 1.07; 95% CI: 0.96-1.18; p = 0.22).

Conclusions: Elevated pretreatment CRP levels are linked to pneumonitis development, underscoring its potential as a predictive biomarker. However, further research is warranted to validate this finding. Additionally, higher CRP levels post-ICI therapy initiation may not correlate with pneumonitis. Similarly, no association was found between pretreatment CRP levels and ILD development.

Keywords: Non Small Cell Lung Cancer, C-reactive Protein, Meta-analysis



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EP.11B.01 Machine Learning-Based Clinical Model for Predicting Thromboembolism in Lung Cancer after Immunotherapy

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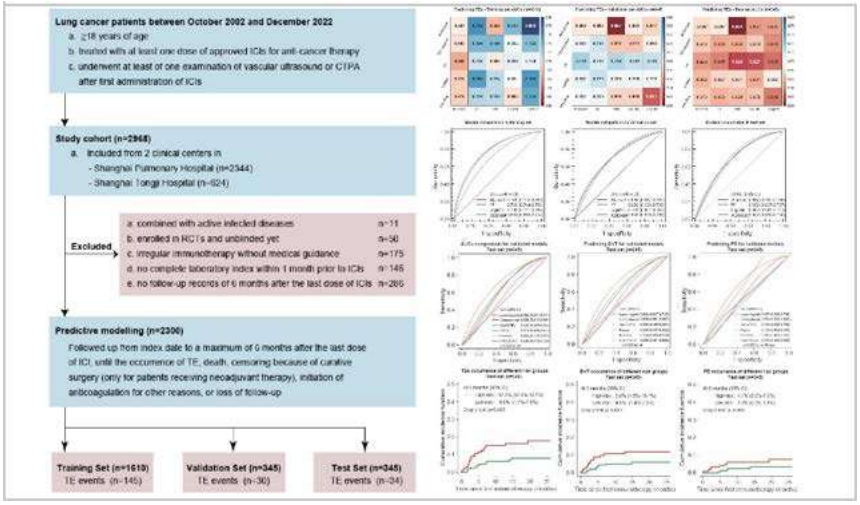
Introduction: The unpredictable thromboembolism events (TEs) remains important in lung cancer patients (LCP) treated with immune checkpoint inhibitors (ICIs), since TEs significantly increased after immunotherapy and associated with adverse survival.

Methods: LCP treated with ICIs were retrospectively reviewed from two clinical centers, and combination of 5 feature selection methods and 5 machine learning (ML) algorithms were compared by area-under-curve (AUC) to identify the final ML model. The performance of the final model was compared with existed VTE-risk score (Khorana, Padua, PROTECHT, ONKOTEV, COMPASS-CAT score), and decision-curve-analysis (DCA) and net-reclassification-improvement-analysis (NRI) applied to assess clinical utility. Shapley-Additive-exPlanation (SHAP) method was used for feature importance ranking and explaining the final model.

Results: Of all 2300 LCP, 1610 were randomly splitted as training set, 345 as validation, and 345 as test set, separately. The model established by logistic regression with 22 features selected by Lasso performed best with a highest AUC of 0.692, and was selected as the final model. The Lasso-Logistic-model outperformed existed VTE-risk scores in TEs risk evaluation ($p<0.050$ for all), and the high-TEs-risk group identified by this model was significantly associated with higher cumulative incidence of TEs (12.3%, $p=0.006$). The positive association between high-risk and adverse survival were found in all LCP, regardless of whether combined with chemotherapy, and especially in stage IV LCP ($p<0.001$ for all). The better net benefits derived by the Lasso-Logistic-model were further verified by DCA and NRI analysis. SHAP analysis revealed that D-Dimer level and ECOG status had the largest impact on TEs risk prediction, which were consistent with traditional statistical analyses.

Conclusions: The established ML model outperformed validated VTE-risk scores for predicting TEs risk, and highly relevant to adverse survival in LCP initiating ICIs, which might assist in selecting LCP who would benefit from thromboprophylaxis.

Keywords: thromboembolism event, lung cancer, immune checkpoint inhibitor



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EP.11B.02 Correlation Analysis of Peripheral Blood Cell Immune Phenotype with Prognosis of Immunotherapy in Advanced Non-Small Cell Lung Cancer

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Introduction: Tumor immune microenvironment plays an important role in tumor immunity, which determines the efficacy of immunotherapy largely.This study aims to was to explore the prognostic value of dynamic changes of different lymphocyte immunophenotypes and serological inflammatory cell markers based on peripheral blood immune microenvironment, as well as PD-L1 expression level and gene mutation based on tissue level in aNSCLC(advanced NSCLC)immunotherapy. Moreover, immune adverse events were collected during immunotherapy in aNSCLC patients.

Methods: From the "CAPTRA-Lung" database, 190 patients with aNSCLC in Shanxi Cancer Hospital from January 2020 to May 2023 were prospectively collected. The patients were further divided into response group (CR, PR) and non-response group (SD, PD).Using flow cytometry to dynamically monitor the distribution of different lymphocyte subsets. NLR, PLR, LMR, SII, SIRI, PNI, ALI and dNLR in peripheral blood and the immune adverse events during immunotherapy were also collected.The follow-up deadline was February 1, 2024.

Results: All patients of median progression-free survival is 11.13 months[95%CI:9.553-12.714], and ORR,DCR are respectively 64.2% and 87.4%.In 106 patients tested PD-L1, the PFS of PD-L1< 1% subgroup is significantly shorter than that of 1-49% PD-L1subgroup (p=0.004) and PD-L1 ≥ 50% subgroup (p < 0.001), but it's not significantly between 1-49% PD-L1 subgroup and PD-L1 ≥ 50% subgroup (p= 0.079).In 133 patients genetic testing, the common types of mutation include KRAS mutation, TP53 mutation, STK11 mutation, ERBB2 insertion mutation, SMARCA4 mutation and so on. The results of survival analysis showed the PFS of KRAS mutation patients have significantly longer PFS than wild-type patients (mPFS:16.27m vs 10.53m, HR:0.6400, 95%CI:0.4287-0.9556, p=0.042). Although the PFS of TP53 positive patients is longer, no statistical correlation is found (p=0.470). According to flow cytometry data, the proportion of CD45+CD3+T cell, CD3+CD8+T cell, CD45+CD3-CD16+CD56+NK cell and CD45+CD4+CD25HICD127LOWTregs cell increase significantly after 3 cycles immunotherapy. Similarly, it's found that these lymphocyte subsets in the response group increased significantly after immunotherapy, but this phenomenon is not observed in the non-response group. CD45+CD3-CD19+B cell have different degrees of significant increase in response group and non-response group .In the patients with detection PD-L1, CD3+CD4+T cells and CD45+CD4+CD25HICD127LOW Tregs cells have statistical differences among two subgroups (50% as threshold), and CD3+CD4+T cells has statistical correlation among three subgroups (1%,50% as threshold).The proportion of baseline CD45+CD4+CD25HICD127LOWTregs cells in patients with KRAS mutation positive was higher with no significant difference (p > 0.05) .Multivariate analysis showed that NLR, dNLR and BMI are risk factors for PFS,but LMR is related to long-term survival. Moreover, it is found that the occurrence of irAEs is in relation to longer PFS (mPFS:13.73m vs 9.73m,HR:1.373,95%CI:0.996-1.895,p<0.001).

Conclusions: This study shows that the lymphocyte immunophenotype and serological inflammatory cell markers in peripheral blood can reflect the changes of tumor immune microenvironment and have the potential to serve as biomarkers for immunotherapy in aNSCLC. Exploring the PD-L1 level,gene changes can provide more predictive value for immunotherapy.And the survival time of irAEs was longer.

Keywords: Non-small cell lung cancer, Immunotherapy, Biomarker

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EP.11B.03 Body Mass Index and Genetic Association in Durable Responders to Immunotherapy in Metastatic Non-Small Cell Lung Cancer

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Introduction: Immunotherapy has revolutionized the management of metastatic non-small cell lung cancer (NSCLC), leading to durable responses in many patients. Preclinical studies suggested obesity might be associated with upregulation of PD-L1 expression and improved response to immune checkpoint blockade. However, there is limited literature exploring the genomic features in different body mass index (BMI) groups and their association with response to immune checkpoint inhibitors (ICI) in NSCLC.

Methods: We conducted a retrospective analysis of patients with metastatic NSCLC diagnosed 1/2017 to 12/2021, who received first or subsequent lines of ICIs. Patients were divided into durable responders (DR) with time on treatment (TOT) ≥ 18 months, and non-durable responders (NDR) with TOT < 18 months. Demographic, clinical and genomic information were collected and compared between the two cohorts, including age, sex, race, smoking status, ECOG performance status (PS), BMI, histology, presence of brain metastasis, presence of immune-related adverse events (iAEs), PD-L1 score, genetic test, type and line of ICI, and chemotherapy use. Chi-squared test and Fisher's exact test were used to analyze categorical variables, while ANOVA and Mann-Whitney were conducted for continuous variables. Multivariate analysis was conducted using logistic regression and included variables that were considered relevant in univariable analysis.

Results: Among 324 identified patients with a median follow up of 13.3 months, the median age was 66 years, with 54.3% being male. There were 67 patients in the DR group, while NDR group had 257 patients. No racial/ethnicity differences were noted in our diverse patient population between DR and NDR groups. Multivariate analysis revealed that an ECOG PS < 2 (OR 0.26, 95% CI 0.12-0.54; P=0.00) and BMI ≥ 25 (OR 0.52, 95% CI 0.29-0.94, p=0.03) were associated with durable response outcome. Overall, there was a significantly lower incidence of STK11 mutations in the DR group compared to the NDR group (2.7% vs. 14.5%, P=0.048). Moreover, subgroup analysis examining genomic testing within stratified BMI and ECOG groups revealed that among patients with BMI < 25, SMARCA4 mutations were significantly more common compared to those with BMI ≥25 (7.8% vs. 0, P=0.02).

Conclusions: Our study demonstrated that in metastatic NSCLC patients treated with ICIs, better ECOG performance status and being overweight or obese were associated with durable responses. Additionally, there were notable genomic associations in overweight/obese patients and in durable responders. Future prospective studies are warranted to further explore genetic features and their implications in durable responders to immunotherapy.

Keywords: Immunotherapy, Genetic alteration, Non-small cell lung cancer

	Durable responders (n=67)	Non-responders (n=257)	Total (n=324	P-value
Age, median (IQR)	66(59-73.4)	67(61-75)	66(60-74	
<65	29(43.3%)	110(42.8%)	139(42.9%)	0.94
≥65	38(56.7%)	147(57.2%)	185(57.1%)	
Sex Male	36(53.7%)	140(54.5%)	176(54.3%)	0.91
Female	31(46.3%)	117(45.5%)	148(45.7%)	
Race White/others	17(25.4%)	83(32.3%)	100(30.9%)	0.15
Black	33(49.3%)	93(36.2%)	126(38.9%)	
Hispanic	17(25.4%)	81(31.5%)	98(30.2%)	
BMI, median (IQR)	25.2(21.6-29.3)	22.6(20.1-26.6)	23.0(20.3-27.3)	**0.01**
BMI<25	34(50.7%)	169(65.8%)	203(62.7%)	**0.02**
BMI≥25	33(49.3%)	88(34.2%)	121(37.3%)	
Smoking history Nerver Smoker	3(4.5%)	28(10.9%)	31(9.6%)	0.11
Smoker	64(95.5%)	229(89.1%)	293(90.4%)	
ECOG 0-1	57(85.1%)	154(59.9%)	211(65.1%)	**0.000**
≥2	10(14.9%)	103(40.1%)	113(34.9%)	
Histology Non-squamous	57(85.1%)	208(80.9%)	265(81.8%)	0.43
Squamous cell carcinoma	10(14.9%)	49(19.1%)	59(18.2%)	
Brain metastasis Yes	20(29.9%)	65(25.3%)	85(26.2%)	0.45
No	47(70.1%)	192(74.7%)	239(73.1%)	
Line of IO First line	50(74.6%)	198(77.0%)	248(76.5%)	0.68
Second and subsequent line	17(25.4%)	59(23.0%)	76(23.5%)	
Type of IO Pembrolizumab	56(83.6%)	216(84.0%)	272(84.0%)	0.96
Nivolumab	9(13.4%)	32(12.5%)	41(12.7%)	
Others	2(3.0%)	9(3.5%)	11(3.4%)	
IO with chemotheray Yes	27(40.3%)	125(48.6%)	152(46.9%)	0.22
No	40(59.7%)	132(51.4%)	172(53.1%)	
PD-L1 (%) <50	32(52.5%)	141(61.3%)	173(59.5%)	0.21
≥50	29(47.5%)	89(38.7%)	118(40.5%)	
TMB N/A	49(73.1%)	194(75.5%)	243(75.0%)	
<10	7(38.9%)	33(52.4%)	40(49.4%)	0.31
≥10	11(61.1%)	30(47.6%)	41(50.6%)	
Actionable alteration N/A	25(37.3%)	113(44.0%)	138(42.6%)	
Yes	8(19.0%)	36(25.0%)	44(23.7%)	0.42
No	34(81.0%)	108(75.0%)	142(76.3%)	
iAEs Yes	22(32.8%)	66(25.7%)	88(27.2%)	0.24
No	45(67.2%)	191(74.3%)	236(72.8%)	

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EP.11B.04 Differential Durable Responses in Intrathoracic Versus Overall Lesions of Non-Small Cell Lung Cancer Treated with Immunotherapy

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Introduction: Tumor response to immunotherapy in non-small cell lung cancer (NSCLC) in intrathoracic versus extrathoracic lesions may differ due to tumor heterogeneity. This study assesses the concordance of intrathoracic versus overall lesion response and identifies clinical factors linked to durable response in NSCLC patients treated with immunotherapy.

Methods: This study analyzed 78 NSCLC patients with both intrathoracic and extrathoracic lesions receiving first-line immunotherapy. Clinical response was evaluated by RECIST v1.1. Durable response was defined as patients achieving complete response (CR), partial response (PR), or stable disease (SD) for ≥24 weeks. Clinical benefit rate (CBR) was defined as percentage of durable responders.

Results: Patients had a median age of 65.0 (range, 37-99) years, with a male-to-female ratio of 1.69 [male (n=29); female (n=49)]. Baseline metastases included brain (n=34, 43.6%); bone (n=25, 32.1%); and liver (n=17, 21.8%). Median duration of immunotherapy was 4.84 (range, 0.2-55.3) months.

Among durable responders (n=27, 34.6%), the median progression-free survival (PFS) and overall survival (OS) were 14.3 (range, 9.0-19.6) and 35.7 (range, 19.4-52.1) months, while those in non-durable responders (n=51, 65.4%) were 2.7 (range, 1.0-4.4) and 10.5 (range, 6.9-14.0) months, respectively (PFS: p<0.001; OS: p<0.001). For intrathoracic durable responders (n=29, 37.2%), the median PFS and OS were 12.2 (range, 7.5-16.9) and 30.7 (range, 13.6-47.8) months, while those in non-durable responders (n=49, 62.8%) were 3.8 (range, 2.6-5.0) and 9.4 (range, 4.9-13.8) months, respectively (PFS: p=0.02; OS: p=0.002).

The concordance of tumor response between overall and intrathoracic lesions only was 80.8% (63/78). The changes were as follows: one PD to CR, three PRs and two PDs to SDs, five SDs and two PDs to PRs, two SDs to PDs. Tumor responses of overall lesions were PR (n=11, 14.1%), SD (n=42, 53.9%), and PD (n=25, 32.1%) with a CBR of 34.6%. Tumor responses of intrathoracic lesions only were CR (n=1, 1.3%), PR (n=15, 19.2%), SD (n=40, 51.3%), and PD (n=22, 28.2%) with a CBR of 37.2%.

Median duration of treatment in both overall and intrathoracic were 11.0 months and 8.3 months (p-value 0.003 and 0.05, respectively). Lower baseline platelet count (<400K) was associated with intrathoracic durable response (p=0.03). TMB, PD-L1 status, or treatment regimen were not significantly different between durable responders and non-responders.

Conclusions: Concordance of response rate between intrathoracic only vs. overall lesions in NSCLC patients was 80.8%. Intrathoracic response evaluation showed higher rates of durable response (37.2% vs 34.6%). Lower baseline platelet count was linked with intrathoracic durable response.

Keywords: Durable response, intrathoracic versus overall lesions, NSCLC

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EP.11B.05 The Differential Effect of Radiation, IL39, and the Combination on Expression of HLA Molecules

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Introduction: Lung cancer is the leading cause of cancer death amongst men and women in the US, and it is one of the leading causes of cancer death in the world. Currently, lung cancer treatments include chemotherapy, radiation, and immunologic therapy. More research has focused on improving radiation and immunologic therapies to specifically target the cancer cells and not subject the body to systemic treatment and side effects. IL-39 is a newly studied signaling molecule with potential implications on the development and progression of cancer. HLA-DQA, HLA-DQB, and HLA-DPA molecules confer anti-tumor effects against various other types of cancer, and thus upregulation would imply potential therapeutic benefit against lung cancer. CD74 is a proinflammatory molecule that supports proliferation of cancer cells. Blocking CD74 and its negative effects would be a significant finding for combating lung cancer. Il-39 and radiation inhibit cancer growth by modulating proliferative, anti-proliferative, pro-apoptotic, and anti-apoptotic molecules. This study aims to view the interaction between IL-39 and radiation on MHC class 2 molecules HLA-DQA, HLA-DQB, and HLA-DPA on the expression and proliferation of lung cancer cells. The experiment also studies the interaction of radiation plus IL-39 and its effects on CD74.

Methods: A549 adenocarcinoma lung cancer cells were treated with three different combinations: radiation, IL-39, or IL-39 plus radiation. RT-PCR was utilized to measure the expression of co-stimulatory molecules in A549 lung cancer cells.

Results: Radiation alone increased the expression of HLA-DQA in lung cancer cells compared to the control. IL-39 treated lung cancer cells increased the expression of HLA-DQA, HLA-DQB, and HLA-DPA compared to the control. Radiation plus IL-39 increased the expression of HLA-DQA. Surprisingly, the combination of radiation plus IL-39 also decreased the expression of CD74.

Conclusions: Radiation, IL-39, and the combination of the two demonstrated different effects on HLA molecules and CD74. While both radiation alone and IL-39 were able to upregulate certain HLA molecules, their combination had the additional benefit of decreasing CD74. This result implies there is potential benefit of the combined treatment, and can encourage further immunotherapy research on IL-39 alone and in combination with radiation.

Keywords: IL-39, HLA-DQA, Lung Cancer

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EP.11B.06 The Impact of Body Mass Index on Immune-Related Adverse Events and Outcomes in Patients with Lung Cancer: A Real-World Study

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Introduction: Immune checkpoint inhibitors (ICIs) have dramatically advanced the treatment landscape of lung cancer. Body mass index (BMI) is a widely used body size measurement and high BMI has been a proven risk factor for multiple malignancies. Obesity is considered a chronic inflammatory state and may influence ICI safety and efficacy by changing T cell functions. This study sought to examine the association between baseline BMI on immune-related adverse events (irAE) and outcomes in patients with lung cancer treated with ICIs.

Methods: Patients with pathology-confirmed lung cancer, newly started on ICIs between 10/01/2018 and 09/30/2021 were retrospectively identified from the Tufts Medical Center cancer registry and pharmacy records. Patient characteristics were extracted from the electronic health record; any irAEs occurring within 12 months after ICI initiation were identified. BMI was categorized into high BMI (>=25 kg/m2) and low BMI (<25 kg/m2). Mann-Whitney U test and Chi-square test were used to compare baseline information. Logistic regression was used to assess the impact of BMI on irAEs. Log-rank test and multivariable Cox regression were performed to assess the impact of BMI on progression-free survival (PFS) and overall survival (OS).

Results: A total of 125 patients were included with a median age of 70 years (range: 50-88), of whom 68 (54.4%) were males, 104 (80.8%) had non-small cell lung cancer, and virtually all (98%) had advanced stages (stage III+IV). Pembrolizumab was the most often used ICI agent (67.2%). When comparing high (N=66) and low BMI (N=59) groups, more Whites (92.4% vs 71.2%, p=0.002), and fewer prior infections 3 months before ICI initiation were observed in the high BMI group (4.5% vs 18.6%, p=0.021). In total 50 irAEs occurred in 39 individuals with the most common irAEs being endocrinopathies (34%) followed by pneumonitis (20%). With multivariable logistic regressions adjusting for age and histology, there were no significant associations between BMI and the occurrence of any irAE (Odd ratio [OR]: 0.942, 95%CI [0.413, 2.125], p=0.885). In contrast, high BMI was marginally associated with the development of endocrinopathies (OR: 2.920, 95%CI [0.879, 11.659], p=0.096], but not with pneumonitis (OR: 0.890, 95%CI [0.233, 3.412], p=0.862). In the advanced-stage patients, there were no differences with regards to PFS (p=0.240) or OS (p=0.530) by log-rank test between the two BMI groups. After adjusting for age, stage, and histology, high BMI showed trends of a superior PFS (Hazard ratio [HR]: 0.689, 95% CI [0.428, 1.107], p=0.123), but unfavorable OS (HR: 1.134, 95% CI [0.637, 2.019], p=0.668), although these results were not statistically significant.

Conclusions: Our findings suggested that in lung cancer patients treated with ICIs, BMI was not significantly associated with the occurrence of any irAEs, but overweight or obese patients were more likely to develop endocrinopathies. The width of the confidence interval suggests that the study may not have been adequately powered to detect this relationship. Baseline BMI was found to have no significant impact on the efficacy of ICIs in lung cancer. Future studies with larger sample sizes are warranted to validate these findings.

Keywords: Body mass index, Immunotherapy, lung cancer

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EPB.07 Choline Metabolism Reprogramming Mediates an Immunosuppressive Microenvironment in Non-Small Cell Lung Cancer

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Introduction: Lung cancer is a prevalent malignancy globally, and immunotherapy has revolutionized its treatment. However, resistance to immunotherapy remains a challenge. Abnormal cholinesterase (ChE) activity and choline metabolism are associated with tumor oncogenesis, progression, and poor prognosis in multiple cancers. Yet, the precise mechanism underlying the relationship between ChE, choline metabolism and tumor immune microenvironment in lung cancer, and the response and resistance of immunotherapy still unclear.

Methods: Firstly, 277 advanced non-small cell lung cancer (NSCLC) patients receiving first-line immunotherapy in Sun Yat-sen University Cancer Center were enrolled in the study. Pretreatment and the alteration of ChE after 2 courses of immunotherapy and survival outcomes were collected. Kaplan-Meier survival and cox regression analysis were performed, and nomogram was conducted to identify the prognostic and predicted values. Secondly, choline metabolism-related genes were screened using Cox regression, and a prognostic model was constructed. Functional enrichment analysis and immune microenvironment analysis were also conducted. Lastly, to gain further insights into potential mechanisms, single-cell analysis was performed.

Results: Firstly, baseline high level ChE and the elevation of ChE after immunotherapy were significantly associated with better survival outcomes for advanced NSCLC. Constructed nomogram based on the significant variables from the multivariate Cox analysis performed well in discrimination and calibration. Secondly, 4 choline metabolism-related genes (MTHFD1, PDGFB, PIK3R3, CHKB) were screened and developed a risk signature that was found to be related to a poorer prognosis. Further analysis revealed that the choline metabolism-related genes signature was associated with immunosuppressive tumor microenvironment, immune escape and metabolic reprogramming. scRNA-seq showed that MTHFD1 was specifically distributed in tumor-associated macrophages (TAMs), mediating functional heterogeneity and the differentiation of macrophages, which may potentially impact endothelial cell proliferation and tumor angiogenesis.

Conclusions: Our study highlights the discovery of cholinesterase (ChE) as a prognostic marker in advanced NSCLC, suggesting its potential for identifying patients who may benefit from immunotherapy. Additionally, we developed a prognostic signature based on choline metabolism-related genes, revealing the correlation with the immunosuppressive microenvironment and uncovering the role of MTHFD1 in macrophage differentiation and endothelial cell proliferation, providing insights into the intricate workings of choline metabolism in NSCLC pathogenesis.

Keywords: non-small cell lung cancer, choline metabolism, immunosuppressive microenvironment

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EP.11C.01 Treatment Options for Tumor Progression after Initial Immunotherapy in Advanced Non-Small Cell Lung Cancer: A Real-World Study

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Introduction: Whether to continue administering immunotherapy to patients with advanced non-small cell lung cancer (NSCLC) who have experienced tumor progression remains controversial after immunotherapy. The aims were to explore survival outcomes after further immunotherapy post-progression and to determine the optimal combination therapy in such cases.

Methods: A total of 507 patients with NSCLC who underwent immunotherapy and experienced tumor progression were retrospectively divided into Immuno-combination and No-immuno groups according to whether additional combination therapy involving immunotherapy was administered post-progression. Progression-free survival (PFS) and overall survival (OS) outcomes were evaluated. Subgroup analyses were performed according to the different treatment regimens of patients in the Immuno-combination group.

Results: Superior PFS outcomes were observed in the Immuno-combination group compared with those in the No-immuno group (3-month PFS: 51.0% vs. 83.9%; 6-month PFS: 24.8% vs. 60.7 %; and 12-month PFS: 6.5% vs. 24.2 %, respectively; P<0.001). Similar intergroup differences were observed for OS outcomes (6-month OS: 73.1% vs. 97.2%; 12-month OS: 22.4% vs. 69.7 %; and 18-month OS: 6.2% vs. 40.4%, respectively; P<0.001). Superior PFS outcomes were observed in the Immuno+Antiangiogenic group than in the Immuno+Chemo group ((3-month PFS: 78.5% vs. 90.6%; 6-month PFS: 51.6% vs. 71.7%; and 12-month PFS: 21.9% vs. 27.1%, respectively; P=0.005). Similar differences in OS were observed between those same subgroups ((6-month OS: 97.4% vs 96.9%; 12-month OS: 63.5% vs 77.1%; and 18-month OS: 33.7% vs 48.4%, respectively; P=0.003).

Conclusions: Patients with NSCLC experiencing tumor progression post-immunotherapy can still benefit from further treatment, with immunotherapy combined with antiangiogenic therapy being the most efficacious option.

Keywords: non-small cell lung cancer, immunotherapy, antiangiogenic therapy

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EP.11C.02 Role of Immune-Related Adverse Events (irAEs) and Albumin in Non-Small-Cell Lung Cancer (NSCLC)

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Introduction: Immune checkpoint inhibitors (ICIs) are used to treat advanced non-small cell lung cancer (NSCLC), but they can cause toxicities known as immune-related adverse events (irAEs), potentially disrupting treatment. We aimed to analyze the characteristics of NSCLC patients who are more likely to develop irAEs in a single-center cohort and assess the effects of irAE history on progression-free survival (PFS).

Methods: We retrospectively reviewed NSCLC patients treated with at least 3 doses of immunotherapy between 2015-2023. Data on patient age, sex, smoking history, histology, type of ICI regimen, BMI, and baseline albumin were collected. History of irAE was determined through clinical chart review. Patient response was assessed using Recist 1.1 coding and chart review to determine progression-free survival (PFS). Group differences were assessed using t-tests/chi-square tests, and Cox proportional hazards modeling was utilized to evaluate univariate and multivariable PFS.

Results: The study included 480 patients (245 female, 235 male). The median age was 66 years old (interquartile range (IQR): 59-73), with the majority (87.7%) being Caucasian and non-current smokers (56.7%). The median baseline albumin level was 4 (IQR: 3.7-4.3). There were 89 out of 480 patients (18.5%) who experienced treatment-limiting irAEs, with pneumonitis being the most common (4.2%). IrAEs were more prevalent in females compared to males (22% vs. 15%, p=0.044), non-current smokers vs. current smokers (22% vs. 14 %, p=0.033), patients with BMI >=30 vs. BMI <30 (24% vs. 16%, p=0.039), and those receiving only immunotherapy vs. chemoimmunotherapy (22% vs. 15%, p=0.048). Univariate analysis indicated significantly better PFS for patients with a history of irAEs (Hazard Ratio [HR]=0.534; 95% Confidence Interval [CI]=0.383-0.746, p=<0.001) and tending to show benefit with higher albumin levels (HR=0.72; 95% CI 0.538-0.962, p=0.026) (Figure 1). Multivariate analysis including all collected variables confirmed a significant correlation of PFS with a history of irAEs on immunotherapy (HR=0.57; 95% CI=0.406-0.799, p=0.001) and showed a benefit of PFS with increased albumin levels (HR=0.747; 95% CI=0.588-1, p=0.05).

Conclusions: We demonstrate that irAE's were associated with certain patient characteristics, including sex, smoking status, BMI and treatment regimen. Furthermore, a history of irAEs and higher baseline albumin levels were independently correlated with improved progression-free survival, suggesting their potential as prognostic factors in NSCLC patients undergoing immunotherapy.

Keywords: Non-Small-Cell Lung Cancer, irAE, Albumin

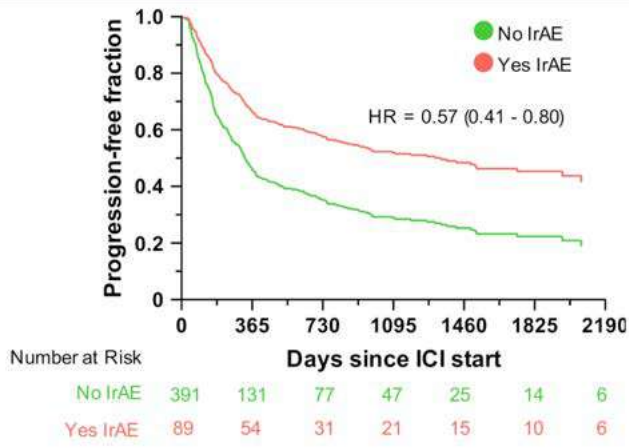

Figure 1: Cox proportional hazards model for progression-free survival with survival curves for patients with and without irAE's.

EP.11C METASTATIC NON-SMALL CELL LUNG CANCER - IMMUNOTHERAPY - IMMUNORESISTANCE
SATURDAY, SEPTEMBER 7, 2024 - 11:58 - 11:59

EP.11C.03 Anlotinib Combined with Immune Checkpoint Inhibitor May Benifit Advanced Smarca4-Deficient Thoracic Tumor Patients in First Line

Y. Lou[1], R. Li[1], B. Liu[1], Y. Li[1], D. Wang[1], W. Zhang[1], B. Han[1], F. Qian[1], Y. Zhang[1], B. Zhang[1], L. Zhang[1], W. Ma[1], [1]Shanghai Chest Hospital, Shanghai Jiaotong University, Shanghai/CN

Introduction: The first-line treatment strategy of patients with advanced SMARCA4-deficient tumors is inconclusive. Although previous studies have shown immunotherapy to be effective, the efficacy and safety of different ICIs combination treatment strategies have not been explored in detail.

Methods: We collected the clinical and pathological information of 55 patients with SMARCA4-dNSCLC and SMARCA4-dUT, after which we evaluated and analyzed the clinicopathological characteristics and survival status of the patients.

Results: The patients were mainly male smokers with a mean age of 66 years old(range:46-81 years old). Histologically, non small cell lung cancer(NSCLC) accounts for the majority(n=40, 72.7%), and only a small proportion of patients carried high PD-L1 expression status(n=3, 5.4%). Additionally,concomitant mutation genes such as TP53,STK11,and KRAS were observed. Survival analysis demonstrated that the progression-free survival(PFS) of patients who received anlotinib in combinnation with immunotherapy was superior to that of patients who received chemotherapy in combination with immunotherapy as a first-line treatment(not reach vs.8.63m, p=0.05)(Figure1). Overall survival(OS) was significantly longer in patients who received first-line immnotherapy compared to those who receive first-line immunotherapy or no immunotherapy(21.67m vs. 8.80m, p=0.027)(Figure2).

Conclusions: SMARCA4-deficient thoracic tumor has unique clinicopathologic features and worse prognosis, and immue checkpoint inhibitors combined with anlotinib may be a better treatment for first-line.

Keywords: SMARCA4-defcient thoracic tumor, Immune Checkpoint Inhibitor, Anlotinib

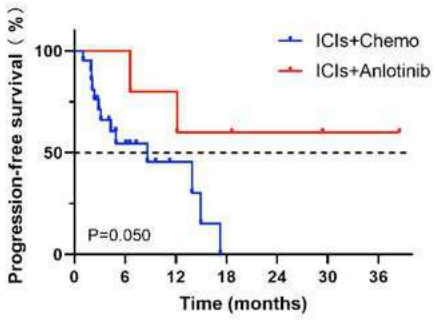

Figure1. PFS in patients treated with Chemotherapy+ICIs versus ICIs+Anlotinib

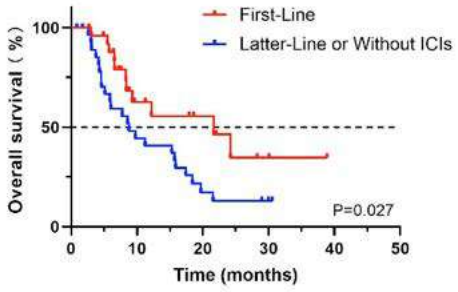

Figure2. OS in patients treated with immunotherapy for first-line versus latter-line or without immunotherapy.

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EP.11C.04 Retrospective Evaluation of Biomarkers (KRAS, TP53, STK11, KEAP1, POLE, PIK3CA, ARID1A) In Patients with NSCLC IV

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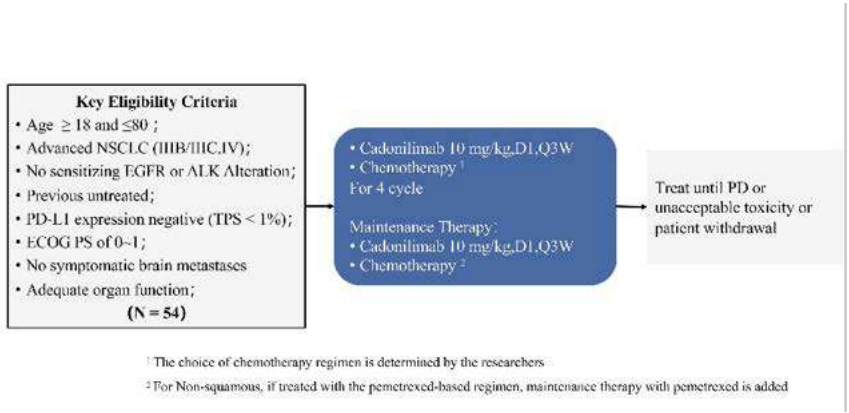
Introduction: Immunotherapies targeting the Programmed Cell Death-1 receptor (PD-1) and its ligand (PD-L1) have led to significantly higher survival rates in patients with metastatic non-small cell lung cancer (mNSCLC). Nevertheless, a high proportion of patients with mNSCLC do not respond to immunotherapy. The detection of PD-L1 expression as a predictive biomarker can indicate which patients are likely to benefit from immunotherapy. However, PD-L1 expression alone does not always correlate with response. In order to optimize the treatment of patients with mNSCLC, additional biomarkers for response and resistance to immunotherapy mono or in combination with chemotherapy are needed.Therefore, the influence of the following mutations KRAS, STK11, KEAP1, TP53, PIK3CA, ARID1A and POLE on PFS and OS in patients with mNSCLC receiving immunotherapy as monotherapy or in combination with chemotherapy will be investigated.

Methods: In retrospective study a total of 505 PD-L1 positive mNSCLC patients were analyzed for the following mutations: KRAS, STK11, KEAP1, TP53, PIK3CA, ARID1A and POLE. The patients were first diagnosed between 2018 and 2022 in a cancer center in northern Germany. Clinical data including sex, age, smoking status, as well as PD-L1 score was captured. Detailed information on the course of treatment and the patient survival will be presented at the conference.

Results: Median age of the 505 patients was 65 years (36-88 years) and 59% (298/505) of them were male. Most of the patients had an ECOG status of 0 or 1 (77%; 389/505) and 89% of them were current or ex heavy smoker (450/505). PD-L1 groups are distributed as follows: 36% (182/505) of the patients had a PD-L1 <1% expression, 25% (127/505) of the patients had a PD-L1 1-49% expression and 39% (196/505) of the patients a PD-L1 ≥50% expression. Overall, a TP53 mutation was detected in 59% (241/409) of patients, a STK11 mutation in 23% (83/359), a KEAP1 mutation in 29% (138/354), a POLE mutation in 15% (31/202), an ARID1A mutation in 13% (27/202), a PIK3CA mutation in 9% (34/374) and a KRAS mutation in 30% (114/379) of patients.

Conclusions: Initial descriptive analysis has shown the distribution of the various biomarkers in a PD-L1 positive patient setting. OS and PFS will be calculated from the start of immunotherapy or immunotherapy in combination with chemotherapy and correlated with the various biomarkers. In addition, an adjusted Cox regression will be performed at the conference to assess the predictive value of the various biomarkers.

Keywords: NSCLC, immunotherapy, biomarker



EP.11D METASTATIC NON-SMALL CELL LUNG CANCER - IMMUNOTHERAPY - CLINICAL TRIALS IN PROGRESS
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EP.11D.01 A Phase II Study of Cadonilimab Plus Chemotherapy as First-Line Treatment for PD-L1-Negative Advanced Non-Small Cell Lung Cancer:LungCadX

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Introduction: Immunotherapy against non-small-cell lung cancer (NSCLC) with PD-L1-negative remains an unmet need. Many phase III clinical trials had demonstrated that the 12-month PFS rate in PD-L1 negative populations was significantly lower compared to PD-L1 positive populations. Cadonilimab is a bispecific antibody that simultaneously targets programmed cell death receptor-1 and cytotoxic T lymphocyte-associated antigen-4. In this study, we aimed to assess the efficacy and safety of cadonilimab combined with chemotherapy for the first-line treatment of PD-L1-negative advanced NSCLC.

Methods: LungCadX (ChiCTR2300071681) is a multi-center, open-label, single-arm, investigator initiated, phase II study. Patients received 4 cycles cadonilimab 10 mg/kg every three weeks (Q3W) plus chemotherapy, followed by cadonilimab maintenance therapy. The chemotherapy was determined by the investigators. The primary endpoint was the 12-month PFS rate by investigator assessment per RECIST 1.1. Secondary endpoints included PFS, OS, ORR,DoR,DCR, and the safety. Exploratory objective was to assess blood/tumor/urine/faeces tissue for potential biomarkers. Adverse events will be monitored throughout the trial and graded according to the CTCAE v5.0.

Keywords: NSCLC, PD-L1 negative, PD-1/CTLA-4 bispecific antibody

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EP.11D.02 An Investigator-Initiated Phase II Study of Combination Treatment of Nivolumab and TM5614, A PAI-1 Inhibitor for Previously Treated NSCLC

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Introduction: There is no established standard 3rd line treatment for patients with advanced non-small cell lung cancer (NSCLC). Although cytotoxic chemotherapeutic agents that are not used as 1st or 2nd line treatment are administrated as 3rd line treatment, their anti-tumor efficacy is insufficient. Anti-programmed death ligand-1 (PD-L1)/programmed death-1 (PD1) treatment is more effective and less toxic than chemotherapy in anti-PD-L1/PD-1 treatment-naïve patients with NSCLC. Therefore, anti-PD-L1/PD-1 therapy is considered an appropriate 3rd line treatment. However, the anti-tumor efficacy is limited in patients previously treated with anti-PD-L1/PD-1 antibody. Today, new drugs are needed to increase the efficacy of anti-PD-L1/PD-1 antibodies.

Methods: This open-label, single-arm, investigator-initiated phase II study is designed to evaluate combination treatment of nivolumab and TM5614, a plasminogen activator inhibitor (PAI)-1 inhibitor as 3rd or more line treatment in NSCLC patients who underwent standard treatment. The primary endpoint is the objective response rate and the secondary endpoints are progression-free survival, overall survival, duration of response and safety. The study protocol conformed to the ethical principles outlined in the Declaration of Helsinki. All patients will provide written informed consent prior to enrollment.

Results: This study is registered to Japan Registry of Clinical Trials with number: jRCT2061230039 (19/July/2023). Recruitment began in September 2023 and is expected to continue for approximately three years. As of April 2024, 13 subjects have been enrolled.

Conclusions: Currently, there is no standard 3rd line treatment for advanced NSCLC, and we hope that the findings of this study will facilitate more effective treatments in this setting.

Keywords: non-small cell lung cancer, anti-programmed death-1 antibody, antibody, plasminogen activator inhibitor-1

EP.11E METASTATIC NON-SMALL CELL LUNG CANCER - IMMUNOTHERAPY - CASE REPORTS
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EP.11E.01 Immune-Related Myasthenia Gravis in Patients with NSCLC: A Case Series

Y-Y.C. Kang[1,2], M-H. Lin[1], C-Y. Wang[1], C-H. Hsu[1], Y-C. Jiang[1], C-F. Chen[1], [1]Kaohsiung Veterans General Hospital, Kaohsiung/TW,[2]Kaohsiung Medical University, Kaohsiung/TW

Introduction: Immune checkpoint inhibitors (ICIs) enhance immune response, offering clinical benefits but also increasing the risk of immune-related adverse events (irAEs). These irAEs stem from off-target inflammatory and autoimmune responses, including the induction or exacerbation of myasthenia gravis (MG). Immune-related MG (irMG) is rare (0.5% of all irAEs) and presents with acute onset and rapid progression. IrMG carries a significantly higher mortality rate than classic MG (28-30% vs. 6%), where most patients present with mild disease (classes I and II), primarily due to respiratory failure. The immunobiology of irMG remains poorly understood, and its distinct features from classic MG pose challenges for optimal diagnosis and treatment. Here, we present a series of irMG cases.

Methods: Patients with NSCLC who developed irMG after receiving at least one dose of ICI were monitored at a single center in Taiwan. The study analyzed immunotherapy cycles, time to irMG onset, diagnostic results, MG symptoms and severity, management strategies, and patient outcomes.

Results: Three stage IV NSCLC patients are presented: two female, none with smoking history, autoimmunity, or driver gene alterations. All had high expression of programmed death-ligand 1 (PD-L1) and received first-line platinum-based chemotherapy. Patients 1 and 3 (100% and 98% PD-L1 expression) developed irMG rapidly after starting pembrolizumab; Patient 2 developed MG only after pembrolizumab cessation due to disease progression and a subsequent switch to gemcitabine. Immunotherapy was discontinued for Patients 1 and 2 upon MG onset due to rapid progression, but continued for Patient 3 as MG symptoms regressed. All patients shared ptosis as a symptom. The two deceased patients (Patients 1 and 2) also experienced elevated troponin, general weakness, muscle discomfort, dyspnea, and concurrent irAEs. Acetylcholine receptor antibodies were positive in Patients 1 and 3; Patient 2, with negative antibodies, had positive repetitive nerve stimulation results. All received glucocorticoids and pyridostigmine as initial treatment. The deceased patients had class V MG; they underwent plasmapheresis, mechanical ventilation, and extensive supportive care, but still succumbed to irMG. Patient 3 (class I) experienced milder, ongoing MG symptoms despite treatment.

Conclusions: High PD-L1 expression correlated with severe irMG in this series. Prompt, aggressive therapy (e.g., plasmapheresis, intravenous immunoglobulin) is crucial for severe irMG, alongside standard treatments like glucocorticoids and pyridostigmine.

+MG diagnosis per consensus criteria established by Guidon, et al. 2021. Abbreviation: AChEI, acetylcholinesterase inhibitor; CT, computerized tomography; ECOG, Eastern Cooperative Oncology Group; ICI, immune checkpoint inhibitor; irAE, immune-related adverse event; MG, myasthenia gravis; MGFA, Myasthenia Gravis Foundation of America; MRI, magnetic resonance imaging; PD-L1, programmed death-ligand 1; RNS, repetitive nerve stimulation

Keywords: Immune-related myasthenia gravis, Immune-related adverse events, NSCLC

Patient case	Patient 1	Patient 2	Patient 3
Sex	Male	Female	Female
Age at ICI initiation (years)	37	62	75
Histology	Squamous cell carcinoma	Lymphoepithelioma-like carcinoma	Squamous cell carcinoma
Staging	cT4N2M1a, stage IVa	pT4N3M1a, stage IVa	cT4N2M1a, stage IVa
ECOG performance status	0	0	1
Immunohistochemical assay	DAKO 22C3	DAKO 22C3	Ventana SP263, DAKO 22C3
PD-L1 expression %	100%	55%	98% (both assays)
Prior and subsequent treatments	Cisplatin/gemcitabine → Cisplatin/docetaxel → **Pembrolizumab**	Cisplatin/pemetrexed → Docetaxel → Paclitaxel → **Pembrolizumab** → Gemcitabine	Cisplatin/gemcitabine → **Pembrolizumab** → Paclitaxel
ICI treatment cycles	1	7	6
Clinical benefit	Partial response	Partial response	Partial response
Time to irMG onset after ICI initiation (days)	16 (Mar 25th 2020 - Apr 10th 2020)	253 (June 24th 2020 - Mar 4th 2021)	27 (May 17th 2019 - June 13th 2019)
Diagnostic tests	1. Acetylcholine receptor antibody: positive 2. RNS (3 and 10 Hz): normal 3. Brain CT: normal 4. Highest creatine kinase: 19179 U/L 5. Highest troponin: >27619 pg/mL	1. Acetylcholine receptor antibody: negative 2. RNS (3 Hz): neuromuscular disorder 3. Highest troponin: 120.2 pg/mL	1. Acetylcholine receptor antibody: positive 2. Brain MRI: normal
MG diagnostic criteria*	Probable	Probable	Probable
MGFA classification	V	V	I
MG symptoms	General weakness, ptosis, diplopia, headache, muscle soreness, dry cough, dyspnea, orthopnea	General weakness, ptosis, dysarthria, numbness over lower limbs, dyspnea, easy choking	Ptosis, hoarseness
MG treatment modality	1. Systemic glucocorticoid 2. Pyridostigmine and neostigmine 3.	1. Systemic glucocorticoid 2. Pyridostigmine 3. Intravenous	1. Systemic glucocorticoid 2.
	Plasmapheresis (4 courses, 5 days per course in Apr and May 2020) 4. Endotracheal tube + mechanical ventilation	immunoglobulin (29th Apr - 3rd May 2021) 4. Plasmapheresis (2 courses, 5 days per course in Mar and Apr 2021) 5. Endotracheal tube + mechanical ventilation	Pyridostigmine
Response to glucocorticoid and AChEI	Positive. AChEI-induced bradycardia	Positive	Positive
Other concurrent irAE(s)	1. Myocarditis 2. Hepatitis	1. Skin rash with ulceration and bullae. 2. Cellulitis >50% body surface area	None
Outcome	Expired on 23rd Jan 2021	Impending death discharge on 1st June 2021	Stable MG, alive

*MG diagnosis per consensus criteria established by Guidon, et al. 2021. Abbreviation: AChEI, acetylcholinesterase inhibitor; CT, computerized tomography; ECOG, Eastern Cooperative Oncology Group; ICI, immune checkpoint inhibitor; irAE, immune-related adverse event; MG, myasthenia gravis; MGFA, Myasthenia Gravis Foundation of America; MRI, magnetic resonance imaging; PD-L1, programmed death-ligand 1; RNS, repetitive nerve stimulation

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EP.11E.02 Intrapleural Plus Systemic Tislelizumab Injection Combined Chemotherapy as Second-Line Treatment in a Case of RET Gene Fusion-Positive Lung Adenocarcinoma Presenting Refractory Malignant Pleural Effusion

C. Chen, The First Affiliated Hospital of Soochow University, Soochow/CN

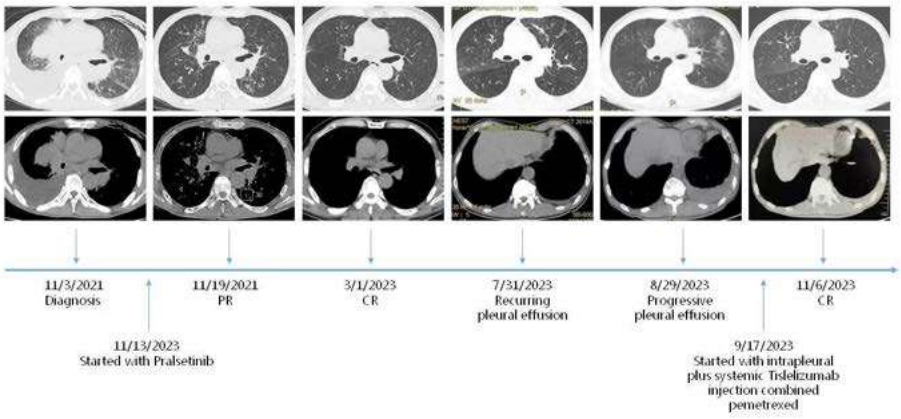
Introduction: RET fusions were discovered in non-small cell lung cancer (NSCLC) and the efficacy of RET-targeted treatment in these patients has been previously established. However, patients with required resistance to RET-TKIs have limited treatment options.

Methods: We present a case of 55-year-old male who was diagnosed with stage IV NSCLC harboring RET fusion and PS >4 who treated with Pralsetini achieved an excellent clinical benefit initiated at the midmonth of November 2021. The patient continued to tolerate Pralsetini without any further notable toxicities.However, the patient again developed a progressive malignant pleural effusion along with a progression of pulmonary nodule in July 2023. The therapy was initiated in late September 2023 and consisted of Pemetrexed 500 mg/m2 and Tislelizumab 200mg. We then exploited intrapleural Tislelizumab 100mg injection as an adjunctive therapy alongside all systemic treatments.

Results: The patient tolerated the administration of intrapleural Tislelizumab injection well and did not have any clinical signs of side effects or toxicities at first follow-up. Also, we conducted a CT follow-up examination, which revealed comprehensive therapeutic response of the NSCLC to this therapy, together with regressed aforementioned pleural effusion. As the patient consistently showed good therapy tolerance, additional cycles of chemo-immunotherapy were administered with unchanged dosage.

Conclusions: This case contributes to propose intrapleural immunotherapy as a feasible treatment option and intrapleural PD-1inhibitor bridging to systemic immunotherapy may represent a promising approach in NSCLC treatment. As with other potential applications of immunotherapy, immune biomarkers need to be better understood to aid in selection of this therapy.

Keywords: RET Fusion, malignant pleural effusion, intrapleural therapy



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EP.11E.03 Therapeutic Efficacy of Immunotherapy and Chemotherapy in Metastatic Nuclear Protein in Testis Carcinoma with NUTM1::NSD3 Mutation Originating from the Bronchus: A Case Report

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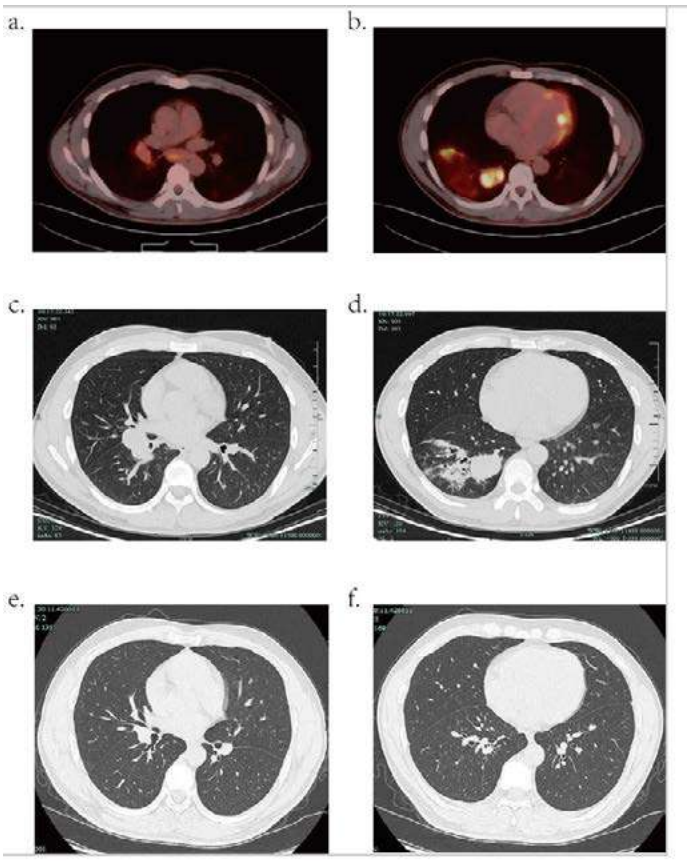
Introduction: Nuclear protein in testis carcinoma (NC) is an exceedingly rare subtype of poorly differentiated thoracic cancers, characterized by a fusion oncogene between nuclear testis antigen and an epigenetic reader. Among these fusion mutations, NUTM1::NSD3 represents the third most common variant in NC, crucial for maintaining proliferation in NC cells in vitro. The overall survival of metastatic NC is typically limited, with reported median OS of 12 months. While there have been isolated reports of NC patients responding to immunotherapy, the efficacy of combining chemotherapy with immunotherapy remains uncertain. Here, we present a case of metastatic NC harboring the NUTM1::NSD3 mutation, demonstrating a partial response to first-line treatment with immunotherapy and chemotherapy.

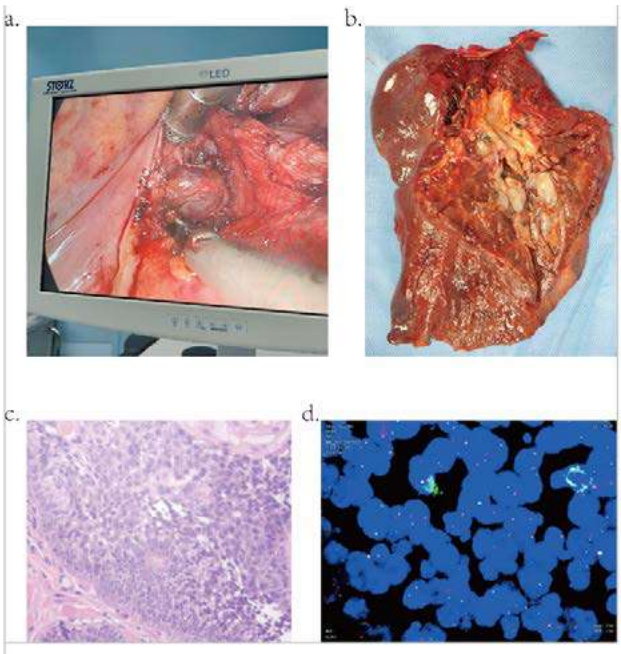
Methods: Clinical data were obtained from the First Affiliated Hospital, Zhejiang University School of Medicine. Tumor, para-tumor, and normal lung tissues were collected during surgery for genomic analysis using the Novaseq-SE50 platform. Structural variation prediction was performed using Delly 2 after quality control.

Results: The patient, a 34-year-old male with a 10 pack-year smoking history, presented with a 5-month history of cough. PET-CT(Fig. 1a-b) and CT(Fig. 1c-d) scans revealed cT4N2M0 (stage IIIB) lung cancer. Diagnosis of NC was confirmed by immunohistochemistry and FISH(Fig. 2c-d) in November 2023. Initial treatment comprised a combination of albumin-bound paclitaxel, carboplatin, and Tislelizumab. After 3 cycles of neoadjuvant therapy, significant tumor shrinkage was observed(Fig. 1e-f). Subsequent R0 resection(Fig. 2a-b) yielded a pathological stage of ypT1bN2M0 (stage IIIA). Whole-genome sequencing identified the fusion mutation of NUTM1 and NSD3. The patient has survived for 6 months since diagnosis with no signs of recurrence or metastasis during follow-up.

Conclusions: This case highlights the potential therapeutic benefit of combining immunotherapy and chemotherapy as first-line treatment for metastatic NUTM1::NSD3 NC. Our findings suggest that immunotherapy may confer clinical benefits for NC patients with specific mutation profiles.

Keywords: Nuclear Protein in Testis Carcinoma, Immunotherapy, Rare Disease





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EP.11E.04 Low-Dose Nivolumab in Advanced NSCLC; Light at the End of the Tunnel

A. Alaga, K. Jeyabalan, A.A. Rushdan, Hospital Sultanah Bahiyah, Alor Setar/MY

Introduction: Immune checkpoint inhibitors (ICIs) have radically changed the treatment and outcomes of numerous types of cancer, including NSCLC. Nivolumab (anti-PD-ligand 1 [PD-L1]) is approved by the Food and Drug Administration (FDA) for use in metastatic non-small cell lung carcinoma (NSCLC). Nivolumab is used at 3 mg/kg or in fixed doses of 240 mg every 2 weeks. However, it has resulted in 'financial toxicity' of NSCLC treatment in many parts of the world. Data from Phase I studies that used multiple-dose levels suggest that, in general, response does not decrease with a decrease in doses. This study evaluated the efficacy of low-dose nivolumab as a salvage therapy for advanced NSCLC in Malaysia to address financial toxicity.

Methods: Outcomes of patients with advanced NSCLC treated with nivolumab as salvage therapy in the respiratory department of Hospital Sultanah Bahiyah from December 2022 until March 2024 were retrospectively analysed. Patients who could not afford standard nivolumab treatment received low-dose nivolumab (40 mg fixed dose every 2 weeks) until disease progressed. The epidemiology of patients and treatment outcomes (progression free survival - PFS) were analysed.

Results: In total, six patients received low-dose nivolumab. PD-L1 positivity was observed in one (16.7%) patient. 3 of them were male and 3 of them were female, with a median age of 53. Out of the 6 patients, 2 of them received nivolumab as a 2nd-line treatment, 3 as 3rd-line treatment, and 1 as a 4th-line treatment. On average, nine cycles of nivolumab were given to each patient, with a maximum of 20 cycles of nivolumab given to one patient. The mean PFS was documented as 18.4 weeks. There were no immune-related adverse events noticed in patients, except one of them developed an exacerbation of underlying psoriasis.

Conclusions: Low-dose nivolumab can be effective in advanced NSCLC and can be an option to reduce financial toxicity. The efficacy of low-dose nivolumab is comparable with minimal adverse events.

Keywords: immunotherapy, low dose, NSCLC

EP.11E METASTATIC NON-SMALL CELL LUNG CANCER - IMMUNOTHERAPY - CASE REPORTS
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EP.11E.05 Outpatient Treatment Strategies for Grade 3-4 Immune-Mediated Hepatitis in Patients with Lung Cancer

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Introduction: The escalating use of immune checkpoint inhibitors in clinical oncology has led to a surge in immune-related adverse events. Among these, immune-mediated hepatitis ranks as the third most common (5-15%). Current guidelines advocate corticosteroids (1-2 mg/kg/day) as first-line therapy, yet corticosteroid pulse therapy offers efficacy with reduced toxicity in other scenarios, such as lupus nephritis. Despite this, a subset of patients remains refractory. Further immunosuppressive intervention with mycophenolate mofetil (MMF) achieves resolution in over 80% of cases. Optimal dosing, duration, and cessation protocols remain challenging.

Methods: This report highlights three cases of grade 3-4 asymptomatic immune-mediated hepatitis managed with outpatient corticosteroid pulse therapy. Patient data were reviewed confidentially and anonymized for presentation.

Results: Patient A: 60-year-old women diagnosed in May 2023 from stage IV small-cell lung cancer (SCLC). Carboplatin + Etoposide + Atezolizumab. Partial response after 4 cycles. Maintenance Atezolizumab for 10 cycles, until asymptomatic grade 3 hepatitis was diagnosed. Outpatient management with methylprednisolone 250 mg iv for 3 days in day-hospital, and 30 mg/day of oral prednisone after bolus. Tapering dose of prednisone until suspension. Partial response without treatment and no corticosteroid-toxicity appeared. Patient B: 62-year-old women diagnosed in June 2021 from stage IV SCLC. Carboplatin + Etoposide + Atezolizumab. Complete response after 6 cycles. Maintenance Atezolizumab for 36 cycles until grade 4 hepatitis was diagnosed. Methylprednisolone 250mg x3, and 60mg/day of prednisone after bolus until achieving grade 1. Upturn to grade 3. MMF 1000 mg/12h for corticosteroid-refractory hepatitis until liver function normalized. MMF stopped. New upturn solved by reintroducing MMF. Tapering dose of MMF ongoing. Complete response without treatment and no corticosteroid-toxicity. Patient C: 62-year-old man diagnosed in May 2022 from stage IVB lung adenocarcinoma. Carboplatin+ Pemetrexed+ Pembrolizumab every 21 days. Partial response after 4 cycles. Maintenance therapy for 16 months until grade 3 hepatitis was diagnosed. Methylprednisolone 250mg x3, 30mg/day of prednisone after bolus, and tapering dose afterwards. Corticosteroid-refractory hepatitis that require MMF 1000/12 h, achieving normalization of liver function without toxicity. Partial response maintained.

Conclusions: Corticosteroid pulse therapy presents as a less toxic alternative to standard corticosteroid regimens, even for grade 3-4 toxicities, as evidenced by our case series in lung cancer patients. This approach facilitates expedited immunosuppressive escalation for steroid-refractory immune-mediated toxicities, particularly immune-related hepatitis, where MMF emerges as a preferred adjunct. Further research is essential to elucidate optimal dosing and cessation protocols for immunosuppressive therapy.

Keywords: Pulse corticosteroid therapy, Immune-related toxicity, PD-1/PD-L1

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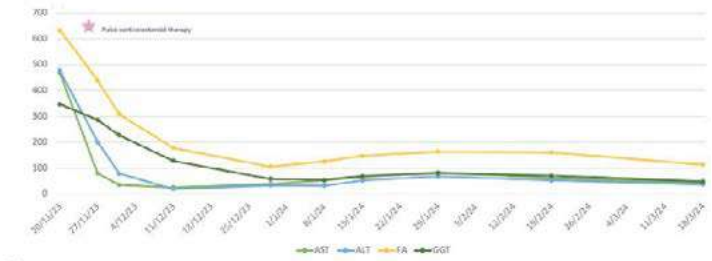

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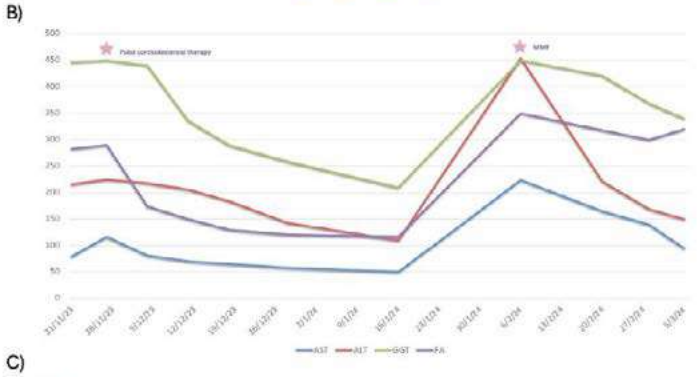

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EP.11E METASTATIC NON-SMALL CELL LUNG CANCER - IMMUNOTHERAPY - CASE REPORTS
SATURDAY, SEPTEMBER 7, 2024 - 11:58 - 11:59

EP.11E.06 "Down-Stage" To Thoracic Surgery after Neoadjuvant Immunochemotherapy

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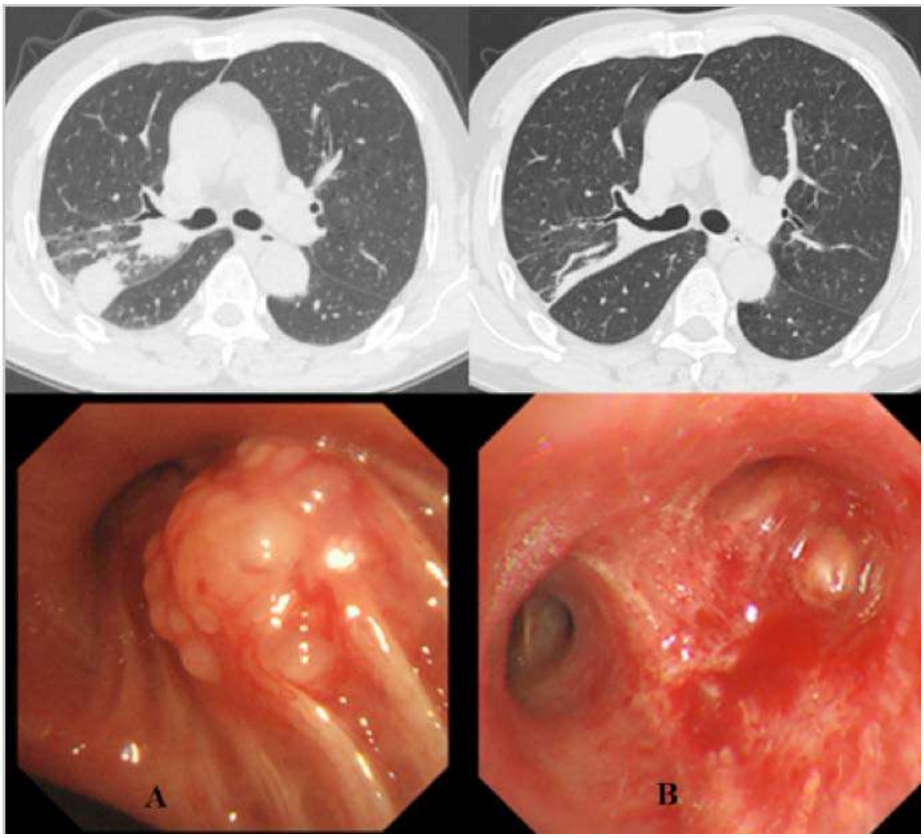
Introduction: A 59-year-old male who smoked two packs of cigarettes per day for an average of 35 years was diagnosed with right upper lobe lung cancer (3.1*2.3*2cm) after a CT scan. The initial presentation included chronic cough accompanied by bloody sputum for over one month. PET/CT indicated primary central lung cancer and lymph node (LN) metastasis accompanied by distal atelectasis without distant or brain tumor invasion. Pathological examination revealed squamous cell carcinoma and hilar LN metastasis by EBUS-TBNA. PD-1 expression was more than 40%. No other gene mutations were detected. The bronchoscope found a neoplasm at the beginning of the right superior bronchia, and intermediate bronchus was suspected to be invaded (figure 1A). The diagnosis was c-T2aN1M0, stage IIb. Patient 's BMI was 22 (58kg/163cm), fev1% was 88% (2.5/2.82 L) and left ventricular ejection fraction was 66%.

Methods: Based on multidisciplinary team's assessment of the disease, if treated directly by surgery, the patient needed to undergo sleeve resection of the right upper lobe and resection of the intermediate bronchus. Concurrently, the bronchus of the middle lobe and lower lobe needed to be anastomotic to the right main bronchus respectively. Even pneumonectomy was under consideration. For less postoperative complications and better quality of life, two-cycle of neoadjuvant therapy completed 33 days before the surgery. Each cycle included 500mg carboplatin, 400mg albumin paclitaxel, and 200mg Sintilimab. The patient was expected to undergo a right upper lobectomy and systematic LN dissection. The adjuvant therapy with the same therapeutic schedule as neoadjuvant therapy would be applied.

Results: The patient was estimated as PR according to the rechecked bronchoscope and CT scan which showed the tumor decreased (2.5*1.5*1cm) (figure 1B). No side effects were recorded during medication. Intraoperative cryopathology showed a negative margin. Paraffin wax pathology resulted in less than 10% of tumor remaining, no residual tumor in LN, squamous cell carcinoma infiltrating bronchial mucosa. The pathological diagnosis was yp-T1N0M0 (MPR), stage Ia. The perioperative outcome was as follows: blood loss less than 100ml, 121 minutes of operating time, 180ml of pleural fluid volume, 3 days of chest tube duration, and 8 days of postoperative hospital stay, with no recorded postoperative complications. During the next 7 months of follow-up, no recurrence or metastasis was found.

Conclusions: Neoadjuvant therapy may have potential to simplify surgical treatment, which means down-stage to thoracic surgery, but benefit patients with the same oncology effect, negative margin, and better perioperative outcome.

Keywords: lung cancer, neoadjuvant therapy, thoracic surgery



EP.12A METASTATIC NON-SMALL CELL LUNG CANCER - TARGETED THERAPY - EGFR
SATURDAY, SEPTEMBER 7, 2024 - 11:58 - 11:59

EP.12A.01 Preclinical Characterization of a Potent, Selective, Brain-Penetrant Inhibitor of Osimertinib-Resistant EGFR Variants

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Introduction: Mutations in the epidermal growth factor receptor (EGFR) gene are found in approximately 15-40% of non-small cell lung cancer (NSCLC). Classical EGFR activating mutations, characterized by a short in-frame deletion in Exon 19 ("Del19") or the L858R missense mutation, lead to ligand-independent EGFR activation that drives mitogenic signaling. Third generation, irreversible tyrosine kinase inhibitors (TKIs) such as osimertinib, have become the standard of care and are used in first-line treatment of NSCLC with EGFR classical mutations. After first-line treatment with osimertinib, approximately 8% of patients relapse with an EGFR on-target mutation, C797S, which blocks covalent binding of third generation TKIs to EGFR. For these patients, there is an unmet need for next-generation EGFR TKIs with: (1) strong potency on EGFR variants containing C797S, (2) selectivity over EGFR wild-type (WT) to mitigate the cutaneous adverse events associated with EGFR WT inhibition, and (3) sufficient brain penetration to address brain metastasis.

Methods: Leveraging in silico physics-based techniques such as Free Energy Perturbation (FEP+), we have identified a potent, selective, and brain-penetrant EGFR inhibitor. We tested our compounds in biochemical assays for EGFR mutants and EGFR WT to measure potency, and evaluated cellular activity in vitro with phospho-EGFR target engagement assays and proliferation assays in cells expressing several EGFR variants. We measured anti-tumor activity of our lead compounds in vivo using tumor xenograft models. To quantify our EGFR WT selectivity in vivo, we compared phospho-EGFR inhibition in tumor xenografts with that in mouse skin.

Results: We have developed an orally-bioavailable, potent, selective, brain-penetrant inhibitor that is active against the C797S resistance mutation while sparing EGFR WT. Biochemical and cellular assays revealed nanomolar potency on EGFR Del19 and EGFR L858R, as well as the osimertinib-resistant mutants EGFR Del19/C797S and EGFR L858R/C797S. Our inhibitor demonstrated EGFR WT selectivity in vitro that is comparable to osimertinib using various cellular models of EGFR WT activity as well as human keratinocytes. In rodents, we observed brain penetration (Kpu,u > 0.3). Oral dosing led to tumor regression in multiple tumor xenograft models at well-tolerated doses that were correlated with tumor phospho-EGFR levels. The doses showing anti-tumor activity spared inhibition of mouse skin phospho-EGFR, which may lead to a therapeutic window that minimizes the cutaneous adverse effects of EGFR WT inhibition.

Conclusions: We have identified and optimized an orally-bioavailable, potent, selective, brain-penetrant EGFR inhibitor. Due to its potency on EGFR mutants with the C797S resistance mutation and the unmet medical need in that population, the preclinical package supports the development of this inhibitor in NSCLC patients that have progressed on osimertinib with a C797S resistance mutation.

Keywords: EGFR, osimertinib, resistance

EP.12A METASTATIC NON-SMALL CELL LUNG CANCER - TARGETED THERAPY - EGFR
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EP.12A.02 What is the Optimal First-Line Regimen for EGFR-Mutated Advanced Non-Small Cell Lung Cancer: A Network Meta-Analysis

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Introduction: Regimens based on epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) are the first-line and standard of care for patients with advanced EGFR-mutated non-small cell lung cancer (NSCLC). There are currently various TKI-based regimens available, and it can be challenging for clinicians to determine the most effective and safe option due to the lack of direct comparisons between these regimens. In this study, we conducted a network meta-analysis (NMA) comparing the efficacy and safety of distinct regimens to determine the optimal regimen for patients with EGFR-mutated NSCLC, thereby facilitating clinical decision-making.

Methods: The PubMed, Embase, Cochrane Library databases and international conference databases were comprehensively searched from their inception to 02 November 2023 for collecting data regarding efficacy and safety from eligible randomized controlled trials (RCTs). Following literature screening and data extraction, a NMA was conducted to compare the efficacy and safety among 21 regimens with a random-effects consistency model in a Bayesian framework using a Markov Chain Monte Carlo simulation technique within the GEMTC package.

Results: A total of 35 RCTs were included, of which 25 were phase III trials and 10 were phase II trials, involving 9718 individuals and 21 regimens. The primary study endpoint across all studies was progression-free survival (PFS). Compared with other interventions, combination therapies based on third-generation TKIs, especially osimertinib plus ramucirumab (OSI_RAM), showed the most favorable PFS prolongation in overall patients (Figure A). Consistently, subgroup analyses showed that third-generation TKIs-based combination regimens were superior to other regimens in most prespecified subgroups with distinct clinicopathological characteristics (Figure A). In terms of overall survival, despite the combination regimens based on third-generation TKIs also showing relatively superior outcomes, erlotinib plus chemotherapy and gefitinib plus chemotherapy were ranked more favorably (Figure B). In terms of safety profile, combination therapies based on third-generation TKIs did not significantly increase the incidence of grade 3 or higher adverse events compared with other regimens.

Conclusions: Combination regimens based on third-generation TKIs, especially OSI_RAM, showed superior efficacy compared with third-generation TKIs monotherapy or other regimens as first-line therapy in EGFR-mutated advanced NSCLC, along with an acceptable safety profile. Our study concluded that combination regimens based on third-generation TKIs (OSI_RAM, OSI plus chemotherapy, OSI plus bevacizumab, amivantamab plus lazertinib and aumolertinib plus apatinib) could be the new and clinically preferable first-line, standard of care for EGFR-mutated advanced NSCLC.

Keywords: epidermal growth factor receptor, non-small cell lung cancer, network meta-analysis

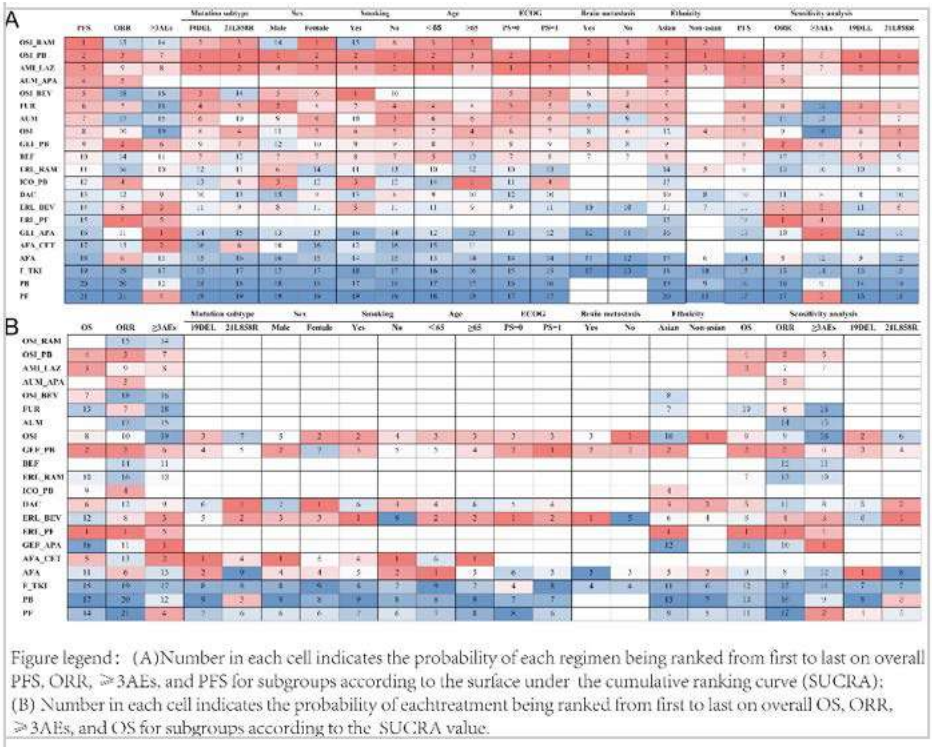

Figure legend: (A)Number in each cell indicates the probability of each regimen being ranked from first to last on overall PFS, ORR, ≥3AEs, and PFS for subgroups according to the surface under the cumulative ranking curve (SUCRA); (B) Number in each cell indicates the probability of eachtreatment being ranked from first to last on overall OS, ORR, ≥3AEs, and OS for subgroups according to the SUCRA value.

EP.12A METASTATIC NON-SMALL CELL LUNG CANCER - TARGETED THERAPY - EGFR
SATURDAY, SEPTEMBER 7, 2024 - 11:58 - 11:59

EP.12A.03 Overall Survival after Treatment with First-Line Osimertinib for EGFR-Mutant Advanced NSCLC in the US

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Introduction: Osimertinib is approved for first-line treatment of EGFR-mutated advanced non-small cell lung cancer (NSCLC). In the FLAURA study, median overall survival (OS) was 38.6 months and 2-year landmark OS was 74%. We assessed OS following first-line osimertinib using real-world data from large longitudinal US oncology databases.

Methods: This retrospective cohort study used electronic medical records from ConcertAI, Flatiron, and COTA. Patients with newly-diagnosed advanced/metastatic disease with exon 19 deletions or exon 21 L858R substitutions who initiated first-line osimertinib monotherapy between 18-Apr-2018 and 31-Oct-2022 were eligible. Patients were followed up until death, loss to follow-up, or 31-Oct-2023. Mortality data were captured from multiple sources from each database, ensuring completeness. OS was estimated using the Kaplan-Meier method.

Results: 432 patients from ConcertAI, 636 from Flatiron, and 234 from COTA were included (Table). Median age ranged from 68-71 years, 67%-70% were female, ECOG score of 0-1 in 49%-70%, and 34%-39% had CNS metastases.

The 24-month survival rate (95% CI) was 57% (53-63) in ConcertAI, 57% (53-61) in Flatiron, and 60% (53-67) in COTA (Figure) with corresponding median OS of 27.7, 28.8, and 29.2 months, respectively. Among patients with ECOG 0 or 1, the median OS was 30.7, 30 and 29.1 months, respectively. Between 26%-32% of patients died prior to 2nd line-of-therapy. Older age, CNS metastases, liver metastases, TP53 comutations, exon 21 L858R, and ECOG ≥2 were associated with higher mortality and shorter median OS. A pooled analysis including additional subgroups is underway.

Conclusions: We observed that real-world OS for osimertinib is lower than observed in clinical trial settings. Between one quarter and one third of patients die prior to receiving 2nd line-of-therapy. These results highlight the pressing need for innovative treatments to improve survival.

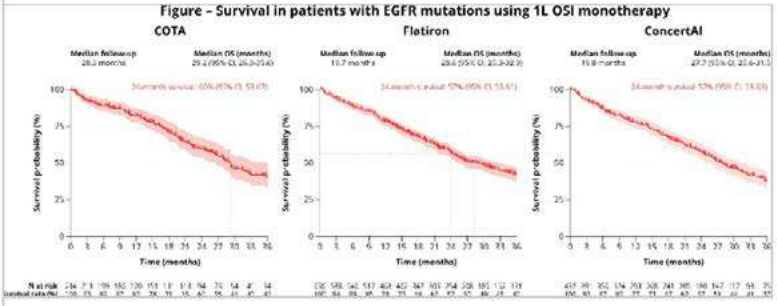
Keywords: osimertinib, overall survival, real-world observational cohort study

Table – Patient baseline and clinical characteristics in each database

		ConcertAI N=432	Flatiron N=636	COTA N=234
Age at index date	Median (range)	71 (35, 88)	69 (35, 85)	68 (36, 89)
Age group n (%)	≥65	296 (69)	41 (65)	142 (61)
	<65	136 (32)	226 (36)	92 (39)
Sex n (%)	Female	304 (70)	424 (67)	162 (69)
	Male	128 (30)	212 (33)	72 (31)
Race n (%)	White	294 (68)	352 (55)	140 (60)
	Asian	62 (14)	88 (14)	24 (10)
	Black/African American	42 (10)	40 (6)	26 (11)
	Other/Unknown	34 (8)	156 (24)	24 (10)
Smoking history n (%)	Non-smoker	270 (63)	350 (55)	124 (53)
	Smoker	154 (36)	286 (45)	100 (43)
Stage at initial diagnosis n (%)	I	22 (5)	34 (5)	6 (3)
	II	18 (4)	19 (3)	3 (1)
	III	35 (8)	37 (6)	12 (5)
	IV	353 (82)	540 (85)	213 (91)
Histology n (%)	Nonsquamous	428 (99)	619 (97)	227 (97)
ECOG at index date n (%)	0	124 (29)	202 (32)	45 (19)
	1	176 (41)	242 (38)	71 (30)
	≥ 2	77 (18)	93 (15)	50 (21)
	Unknown	55 (13)	99 (16)	68 (29)
CNS metastases at index* n (%)	Yes	163 (38)	213 (34)	92 (39)

ECOG, Eastern Cooperative Oncology Group; MRI, magnetic resonance imaging.
*Confirmed by MRI or other imaging.

Figure – Survival in patients with EGFR mutations using 1L OSI monotherapy



EP.12A METASTATIC NON-SMALL CELL LUNG CANCER - TARGETED THERAPY - EGFR
SATURDAY, SEPTEMBER 7, 2024 - 11:58 - 11:59

EP.12A.04 Patterns of Osimertinib Dose-Reduction and Impact on Outcomes in EGFR-Mutation Positive Non-Small Cell Lung Cancer

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Introduction: EGFR mutations are the most common targetable driver mutations found in lung adenocarcinoma. EGFR exon 19 deletion and exon 21 L858R mutations account for ~ 85% of the somatic EGFR alterations and predict sensitivity to EGFR tyrosine kinase inhibitor (TKI). Third generation TKI, osimertinib, has shown overall survival benefit and superior CNS activity compared to earlier generation TKIs in patients with treatment naive EGFR positive NSCLC. The impact of dose reductions/modifications on outcomes including CNS disease in real world setting has not been well characterized.

Methods: This was a retrospective study including 94 patients with NSCLC harboring classical EGFR mutations who received osimertinib therapy between 10/1/2017-10/31/2023 at the Ohio State University. Medical records were extracted via chart review and data was collected in REDCap. Demographics and clinical characteristics were summarized using descriptive statistics and compared between patients with and without dose reduction using Kruskal-Wallis test (continuous outcomes) and Fisher's exact test (categorical outcomes). Kaplan-Meier survival analysis was used to assess the survival outcomes. All statistical analysis was done in SAS 9.4

Results: Median age of 94 patients at diagnosis was 66.9 years (range 37-89). Our cohort included 64.9% females and 35.1% males, majority (77%) of patients were white, 10% Asian, 5.1% were African Americans, 3% other/unknown. All patients received first-line osimertinib. Twenty patients (21.5%) underwent dose reduction at any time during treatment. Median time to first dose reduction was 4.8 months (IQR: 0.6-34.5). Fatigue (25%), diarrhea (25%) and nausea (20%) were the most common reasons for dose reductions. Other causes included rash (15%), thrombocytopenia (10%), anemia (5%) and pneumonitis (5%). Median time on treatment with osimertinib was 8.3 months (IQR: 3.2-20.0) in patients who underwent dose reduction versus 9.2 months (IQR: 0.8-40.7) in patients without. CNS progression was seen in 57.1% of patients who underwent dose reduction compared to 31% without dose reduction (p=0.217). Median overall survival (OS) for the entire cohort was 26.7 months (95% CI: 20.73, 34.79). There was no significant difference in OS between patients who underwent dose reduction and those who did not. Patients who required dose reduction were older (mean age: 71.3 years) than those who did not require dose reduction (mean age: 65.2 years, p=0.03). There was no significant association between sex and dose reduction (p=0.2687). There was no significant association between race and dose reduction (p=0.07).

Conclusions: In our cohort, older patients more frequently required dose reduction with osimertinib therapy. Outcomes for patients with and without dose modifications were overall similar. Patients with dose reduction experienced higher rates of CNS progression, though this was not statistically significant in our study.

Keywords: NSCLC, EGFR, osimertinib

EP.12A METASTATIC NON-SMALL CELL LUNG CANCER - TARGETED THERAPY - EGFR
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EP.12A.05 Evaluation of the Role of VAF/cellularity as Proxy of Gene Aberration in EGFR Mutated Advanced NSCLC During Osimertinib

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Introduction: The efficacy of Osimertinib in EGFR mutated advanced non-small cell lung cancer (aNSCLC) is associated to type of EGFR mutations (EGFRm) and line of treatment. Recently, through the use of Next Generation Sequencing analysis (NGS), we have gained access to information regarding not only type of mutation but also clonality and genetic aberrancy that could help in identifying diversity of response to targeted treatments. We have previously demonstrated that variant allele frequency (VAF), as a proxy of clonality, did not impact in efficacy of Osimertinib as first line treatment in aNSCLC harbouring common EGFRm. We aimed to test if VAF/cellularity ratio (VAF/cell) could be better than VAF in highlighting differences in efficacy during Osimertinib treatment.

Methods: We retrospectively collected data of 84 aNSCLC harbouring a common EGFRm (Ex19dels or Ex21 L858R) treated with at least one cycle of first-line Osi from January 2019 to March 2023 at Fondazione IRCCS Istituto Nazionale Tumori of Milan. NGS analyses were performed at baseline using three different panels (evaluating respectively: Custom panel 7 genes, Hotspot Panel 50 genes, Oncomine Cancer Assay plus DNA 500 genes). Patients were divided into two subgroups according to median (medHigh vs medLow) VAF/cell. Moreover, a subgroup analyses according 3rd quartile (3QVAF/cell) cutoff (3QHigh vs 3QLow) was performed, postulating that an increase VAF/cell ratio may be a surrogate of large genomic aberration or amplification involving EGFR. Median progression free survival (mPFS) differences between subgroups were analysed. Survivals were estimated through Kaplan-Meier method and compared by Cox-proportional Hazard model.

Results: In our cohort, VAF/cell has a positive skewed distribution with mVAF/cell 0,74 and 3QVAF/cell 1,13. With a median follow up of 24,8 months (mo), mPFS in the overall population was 20,9 mo (0.95CI 15-31,1). No differences in mPFS were found according to panel used (p=0.5) and mVAF/cell (HR 0,7, p=0.25: medHigh 26,4 mo, 0.95CI 16-54,5 vs medLow 20,3 mo, 0.95CI 11,9-37,4). Intriguingly, a trend toward a worse PFS was seen if patients were divided according 3QVAF/cell cutoff (HR 1,83, p=0.09: 3QLow 13,5 mo, 0.95CI 11,7-NA vs 3QHigh 23,3 mo, 0.95CI 16-42).

Conclusions: Our study suggests that EGFRm VAF/cell may represent a more reliable surrogate than tumour clonality, as it may be able to highlight genomic imbalance involving EGFR. In particular, a higher VAF/cell ratio may represent a proxy of tumours with aberration involving EGFR, such as loss of heterozygosity or copy number gain, that could give worse outcome during Osimertinib treatment.

Keywords: NSCLC, EGFR, NGS

EP.12A METASTATIC NON-SMALL CELL LUNG CANCER - TARGETED THERAPY - EGFR
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EP.12A.06 Diarylheptanoid 35d Overcomes EGFR TKI Resistance by Inducing EGFR Degradation in EGFR-Mutant Lung Adenocarcinoma

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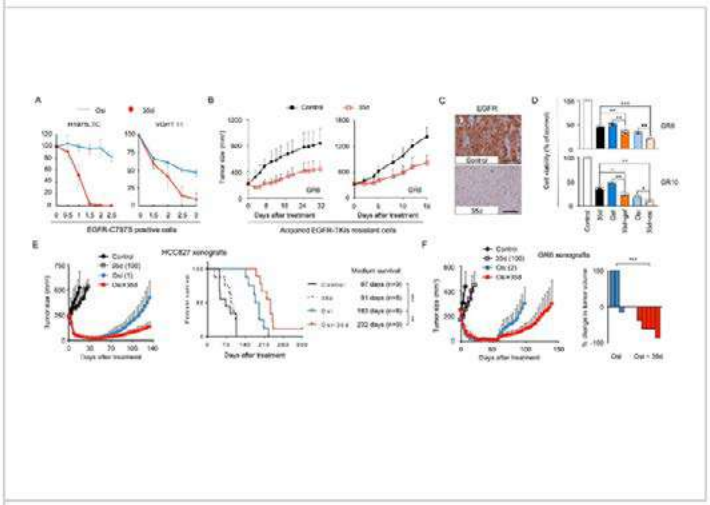
Introduction: EGFR-mutant lung adenocarcinomas (LUAD) patients often respond to EGFR tyrosine kinase inhibitors (TKIs) initially, but eventually develop resistance to TKIs. The switch of EGFR downstream signaling from TKI-insensitive to TKI-insensitive is a critical mechanism driving resistance to TKIs. Identification of potential therapies to target EGFR effectively is a potential strategy to treat TKI-resistant LUADs.

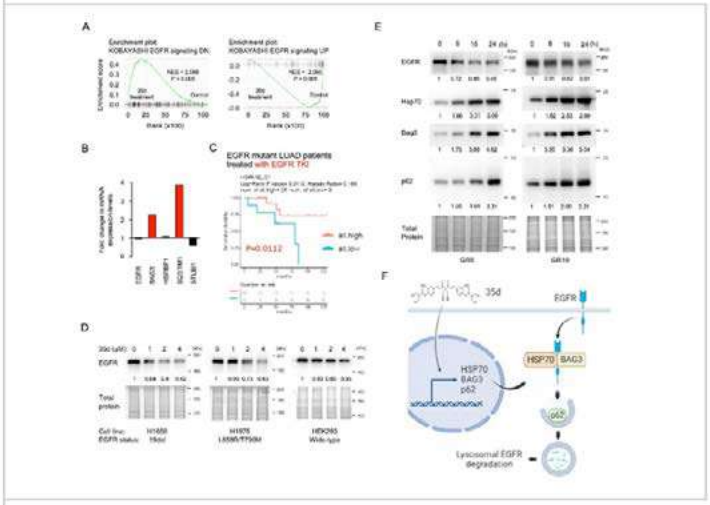
Methods: EGFR mutant TKI-sensitive and multiple TKI-resistant LUAD cells were investigated to examine the effects of 35d and Osimertinib in vitro and vivo. Global transcriptome analysis by RNA-sequencing was used to explore the specific mechanisms in TKI-resistant cells treated with 35d. Body weight monitoring and histology morphology analysis of multiple tissues form the mice bearing TKI-resistant tumors were performed to examine the long-term safety of the Osimertinib-35d combination treatment. Correlation between HSPA1B expression and survival in LUAD patients was performed based on the east Asia cohort of LUAD obtained from OncoSG.

Results: Diarylheptanoid 35d effectively suppressed EGFR protein expression, killed multiple TKI-resistant LUAD cells in vitro, and suppressed tumor growth of EGFR-mutant LUAD xenografts with variant TKI-resistant mechanisms including EGFR C797S mutations in vivo. Furthermore, our data showed that combination of 35d significantly inhibits tumor re-progression on Osimertinib and prolongs mice survival. Mechanically, 35d triggers hsp70-mediated lysosomal pathway through transcriptional activation of several components in the pathway, such as HSPA1B, to induce EGFR protein degradation. Clinical significance analysis in LUAD showed that higher HSPA1B expression in LUAD tumors associated with longer survival of EGFR-mutant TKI-treated patients.

Conclusions: Collectively, our results suggest that 35d as a promising lead compound to suppress EGFR expression and provide important insights into the development of combination therapies for TKI-resistant LUADs, which could have translational potential for the treatment of this deadly disease.

Keywords: EGFR, lung cancer, EGFR-TKI resistance





EP.12A METASTATIC NON-SMALL CELL LUNG CANCER - TARGETED THERAPY - EGFR
SATURDAY, SEPTEMBER 7, 2024 - 11:58 - 11:59

EP.12A.07 Restoring Expression of Tumor Suppressor PTEN by Engineered Circular RNA Enhances Osimertinib Sensitivity in Non-Small Cell Lung Cancer

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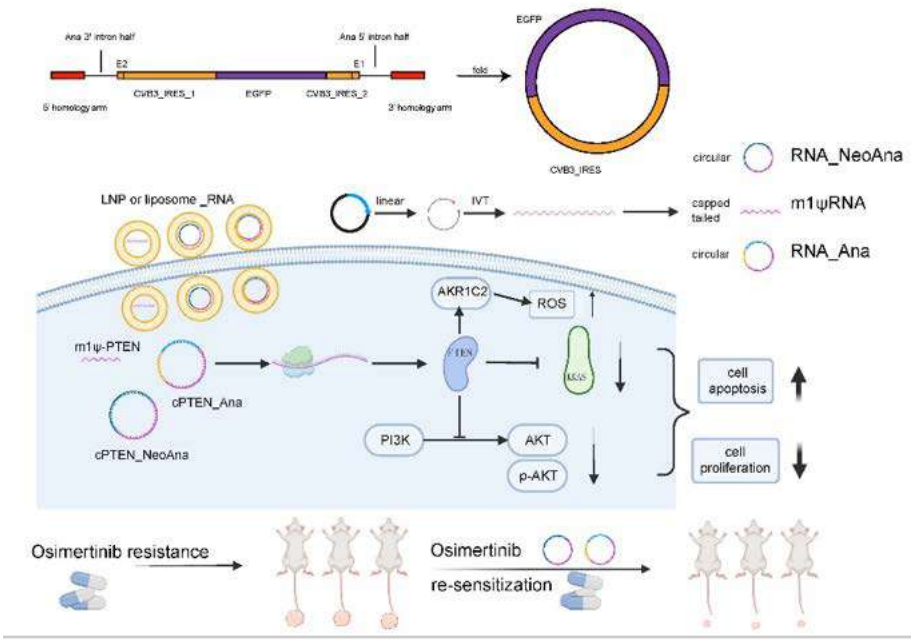
Introduction: The tumor suppressor PTEN directly inhibits PI3K/AKT pathway, which is con activated in lung cancer cells with oncogenic mutations of EGFR, but loss expression of PTEN protein is common in lung cancer. It is hypothesized that restoring PTEN expression may be a therapeutic strategy for Osimertinib-resistant lung cancer.

Methods: Circular RNAs (circRNAs) are covalently closed single-stranded RNAs that are resistant to exonuclease-mediated degradation. Compared with linear mRNA, circular RNA is more stable and efficient as translate templates, thus circRNA has been considered as "the next generation" of mRNA. By splicing CVB3 IRES into 2 parts, we developed a new Group I permuted intron-exon (PIE) self-splicing system (named NeoAna) for in vitro circRNA synthesis. Then, a microfluid system was established to synthesize lipid nanoparticles for circRNA delivery. Osimertinib-resistant HCC827 and PC9 cells were used for in vivo and in vivo experiments.

Results: First, we established the NeoAna system to synthesize circRNA transcripts in vitro without extra sequences in final products. CircRNA engineered by NeoAna system has minimized immunogenicity, enhanced stability, and longer protein translation duration. A circRNA template (cPTEN_NeoAna) was synthesized with to restore PTEN protein expression. Indeed, cPTEN_NeoAna significantly decreased proliferation of Osimertinib-resistant lung cancer cells and induced apoptosis. In mice bearing xenograft tumor of Osimertinib-resistant cells, intratumor delivery of cPTEN_NeoAna plus Osimertinib significantly reduced tumor growth and tumor volume compared with Osimertinib only. In addition, cPTEN_NeoAna is slightly superior to PTEN circular RNA synthesized with conventional PIE system or m1ψ-PTEN in enhancing Osimertinib sensitivity both in vitro and in vivo. Mechanically, in addition to inhibition of PI3K-AKT pathway, restoring PTEN expression in Osimertinib-resistant cells also decreased KRAS protein expression. cPTEN_NeoAna also increases the sensitivity of Osimertinib by decreasing AKR1C2 expression and increasing intracellular ROS levels in Osimertinib-resistant cells.

Conclusions: Overall, the NeoAna provides an alternative circRNA platform for RNA medicine and restoring PTEN expression could be a promising strategy to overcome EGFR-TKI resistance.

Keywords: Osimertinib resistance, PTEN delivery, RNA therapy



EP.12A METASTATIC NON-SMALL CELL LUNG CANCER - TARGETED THERAPY - EGFR
SATURDAY, SEPTEMBER 7, 2024 - 11:58 - 11:59

EP.12A.08 Furmonertinib as First-Line Therapy for Chinese Patients with EGFR Mutation-positive NSCLC: A Real-World Study

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Introduction: Furmonertinib is the standard treatment option in the first-line setting for locally advanced or metastatic non-small cell lung cancer (NSCLC) with sensitive epidermal growth factor receptor (EGFR) mutations in China. However, there is limited real-world data available.

Methods: We conducted a retrospective study at a single center, analyzing a cohort of 72 NSCLC patients who tested positive for EGFR mutations and were treated with Furmonertinib as their initial therapy between August 2022 and March 2024. The primary endpoint was progression-free survival (PFS), with secondary endpoints including objective response rate (ORR), overall survival (OS), and safety profile.

Results: The median follow-up was 14.7 months (95% confidence interval [CI], 14.3-15.1). The ORR was 77.8% (95%CI, 67.9 - 87.6). The intracranial ORR was 84.6% (95%CI, 69.8-99.5). The median PFS was 19.9 months (95%CI, 14.4 - 25.4). mPFS for patients without brain metastases was not reached, and mPFS for patients with brain metastases was 16.7 months (95%CI, 14.7 - 18.6). Univariate analysis found that age (<65 years vs ≥65 years, P=0.031), smoking status (yes vs no. P=0.042), liver metastases (No vs Yes, P=0.000) and ECOG score (0/1 vs 2, P=0.000) were associated with a poor prognosis. However, multivariate analysis indicated a potential trend towards extended PFS in patients younger than 65 years (p=0.055, HR 0.42, 95%CI, 0.17-1.02), although the p-value was only marginally significant. Adverse events were noted in 24 patients who received furmonertinib as a first-line treatment. Diarrhea (8.3%) (6/72), anemia (12.5%) (9/72), and liver injury (9.7%) (7/72) were the most frequently reported adverse events. Grage 3 or above were found in 5.6% (4/72) patients.

Conclusions: In a real-world setting, Furmonertinib appears to be a favorable treatment option for EGFR mutation-positive NSCLC patients. The manageable nature of adverse events further supports its use in clinical practice.

Keywords: NSCLC, EGFR, Furmonertinib

EP.12A METASTATIC NON-SMALL CELL LUNG CANCER - TARGETED THERAPY - EGFR
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EP.12A.09 Oligoprogression and Osimertinib Continuation Post-progression in Patients with EGFR-Mutations.

V. Mai, J. Lee, L. Zhan, M.C. Brown, K. Balaratnam, K. Khan, S. Cheng, S. Barghout, F. Al-Agha, R. Raptis, K. Kuang, L. Eng, A.G. Sacher, P.A. Bradbury, N.B. Leighl, M. Cabanero, R. Hsu, P. Pal, M.S. Tsao, F.A. Shepherd, W. Xu, G. Liu, University Health Network, Toronto/ON/CA

Introduction: Treatment post-progression is commonly observed with many tyrosine kinase inhibitors (TKI) for non-small cell lung cancer. We evaluated the outcomes of patients on osimertinib who were treated versus not treated post-progression, stratified on whether there was oligoprogression versus systemic (non-oligo)-progression.

Methods: Patients at Princess Margaret Cancer Centre (Toronto; CARMA-BROS NCT:04151342) diagnosed from December, 2011 to June, 2021 with classical EGFR mutations who failed osimertinib (after any line) were analyzed for their clinico-demographic data, sites of progression, subsequent treatments and outcomes. Oligoprogression was defined as having five or fewer sites of progression in a maximum of two organs, all identified within 60 days of the first progression on osimertinib.

Results: Of 127 patients progressing on osimertinib, 31% received first-line; remainder as subsequent-line; 4% had clinical progression only; 54% met radiological definition of oligoprogression, of which 59% continued osimertinib post-progression for at least 60 days; amongst all patients having oligoprogression, there was a median of 4.6 (95%CI:1.4-7.1) months continuing osimertinib from first date of progression. In contrast, among the 43% who had systemic (non-oligo)-progression, only 35% continued osimertinib post-progression for at least 60 days; the median time on osmertinib post-progression amongst all patients with systemic progression was 1.1 (95% CI:0.5-2.0) months. Among patients evaluable post-progression, Kaplan-Meier curves from date of progression to time of osmertinib discontinuation are presented in Figure. Only 24% had molecular testing at osimertinib-progression, with 53% with secondary mutations, 4% neuroendocrine-transformed, and 4% sarcomatoid-transformed. Almost half (48%) received no subsequent therapy post-osimertinib: older patients ($p<0.001$) and those with poorer performance status at time of osimertinib-progression ($p=0.01$) were less likely to receive subsequent therapy. Increasing age was also associated with worse performance status ($p=0.06$). Those not receiving subsequent therapy had a median OS of only 0.3 (95% 0-0.8) months, of which half had died while still on osimertinib; those receiving subsequent therapy had a median OS of 8.2 (95%CI 6.0-11.4) months. Among those receiving subsequent therapy, 73% received chemotherapy, 20% received TKI/trial, and 8% received immunotherapy-based treatments. Lung/pleura, bone and brain were the most common sites of progression with osimertinib.

Conclusions: Osimertinib treatment post-progression provided benefit (median 4.6 months) in patients with EGFR-mutations in the oligoprogression setting, but not when there is systemic progression. However, almost half the patients received no subsequent therapy, particularly older patients and those with poor performance status, thus identifying an unmet need for osimertinib replacements and in the post-osimertinib setting.

Keywords: Osimertinib, Non-small cell lung cancer, Metastatic

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EP.12A.10 Multi-Omics Uncovers Signatures Associated with Resistance to Osimertinib in EGFR-Mutant Non-Small Cell Lung Cancer Patients

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Introduction: Targeted therapy with tyrosine kinase inhibitors (TKIs) against Epidermal Growth Factor Receptor (EGFR) is part of clinical routine for around 10-15% of advanced non-small cell lung cancer (NSCLC) patients with tumors harboring activating mutations in the kinase domain of EGFR. Osimertinib is a third-generation EGFR TKI displaying potency to both activating kinase domain EGFR mutations and the T790M gatekeeper mutation. Osimertinib is approved by the FDA and EMA for usage in the first-line setting to NSCLC patients with EGFR activating mutations regardless of presence of T790M. Despite improved clinical response following osimertinib treatment compared to treatment with first-generation EGFR TKIs, resistance is inevitable. Intriguingly, a significant fraction of resistant cases following osimertinib treatment cannot be linked to additional genetic aberrations. Here we analyzed if circulating RNAs, including mRNAs and microRNAs, as well as circulating proteins could provide clues of molecular factors associated with acquired resistance to osimertinib.

Methods: Plasma was collected at baseline and progression of disease using paired samples from 20 patients enrolled in the multicenter phase II study First-line treatment with osimertinib in EGFR-mutated non-small cell lung cancer (FIOL). Plasma was centrifuged at 16000g followed by exosomal RNA extraction using Qiagen exoRNeasy Midi kit according to manufacturers' instructions. Total RNA was subjected to paired-end 150 Illumina sequencing (mRNA-seq, lncRNA-seq) or single-end 50 Illumina sequencing (microRNA-seq). For systematic protein analysis, plasma was subjected to the SomaLogic SomaScan 7K Assay Kit.

Results: Systematic transcriptome profiling revealed hundreds of differentially expressed mRNA transcripts, adjusted p-value <0.05, while only 13 microRNAs and 21 proteins displayed differential expression using an identical statistical cutoff. Interestingly, 20 out of 21 differentially expressed proteins were upregulated at disease progression while 12 out of 13 differentially expressed microRNAs were downregulated at disease progression. Baseline samples clustered in a distinct manner compared to samples from disease progression when using mRNAs and lncRNAs as input. We are currently investigating the therapeutic impact of modulating the expression of top-candidate RNAs and proteins in cell lines with acquired resistance to osimertinib. Additional data will be presented at the meeting.

Conclusions: Our study demonstrates the usage of circulating RNAs and proteins from plasma to unveil resistance signatures to the third-generation TKI osimertinib. Furthermore, it highlights the involvement of multiple RNAs and proteins of potential functional impact in osimertinib-refractory NSCLC patients.

Keywords: Non-small cell lung cancer, Osimertinib, Resistance

EP.12A METASTATIC NON-SMALL CELL LUNG CANCER - TARGETED THERAPY - EGFR
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EP.12A.11 Effect of Antibiotic Exposure on the Efficacy of EGFR TKIs in Patients with Advanced EGFR Mutation-Positive Non-Small Cell Lung Cancer (NSCLC)

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Introduction: Infections are often associated with clinical deterioration of advanced NSCLC. Most antibiotics induce dysbiosis in the gut microbiome affecting immune homeostasis and deregulating metabolism. The effect of antibiotic use on the efficacy and toxicity of EGFR-TKIs should be explored.

Methods: This study was a historical cohort design. Data analysis was performed on patients with advanced EGFR mutation-positive NSCLC treated with the first line of EGFR TKIs at Phramongkutklao Hospital, Bangkok, Thailand. The primary endpoint was progression-free survival (PFS). The secondary endpoints were overall survival (OS), objective response rate (ORR), and treatment-related toxicity. Statistical analysis was performed with univariate tests, and multivariate models to evaluate the differences.

Results: A total of 189 eligible patients were enrolled. Twenty-nine of 189 patients (15.3%) were in the antibiotic use group (group A), and one hundred sixty of 189 patients (84.6%) were in the no antibiotic use group (group B). The median PFS of patients in group A, and patients in group B were 5.9 months (95%CI 3.68-8.25), and 11 months (95%CI 9.54-12.46) (p-value=0.005), respectively. The median OS of patients in group A, and group B were 9.3 months (95%CI 5.17-13.49), and 23 months (95%CI 17.74-28.26) (p-value=0.015). The objective response rate of patients in group A, and group B were 35.7%, and 61.29% (p-value=0.012). On multivariate analysis, antibiotic use was independently associated with shorter OS. Patients in group A had a statistically significant increased incidence of transaminitis compared with patients in group B (10.34% vs 1.88%, p-value=0.04).

Conclusions: Antibiotic use independently decreased both PFS and OS. The antibiotic use could be an independent predictor of shorter clinical outcomes (including PFS, OS, and ORR), and higher incidence of mild-grade transaminitis in patients with advanced EGFR mutation-positive NSCLC treated with first-line EGFR TKIs.

Keywords: EGFR TKIs, Antibiotic use, Advanced NSCLC

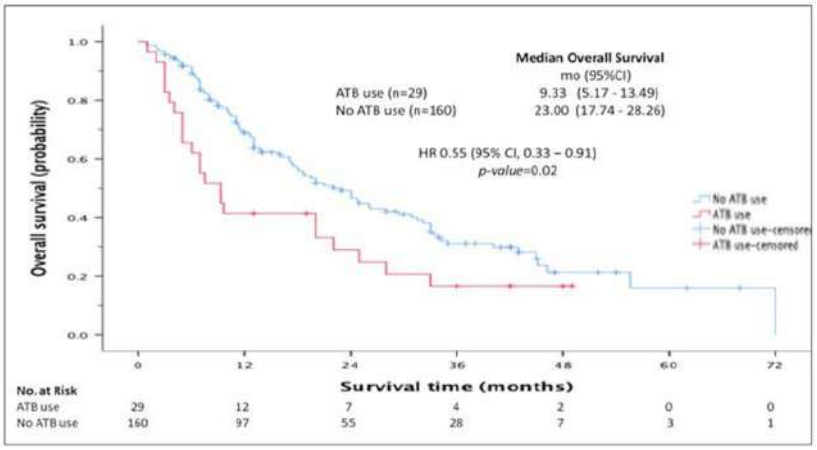

Figure 2. Kaplan-Meier curves comparing overall survival (OS) in between both groups; patients with the antibiotic use group (group A), and patients without the antibiotic use (group B).

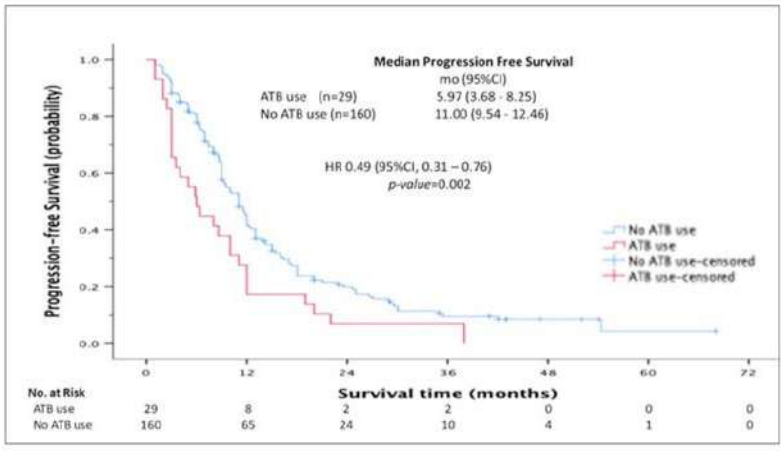

Figure 1. Kaplan-Meier curves comparing progression-free survival (PFS) in between both groups; patients with the antibiotic use group (group A), and patients without the antibiotic use (group B).

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EP.12A.12 Lazertinib as Second-Line or Greater Treatment is More Effective in Patients who Showed Extended Response to Prior TKI in Advanced NSCLC

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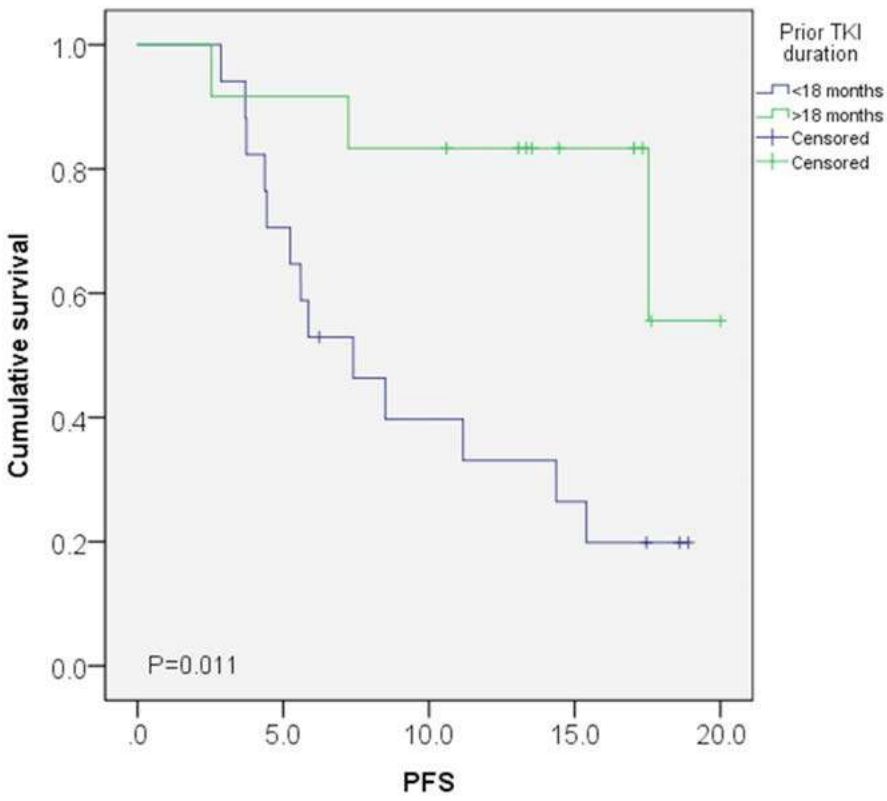
Introduction: Lazertinib is an oral, third-generation EGFR-TKI, and it specifically targets the EGFR T790M mutation along with activating mutations Ex19del and L858R. More real-world data are needed to evaluate its efficacy and safety in treating locally advanced and metastatic non-small cell lung cancer (NSCLC) following prior EGFR TKI treatment.

Methods: This multicenter retrospective study was conducted at seven university hospitals affiliated to Catholic Medical Center (CMC) in Korea. A clinical data warehouse (CDW) platform was used to access and extract information.

Results: Total of 48 patients were assessed. The majority were female (75%) and diagnosed with adenocarcinoma (95.8%). Patients had exon 19 deletion in 56.3 and L858R mutation in 41.7%. The median progression-free survival (PFS) was 15.4 months. At 6, 12, and 18 months, PFS rates were 79.1%, 53.6%, and 27.3%, respectively. When PFS was analyzed by prior TKI duration (<18 months vs >18months), significant differences were noted at the 6 and 9-month marks (P=0.013 and P=0.010, respectively). In multivariate analyses for PFS, only prior TKI duration and ECOG score showed statistical significance (P=0.026 and P=0.049, respectively). In multivariate analysis for OS, ECOG score showed statistical significance (P=0.006). Among 48 patients, 34 (70.8%) experienced adverse events (AEs) related to lazertinib. The most frequent AEs were skin reaction (29.8%), diarrhea (21.3%), and peripheral neuropathy (20.8%).

Conclusions: The results suggest that lazertinib is effective in 2nd or more line settings, with tolerable safety profile. More patients' data are necessary to find possible prognostic markers associated with outcomes of the patients.

Keywords: lazertinib, non-small cell lung cancer, EGFR mutation



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EP.12A.13 CRISPR with Double Mismatch Guide RNA Enhances Detection EGFR Mutation in Circulating Cell-Free DNA of Lung Cancer Patients

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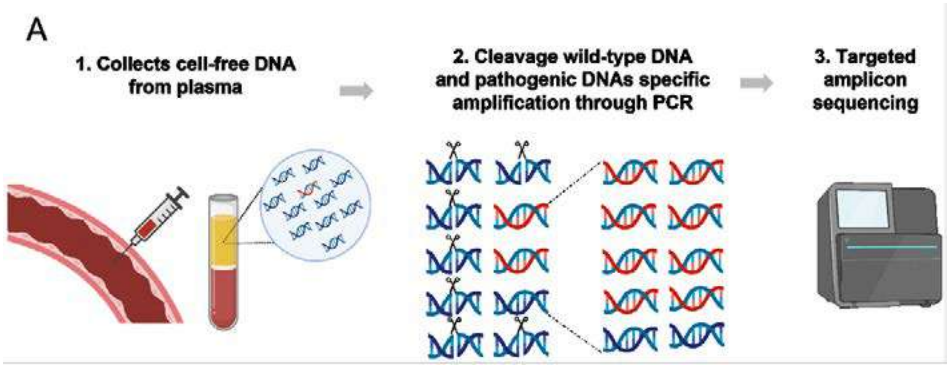
Introduction: Many efforts have been made to detect the pathogenic mutated DNA from cell-free circulating DNA (cfDNA) in blood, which is less invasive and more practical than tissue biopsy that requires complicated surgical procedures. But detection of mutated DNA in blood by high throughput sequencing is hampered by their sparsity.

Methods: In this study, we have developed a highly sensitive system that can amplify rare mutated DNA in a patient's blood to the extent enough to make a reliable detection by selectively removing normal DNA using CRISPR/Cas12a, called as the CRISPR/Cas12a amplification system. Using CRISPR/Cas12a amplification system, we sought to detect EGFR L858R and exon 19 deleted mutation, known as biomarkers related to NSCLC, in cfDNA of 48 patients with non-small cell lung cancer (NSCLC).

Results: As a result, we successfully verified that our amplification method could detect mutated DNA in all 7 L858R positive samples and 6 of 11 exon 19 deletion positive samples previously diagnosed from tissue biopsy. It showed that our method can be utilized to prevent unreliable diagnosis.

Conclusions: In conclusion, our CRISPR/Cas12a amplification system was proved to be a robust validation tool for detection of EGFR mutations from cell-free DNA and suggested that this technique can be applied to various genetic diseases.

Keywords: CRISPR, EGFR mutation, Cell-free circulating DNA



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EP.12A.14 Multicentered Real-World Evidence of Osimertinib Treatment in EGFR-Mutant Advanced Non-Small Cell Lung Cancer (NSCLC) In Thailand

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Introduction: Osimertinib is the only available third-generation EGFR-TKI in Thailand. Only Civil Servant Medical Benefits Scheme (CSMBS) patients could reimburse osimertinib as the second- or later-line treatment for T790M-mutant patients. Universal Coverage (UC) and Social Security Scheme (SSS) patients have to pay out of pocket. We aimed to explore the utility and outcomes of osimertinib usage in real-world basis from multi-university-based centers in Thailand.

Methods: EGFR-mutant (EGFRm) advanced lung cancer patients received any lines of osimertinib treatment during 2015-2023 were enrolled from 5 university-based hospital. Medical records were reviewed. Overall survival (OS) and progression-free survival (PFS) were estimated by Kaplan-Meier method.

Results: Total of 483 patients were included. Only 81 patients (17%) received osimertinib as first-line (1L) treatment while 54% received as the second-line (2L) treatment to overcome T790M. Liquid biopsy was a major technique (67.4%) for T790M detection. Seventy percent of patients were female with median age of 66 and were non-smokers (70%). Most patients could reimburse osimertinib under CSMBS (55%) and self-pay (45%). At a median follow-up time of 17.4 months, there was statistically significant difference in PFS between 1L-treated patients at 25.3 months and 2L-treated patients at 11 months [HR=2.3, 95% CI (1.65-3.19), P<0.001] (Figure 1A). However, sequencing of osimertinib treatment did not significant affect the OS (P=0.792). The overall-response rate (ORR) was significantly higher in the 1L-treated patients compared to 2L or later-treated patients (74% vs 50%, P <0.001). In both 1L and 2L-treated settings, dose-reduction/interruption occurred 19% and did have significantly longer OS compared to no dose-reduction/interruption patients (Figure1B). Brain metastases at baseline were found at 37% for 1L-treated patients and 32% for 2L-treated patients, both groups of patients had only 10% CNS progression. Self-pay/Insurance and CSMBS/State enterprise patients had significantly longer OS compared to UC patients. Eighteen percent of patients had adverse events which were mostly grade 1-2. Only 3 patients had grade 3 pneumonitis which led to stop treatment.

Conclusions: This real-world study showed osimertinib's efficacy in survival, ORR, CNS control, and tolerability in both 1L and 2L to later-line treatment in Thai population. Dose-reduction and dose-interruption did not lower the treatment efficacy. Our study showed early initiation of treatment is associated with better outcomes, but if the patients could reimburse the drug in all healthcare schemes as the 2L or later-line of treatment, this will be very useful for a lot of patients in Thailand whom could not access to the drugs.

Keywords: Osimertinib, EGFR-mutant, Advanced NSCLC

Figure 1: Survival outcomes

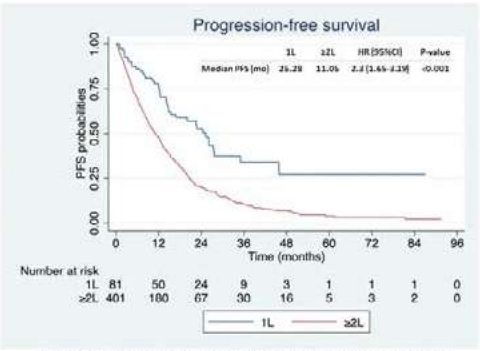

Figure 1A: Progression-free survival according to line of treatment

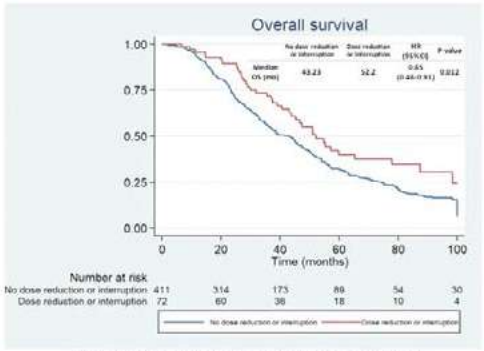

Figure 1B: Overall survival according to dose adjustment

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EP.12A.15 ACTN4 as a Predictive Biomarker for Osimertinib Efficacy in EGFR Mutant Non-Small Cell Lung Cancer

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Introduction: Actinin-4 (ACTN4) is an actin-bundling protein involved in cancer invasion and metastasis. This study aimed to evaluate the potential of ACTN4 expression as a predictive biomarker for osimertinib efficacy in EGFR mutant non-small cell lung cancer (EGFR-mt NSCLC).

Methods: We retrospectively analyzed 63 patients with EGFR-mt NSCLC treated with osimertinib as a first-line therapy at Nippon Medical School from August 2018 to October 2021. Immunohistochemistry staining of tumor tissues before the initiation of osimertinib administration was performed. Patients were categorized as ACTN4-positive (ACTN4(+)) if ≥30% of tumor cells were ACTN4-positive, and ACTN4-negative (ACTN4(-)) if <30%. We compared progression-free survival (PFS) and overall survival (OS) between these groups, employing the Inverse Probability of Treatment Weighting (IPTW) method to adjust for background characteristics.

Results: Among 63 patients (median age, 73 [34-89] years; female, 41; ECOG PS 0-1, 52; adenocarcinoma, 63; EGFR 19del/L858R/uncommon, 32/24/7), 33 patients were classified in ACTN4(+) group and 30 patients were classified in ACTN4(-) group. The IPTW-adjusted OS of patients in the ACTN4(+) group was significantly shorter than that of patients in the ACTN4(-) group (median, 33.7 [95% CI, 24.2-NR] months versus 50.7 [95% CI, 49.7-NR] months; HR, 2.76 [95% CI, 1.02-7.45]; p = 0.037). The IPTW-adjusted PFS of patients in the ACTN4(+) group was significantly shorter than that of patients in the ACTN4(-) group (median, 12.3 [95% CI, 5.3-15.6] months versus 16.9 [95% CI, 13.3-22.3] months; HR, 1.87 [95% CI, 1.01-3.48]; p = 0.035).

Conclusions: IPTW analysis revealed that ACTN4 expression was a useful biomarker for identifying patients with poor efficacy of osimertinib. ACTN4 expression may be a predictive biomarker for the poor efficacy of osimertinib in EGFR-mt NSCLC. Based on ACTN4 expression in tumors, the development of treatments for EGFR-mt NSCLC may be considered.

Keywords: non-small cell lung cancer, EGFR, Osimertinib

Survival	Black	Asian	White	Sig.
Erlotinib (n=110)				
mPFS	10m[5-15]*,&	20m[15-26] *	17m[13-21]&	***p=0.025 &p=0.009**
mOS	34m[3-65]*	64m[27-82]*,&	31m[24-38]&	*p=0.223 &p=0.264
Osimertinib (n=169)				
mPFS	9m[7-11]*,&	17m[11-23]*	16m[12-20]&	*p=0.192 &p=0.251
mOS	24m [13-38]*	39m [21-49]*,&	38m [15-43]&	*p=0.154 &p=0.179

EP.12A METASTATIC NON-SMALL CELL LUNG CANCER - TARGETED THERAPY - EGFR
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EP.12A.16 High-Dose Aumolertinib Combined Intrathecal Chemotherapy for the Treatment of EGFR-Mutated NSCLC with Leptomeningeal Metastasis

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Introduction: Leptomeningeal metastases (LMs), the spread of tumor cells into the leptomeninges and CSF, had a poor prognosis and limited treatment efficacy in advanced NSCLC with a median survival limited to 3 months. Due to the different sites of invasion, the manifestations of LM are complex and diverse, and lack of specificity. Meningeal irritation, intracranial hypertension, cranial nerve damage and even spinal cord injury are common manifestations. The incidence of LMs was reported approximately 9.4% in epidermal growth factor receptor (EGFR) mutation patients. Several therapeutic options had been applied to manage LMs. Some studies had shown that high-dose of third-generation EGFR-TKIs can significantly prolong PFS to 8.6 months. Implement intrathecal chemotherapy has also shown positive effects.

Methods: We report five first-line or treated L858R EGFR-mutated patients (pts) with LMs, with a median age of 56 years, who are mostly female (80%). The most common co-mutations were TP53 and DNMT3A, and 2 pts were combined with T790M mutations. All pts received third-generation EGFR-TKI Aumolertinib (165mg orally once daily) combined intrathecal pemetrexed chemotherapy (Ommaya reservoir). Pemetrexed was performed in different doses depending on the individual patient's tolerance. In the initial stage (cycles 2-4), 2 pts were given 30 mg (administered on days 1 and 8) once every 3 weeks (group A); 2 pts were given 30mg D1 q3W (group B:); 1 pt was given 10mg D1, 8, 15 q3W (group C). All pts received 30mg q4W as maintenance therapy.

Results: As of March 20, 2024, the median treatment duration was 10 months. Objective response rate (ORR) and disease control rate (DCR) were 60% and 100%, respectively. The intracranial ORR was 100%. It is noteworthy that the median ECOG PS was 3 before treatment and decreased to 1 after combination therapy. LM-related symptoms improved significantly in all pts after 3 weeks of treatment. After 6 weeks combination treatment, the brain MRI of all pts showed a significant decrease in LM lesions; and the lesion of 1 patient (group A) intracranial complete response (CR) with the continuation of treatment. In our long-term follow-up of 1 patient (group A), CEA levels in CSF and blood were observed to be positively correlated with remission, while cfDNA levels in CSF and blood showed irregular fluctuations. All pts reported ≥1 treatment-related AEs (TRAEs), most of the AEs were related to chemotherapy. 2 pts had grade 3 TRAE, and none had grade 4 TRAE. Leukopenia, anemia, serum creatinine increase, dizziness, nausea, vomiting, and decreased appetite were the most common AEs.

Conclusions: Our case series demonstrated that aumolertinib(165mg) combined Ommaya reservoir intrathecal chemotherapy had a positive efficacy on LMs from NSCLC, which has rapid and long remission period of LM lesions. Overall, high-dose aumolertinib showed controllable toxic side effects, and significant improvement ECOG PS of pts. The case series provide a feasible strategy for clinical treatment decision, the long-term follow-up data and large sample prospective studies are required for further validation.

Keywords: Aumolertinib, Leptomeningeal metastasis, Intrathecal Chemotherapy

EP.12A METASTATIC NON-SMALL CELL LUNG CANCER - TARGETED THERAPY - EGFR
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EP.12A.17 Impact of Osimertinib and Cranial Therapy on EGFR-Mutated Lung Cancer with Brain Metastasis: A Single-institution Retrospective Study

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Introduction: The third-generation tyrosine kinase inhibitor (TKI), Osimertinib, has demonstrated exceptional CNS activity in the FLAURA study. Multiple first-line treatment options are available for EGFRmt NSCLC, including TKI therapy at 80 mg orally daily with or without initial cranial local therapy (CLT). Failure pattern analyses revealed that 51.8% of patients not receiving initial CLT developed their first progressive disease in the brain, and 59.0% of cranial progression occurred solely at the original sites. This suggests the potential clinical importance of initial CLT. The Bloom study further showed that Osimertinib, administered at 160 mg once daily, exhibited significant therapeutic effectiveness in the CNS and a manageable safety profile for EGFRm NSCLC patients with leptomeningeal disease.

Methods: This retrospective study aims to delineate the clinical characteristics, treatment modalities, and survival outcomes of EGFRmt NSCLC patients with CNS disease, treated with front-line Osimertinib, with or without initial CLT. We evaluated patients diagnosed with EGFR mt NSCLC with CNS disease at the time of diagnosis at a single academic institution (2004-2023).

Results: Our study evaluated 58 patients with EGFRmt NSCLC and CNS disease. Most were female (75%, 43/58) and nearly half were self-identified Asians (47%, 27/58). Majority (88%, 51/58) were diagnosed at Stage IV, with 88% (45/51) having brain metastasis. 81% (47/58) patients received Osimertinib alone for brain metastasis, and 14% (8/58) concurrently underwent first-line radiation (five SRS, two whole brain radiation, one SBRT). Among those who developed brain metastasis post-first-line treatment, the average duration to brain metastasis was 775 days (25.5 months, range 10-60 months). After progression on first-line treatment, 54 patients were evaluated: eight had a complete response (CR), 35 had a partial response (PR), five had stable disease (SD), and four had progressive disease, with two showing a mixed response. The median response time was 8.8 months (range 0.9-44.8 months). After CNS disease progression on first-line treatment, 26 patients received further treatment: 15/26 received EGFR TKI alone (most at 160mg dose), two received combination EGFR TKI with radiation, two received EGFR TKI with chemo and radiation, and one received EGFR TKI with chemotherapy.

Conclusions: The findings from our study indicate that the majority of patients with EGFRmt NSCLC and CNS disease are females, self-identified as Asian, diagnosed at Stage IV with brain metastasis. Osimertinib, often combined with first-line radiation, appears to be a common treatment for brain metastasis in these patients. Following first-line treatment with Osimertinib, a considerable number of patients show either complete or partial response, suggesting the potential efficacy of the treatment. However, for patients with progressive disease, the response time varies significantly. Upon progression of CNS disease after first-line treatment, EGFR TKI, especially at a 160mg dose, is the most commonly employed therapy in our cohort. Some patients also receive combination treatments involving radiation and chemotherapy. Overall, our study highlights the predominance of EGFRmt NSCLC with CNS disease in females and the potential effectiveness of treatments like Osimertinib. However, further research is needed to optimize treatment strategies, particularly for patients with progressive disease.

Keywords: EGFR, Osimertinib, CNS radiation

EP.12A METASTATIC NON-SMALL CELL LUNG CANCER - TARGETED THERAPY - EGFR
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EP.12A.18 Afatinib vs. Osimertinib as First-Line Treatment for Metastatic Non-Small Cell Lung Cancer Harboring EGFR Mutations

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Introduction: The optimal treatment approach for advanced non-small cell lung cancer (NSCLC) harboring epidermal growth factor receptor (EGFR)-mutant remains the matter of debate. Currently, osimertinib is the preferred treatment of choice in the first-line setting, however, in Vietnam, the accessibility is limited due to high treatment cost and lack of reimbursement. On the other hand, the lastest real world studies of afatinib in Vietnam and other Asian countries has provided evidence of durable survival benefit and manageable toxicity profile thank to flexible dose adjustment approach. Given the lack of head-to-head comparison between these two EGFR TKIs, this study aimed at comparing the survival outcomes and safety of patients with metastatic NSCLC harboring EGFR mutations treated with osimertinib or afatinib in the first-line setting.

Methods: Patients with advanced and recurrent non-small cell lung cancer who harbored EGFR mutations given either osimertinib or afatinib as first-line therapy from January 2018 to December 2022 were retrospectively recruited and analyzed. The primary endpoint of the study was the time on treatment (TOT). Two secondary endpoints included overall survival and tolerability.

Results: There was a total of 156 patients enrolled in this study. The afatinib cohort included 84 patients, whereas 72 patients received osimertinib. With median follow-up time of 16.5 months in osimertinib group and 24.3 months in afatinib group, there was no significant difference on the time on treatment between two cohorts (median: 18.6 (95% CI: 13.5-23.6) vs 16.1 (95% CI: 14.7-17.5) months, p value = 0.79). Patients with Del19 had the median TOT of 15.7 months in the afatinib group and 15.6 months in the osimertinib group (p value = 0.99), Among those with L858R, the median TOT was 19.0 months and 18.6 months in the cohort treated with afatinib and osimertinib, respectively (p value = 0.60). On the brain metastases status, osimertinib seemed not provide significant survival benefit over afatinib (p value = 0.87). There was no between-group difference according to gender, age, and smoking status. At the data cut-off, overall survival was immature. The survival rate at 12 months was 88% and 82% in those treated with afatinib and osimertinib, respectively. Both afatinib and osimertinib have manageable toxicity profile with low tolerability-related discontinuation rate (2.4% vs 1.4%, respectively).

Conclusions: In this single-center real-world retrospective study, osimertinib failed to demonstrate the superiority of survival outcome over afatinib in the first-line setting. These findings warrant larger prospective studies to establish the optimal treatment sequence for Asian patients with EGFR mutant NSCLC.

Keywords: NSCLC, afatinib, osimertinib

EP.12A METASTATIC NON-SMALL CELL LUNG CANCER - TARGETED THERAPY - EGFR
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EP.12A.19 Race May Affect Survival in 1L Patients with Metastatic Non-Small Cell Lung Cancer (mNSLC) Onegfr-Targeted Therapy

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Introduction: Black Americans with EGFR-mutated mNSCLC exhibit inferior survival in limited retrospective analyses. East Asians are more likely to develop EGFR-mutated mNSCLC; trials suggest superior efficacy of erlotinib and osimertinib among East Asian patients vs. other races. Limited data are available on racial disparities in survival with EGFR TKI use.

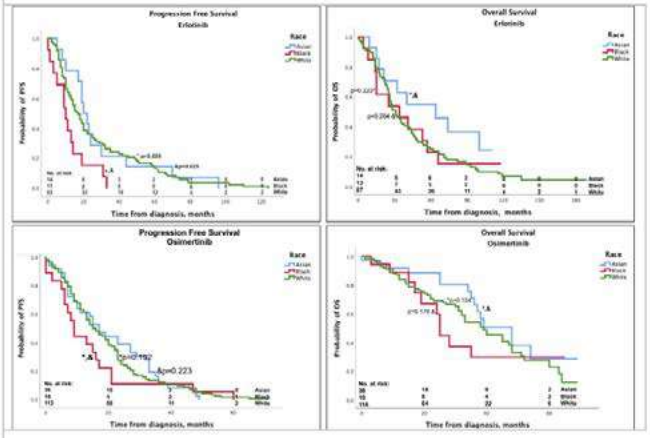
Methods: We performed a single-institution retrospective analysis of patients (pts) with EGFR-mt mNSCLC treated between 2007 and 2023 with a 1L EGFR TKI. Pts on clinical trials were excluded. Baseline demographics, disease characteristics, treatment history, and clinical outcomes were abstracted from the electronic medical record. Baseline characteristics were compared using independent sample t-tests and chi-square analyses. Median PFS and OS were compared using Kaplan-Meier log-rank analysis and multivariable Cox linear regression. P-values <0.05 were considered statistically significant.

Results: Among 355 treatment-naïve mNSCLC pts with EGFR mutations, median age at diagnosis was 63y, 65.1% were female, 251 (70.7%) White, 60 (16.9%) Asian, and 37 (10.4%) Black. 52.1% of pts received osimertinib, 33.5% erlotinib, 13.0% afatinib, and 1.4% gefitinib. Among erlotinib pts (n=110), mPFS was significantly poorer for Black pts (10m[95%CI:5-15]) compared to White (17m[13-21];p=0.009) or Asian pts (20m[15-26];p=0.025), independent of age or sex. Among osimertinib pts (n=169), mPFS trended inferior for Black (9m[7-11]) compared to White (16m[12-20];p=0.192) or Asian pts (17m[11-23];p=0.251). mOS for erlotinib trended superior for Asian (64m[27-82]) compared to Black (34[3-65]; p=0.223) or White pts (31m[24-38];p=0.264). Likewise, mOS for osimertinib trended superior for Asian (39m[21-49]) compared to Black (24m[13-38];p=0.154) or White pts (38m [15-43];p=0.179). White pts were the only race to show mPFS improvement on osimertinib (33m[13-21]) vs erlotinib (22m[12-20];p=0.033).

Conclusions: In a single US institution, Black patients had shorter PFS on erlotinib and trended towards shorter PFS on osimertinib compared to White or Asian patients. Asian patients trended towards superior OS on both TKIs.

Keywords: Racial disparity, Erlotinib, Osimertinib

Survival	Black	Asian	White	Sig.
Erlotinib (n=110)				
mPFS	10m[5-15]*,&	20m[15-26] *	17m[13-21]&	***p=0.025 &p=0.009**
mOS	34m[3-65]*	64m[27-82]*,&	31m[24-38]&	*p=0.223 &p=0.264
Osimertinib (n=169)				
mPFS	9m[7-11]*,&	17m[11-23]*	16m[12-20]&	*p=0.192 &p=0.251
mOS	24m [13-38]*	39m [21-49]*,&	38m [15-43]&	*p=0.154 &p=0.179



EP.12A METASTATIC NON-SMALL CELL LUNG CANCER - TARGETED THERAPY - EGFR
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EP.12A.20 EGFR Inhibitors Combined with Intrathoracic Perfusion Manages Malignant Pleural Effusion in EGFR-Mutated Metastatic Lung Adenocarcinoma

W. Huang, S. Liao, X. Lei, Z. Chen, K. Xu, Y-F. Wang, Q. Zhou, J. Liu, Sichuan University West China Hospital, Chengdu/CN

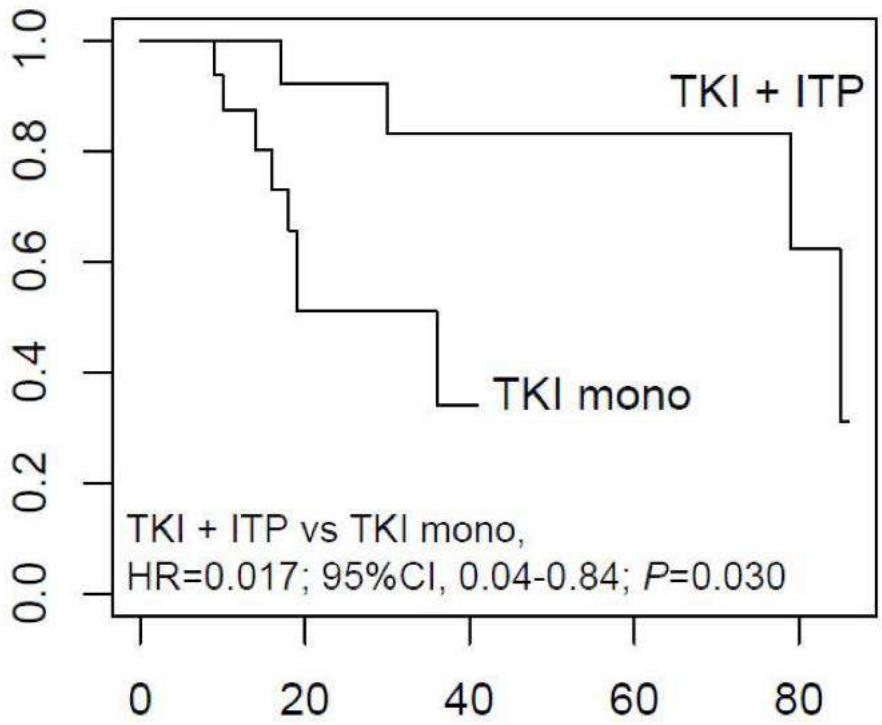
Introduction: Malignant pleural effusion (MPE) is a conventional complication for metastatic lung carcinoma with poor prognosis and noteworthy clinical symptoms. Epidermal growth factor receptor (EGFR) inhibitors were standard medical treatment for those with specific EGFR mutations and proved effective in primary tumors rather than some metastatic sites. FLAURA2 study has showed the potential of first-line chemotherapy combined with Osimertinib in reducing the risk of disease progressing and death. We aimed to retrospectively assess the safety and efficacy of EGFR inhibitors combined with first-line intrathoracic perfusion for EGFR-mutated stage IV lung adenocarcinoma.

Methods: Patients diagnosed with histologically confirmed stage IV lung adenocarcinoma with EGFR 19-del or L858R mutations in Lung Cancer Center, West China Hospital of Sichuan University from January 2013 to December 2019 were identified, among which were detected malignant pleural effusion by chest computed tomography or thoracic ultrasound. All the patients received next generation sequencing or quantitative real-time polymerase chain reaction to identify the targeted gene mutations. They received Gefitinib, Erlotinib, or Osimertinib plus platinum-based intrathoracic perfusion or tyrosine kinase inhibitor monotherapy. Objective response, safety and patient-derived comfort assessment were analyzed.

Results: A total of 31 patients were included in the study with a median age of 52 years (range, 49-85 years), in which 16 (51.6%) were males, and 16 (51.6%) were stage IVA. As for genetic mutation subtypes, 14 (45.2%) of them were found EGFR 19-del mutation, 16 (51.6%) were found EGFR L858R mutation, and one (3.2%) were EGFR T790M mutation. Thirteen patients (41.9%) received tyrosine kinase inhibitor and platinum-based intrathoracic perfusion. The median overall survival was 19 months (range, 3-41 months) versus 45 months (range, 17-86months) for monotherapy and combined treatment, respectively, and combined treatment was associated with favored prognosis (HR=0.017; 95%CI, 0.04-0.84; P=0.030; Figure 1).

Conclusions: Tyrosine kinase inhibitor plus first-line intrathoracic chemotherapy perfusion would manage the disease progression patterns and improve the prognosis of stage IV lung adenocarcinoma with EGFR sensitive mutations. Efficacy, safe outcomes and patient-derived comfort assessment in a large cohort would be presented subsequently.

Keywords: Intrathoracic Perfusion, Malignant Pleural Effusion, EGFR Inhibitors



EP.12A METASTATIC NON-SMALL CELL LUNG CANCER - TARGETED THERAPY - EGFR
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EP.12A.21 Nimotuzumab Plus Chemotherapy in the Posterior Line Therapy of EGFR-TKIs Resistant Lung Adenocarcinoma: A Case Series Study

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Introduction: There is a paucity of effective therapy options for patients with epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) resistant lung adenocarcinoma. Here, we report a case series study to assess the efficacy and safety of nimotuzumab combined with chemotherapy, a humanized anti-EGFR monoclonal antibody, in lung adenocarcinoma with EGFR-TKIs resistance.

Methods: We collected nimotuzumab plus chemotherapy in patients with metastatic, stage IV, EGFR-mutated, posterior line therapy (one patient was secondary line therapy) failed, EGFR-TKIs resistant lung adenocarcinoma. Patients received chemotherapy with nimotuzumab (600 mg every three weeks). The primary endpoint was overall survival (OS). Progression-free survival (PFS), objective response rate (ORR), disease control rate (DCR), and safety were used as secondary endpoints. Efficacy was evaluated by RECIST 1.1. Safety was classified by CTCAE version 5.0 and performed based on descriptive analysis.

Results: Between Nov, 2018 and Dec, 2023, 19 patients were collected, with a median follow-up of 14.52 months (95% CI: 9.76-21.49). The median age was 61.0 years (range: 42.0-79.0). There was one patient treated with second-line treatment, and others with third-line and above treatment (Table). Nimotuzumab plus chemotherapy showed favorable survival outcomes in OS (1-year OS: 64.2%, 95% CI: 36.2-82.4; 2-year OS: 55%, 95% CI: 26.6-76.4) and PFS (1-year PFS: 33.4%, 95% CI: 13.7-54.7). The median PFS was 4.44 months (95% CI: 3.25-12.39). An ORR was noted in 26.3% (95% CI: 9.1-51.2) patients, and the DCR was 89.5% (95% CI: 66.9-98.7). All patients were treated with nimotuzumab for 2-13 treatment cycles, of which 3 patients who still receive nimotuzumab now. The most common Grade 3-4 treatment-related adverse events (TRAEs) were myelosuppression (21.05%), nausea (5.26%), vomiting (5.26%), gastrointestinal reaction (5.26%), neutropenia (15.79%), leukopenia (21.05%), and thrombopenia (10.53%). No Grade 3-4 nimotuzumab-related AEs were observed.

Conclusions: The encouraging efficacy and tolerable toxicity results support further clinic study of nimotuzumab as a potential alternative treatment for patients with EGFR-TKIs resistant lung adenocarcinoma.

Keywords: EGFR-TKIs resistant lung adenocarcinoma, posterior line therapy, nimotuzumab

Characteristics		Total (n=19)
Gender, n (%)		
	Male	9 (47.4%)
	Female	10 (52.6%)
Median age, years (range)		61.0 (42.0, 79.0)
KPS, n (%)		
	70	3 (15.8%)
	≥80	16 (84.2%)
EGFR mutation, n (%)		19 (100.0%)
Without ALK/ROS fusion gene, n (%)		19 (100.0%)
Treatment lines, n (%)		
	2	1 (5.3%)
	≥3	18 (94.7%)

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EP.12A.22 Aumolertinib with Chemotherapy as First-Line Treatment in Patients with EGFR-Mutated Advanced NSCLC: A Real-World Study

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Introduction: Aumolertinib, a third-generation EGFR-tyrosine kinase inhibitor (TKI), has shown efficacy in EGFR-mutated (EGFRm) NSCLC. The FLAURA2 study revealed that first-line osimertinib combined with platinum-pemetrexed chemotherapy significantly improves progression-free survival (PFS) over osimertinib monotherapy. Given aumolertinib's superior efficacy and safety profile, we explored whether adding platinum-pemetrexed chemotherapy could further enhance PFS while maintaining an excellent safety profile.

Methods: This real-world study enrolled patients with advanced EGFR-mutated NSCLC (exon 19 deletion or L858R mutation) who had not received prior treatment for advanced disease. Patients were treated with aumolertinib (110mg once daily) and platinum-pemetrexed chemotherapy (every 3 weeks for 4 cycles), followed by maintenance pemetrexed and aumolertinib. The primary endpoints were PFS. Overall survival (OS), objective response rate (ORR), disease control rate (DCR) and safety were also assessed.

Results: A total of 94 patients were retrospectively enrolled and evaluated. The median age was 62.5 years, and the distribution of EGFR exon 19 deletion / L858R mutation was 54.2%/45.8%. At the data cutoff (March 27, 2024), the median follow-up was 15.8 months. The combination of aumolertinib and chemotherapy yielded a median PFS of 30.5 months. Notably, patients with the 19 deletion exhibited a significantly prolonged PFS compared to those with L858R mutation (median not reached vs. 19.2 months; p=0.027). Furthermore, there was a significantly improvement in PFS among patients with central nervous system (CNS) metastasis compared to those without CNS metastasis (p=0.011). OS has not been reached, with 1-, 2-, and 3-year OS rates of 100%, 84%, and 76.9%, respectively, showing a trend towards improvement compared to data from the FLAURA2 study. Objective response (complete or partial) was observed in 78% of patients, and DCR was 100%. The incidence of all-grade adverse events (AEs) was 90.4% (85/94),with Grade ≥ 3 AEs occurring in 34.0% (32/94) of patients (Table 1). A total of 3.2% (3/94) of patients discontinued treatment due to AEs. The most frequent Grade ≥ 3 AEs were neutropenia (9.6%) and thrombocytopenia (8.5%). No Grade ≥ 3 gastrointestinal disorders, skin toxicity, or fatigue were reported.

Conclusions: This study presents the first report of PFS outcomes for initial treatment with aumolertinib and chemotherapy in patients with EGFR-mutated advanced NSCLC. Aumolertinib combined with chemotherapy appears to be safer compared to the findings in the FLAURA2 study. This study proposes a safer and feasible option for the first-line treatment of EGFR-mutated advanced NSCLC.

Keywords: aumolertinib, EGFR mutation, first-line treatment

Patients with AEs	**Any Grade,%**	**CTCAE≥Grade 3,%**
All AEs	**90.4**	**34.0**
Gastrointestinal disorders	**36.2**	**0.0**
Nausea	22.3	0.0
Loss of appetite	12.8	0.0
Vomiting	10.6	0.0
Constipation	6.4	0.0
Diarrhea	10.6	0.0
Haematological toxicities	**68.1**	**23.4**
Leukopenia	34.0	5.3
Neutropenia	31.9	9.6
Thrombocytopenia	29.8	8.5
Anemia	28.7	1.1
Skin disorders	**34.0**	**0.0**
Mouth ulcer	19.1	0.0
Rash	18.1	0.0
Edema	2.1	0.0
Paronychia	1.1	0.0
Fatigue	8.5	0.0

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EP.12A.23 PD-L1 Induced Resistance to EGFR-TKIs in Lung Adenocarcinoma

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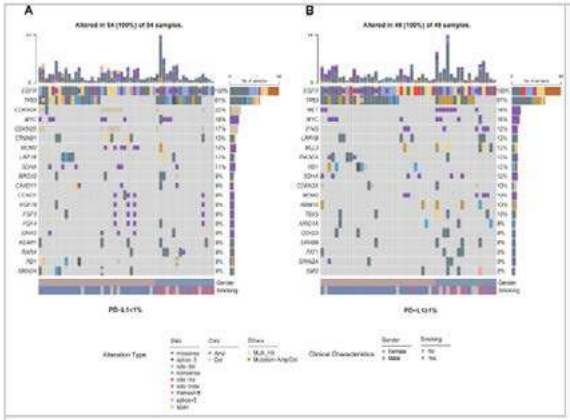
Introduction: In advanced Non-Small Cell Lung Cancer (NSCLC), concurrent PD-L1-positive and activating epidermal growth factor receptor (EGFR) mutations often lead to limited efficacy with EGFR-tyrosine kinase inhibitors (EGFR-TKIs), and the underlying mechanism remains unidentified.

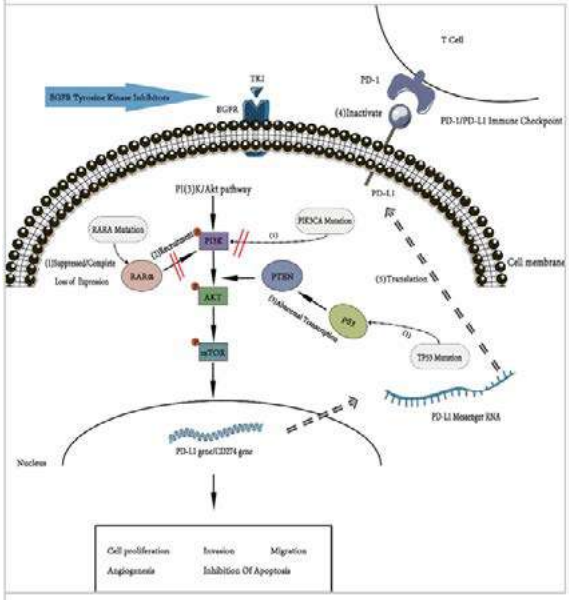
Methods: We enrolled 103 EGFR-mutant LUAD patients across three centers, assessed PD-L1 expression, and conducted next-generation sequencing (NGS) for gene mutation analysis. We also expanded the enrollment to include EGFR-mutant patients treated with either EGFR-TKIs alone or in combination with chemotherapy as first-line therapy and evaluated progression-free survival (PFS) following different treatment strategies.

Results: Our data showed that SMO and MET gene amplification, biological processes, and signaling pathways associated with DNA recombination, cell cycle transition, and abnormal phosphorylation were significantly concentrated in the PD-L1 ≥1% than PD-L1<1% group. Clonal RARA and PIK3CA alterations were observed more frequently observed than PD-L1≥1%. On the contrary, the TP53 subclonal mutation accounted for the majority. EGFR-TKI combined with chemotherapy (TKI+C) overcame primary resistance, prolonging median PFS by 9.8 months, with no significant difference compared to PD-L1<1%.

Conclusions: This study presents the molecular mechanism of PD-L1-induced primary resistance to EGFR-TKI, while EGFR-TKI combined with chemotherapy may suggest a potential shift in the current first-line treatment approach.

Keywords: Lung Adenocarcinoma (LUAD), Epidermal Growth Factor Receptor (EGFR), Programmed Death-Ligand 1 (PD-L1)





EP.12A METASTATIC NON-SMALL CELL LUNG CANCER - TARGETED THERAPY - EGFR
SATURDAY, SEPTEMBER 7, 2024 - 11:58 - 11:59

EP.12A.24 Prognostic Value of Functional Subtype Classification of Co-Occurring TP53 Mutations in Patients with EGFR-Mutant NSCLC Treated with TKI

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Introduction: Patients with non-small cell lung cancer NSCLC harboring epidermal growth factor receptor (EGFR) mutations represent a distinct subgroup that can benefit from targeted therapy with tyrosine kinase inhibitors (TKIs). However, the co-occurrence of TP53 mutations in EGFR-mutant NSCLC has been associated with poorer clinical outcomes, including shorter progression-free survival (PFS) and overall survival (OS) rates. Understanding the prognostic value of TP53 mutations, particularly in relation to their functional subtype classification, is crucial for optimizing treatment strategies in this patient population.

Methods: This retrospective study which was reviewed by institutional IRB and granted exempt status included patients diagnosed with sensitive EGFR mutation-positive NSCLC who were treated with first- or second-generation TKI therapy between 2013 and 2017. Patient demographics, treatment details, and molecular characteristics, including EGFR and concurrent TP53 mutation status, were collected. TP53 mutations were classified as pathogenic or non-pathogenic/unknown based on current literature. Treatment response rates and PFS were compared between TP53 mutant and wild-type groups, as well as among subgroups with pathogenic TP53 mutations. Statistical analyses were performed using chi-square tests, one-way ANOVA, and Kaplan-Meier curves.

Results: Of the included patients (n=73), those with TP53 mutations (n=31) were younger (median age 61.6 years) compared to TP53 wild-type patients (n=42, median age 72 years). Although demographic differences were noted, only age reached statistical significance (p = 0.003669). While numerical differences in treatment response rates and PFS were observed between TP53 mutant and wild-type groups, these were not statistically significant (fig 1A). However, the subgroup analysis revealed that patients with known pathogenic TP53 mutations (n=17) had significantly lower PFS (8.9 months) compared to TP53 wild-type patients (11.6 months) (p=0.0057) (fig 1B).

Conclusions: Our results suggests that while there are no significant differences in treatment response rates and PFS between TP53 mutant and wild-type NSCLC patients overall, the presence of pathogenic TP53 mutations may serve as a prognostic factor for shorter PFS in EGFR-mutant NSCLC patients treated with TKIs. Further research is needed to understand the underlying mechanisms and explore personalized treatment approaches based on individual molecular profiles. This study underscores the importance of ongoing efforts to improve outcomes for patients with EGFR-mutant NSCLC, particularly those harboring co-occurring TP53 mutations.

Keywords: NSCLC, TKI, TP53

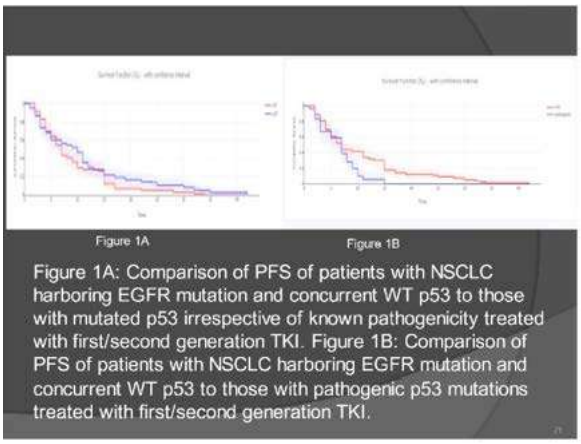

Figure 1A: Comparison of PFS of patients with NSCLC harboring EGFR mutation and concurrent WT p53 to those with mutated p53 irrespective of known pathogenicity treated with first/second generation TKI. Figure 1B: Comparison of PFS of patients with NSCLC harboring EGFR mutation and concurrent WT p53 to those with pathogenic p53 mutations treated with first/second generation TKI.

EP.12A METASTATIC NON-SMALL CELL LUNG CANCER - TARGETED THERAPY - EGFR
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EP.12A.25 Concurrent RB1/TP53 Alterations in Targetable EGFR-Mutant Lung Adenocarcinoma Imply Aggressive Treatment

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Introduction: Concurrent RB transcriptional corepressor 1 (RB1)/tumor protein p53 (TP53) alterations in EGFR-mutant lung adenocarcinomas are at unique risk of histologic transformation and define inferior clinical outcomes. Whether those patients would benefit more from EGFR-tyrosine kinase inhibitor combined with other therapy remains unknown. The aim of this study was to investigate clinicopathological characteristics, compound mutation, and prognosis of patients with EGFR-mutant lung adenocarcinoma harboring concurrent RB1/TP53 alterations.

Methods: 76 patients with EGFR-mutant lung adenocarcinomas carrying contaminant RB1/TP53 mutations identified by next-generation sequencing from 2020 to 2023 were enrolled in current study. For patients with early-stage EGFR-mutant lung adenocarcinoma,19 patients who had received adjuvant EGFR-tyrosine kinase inhibitor were compared to 6 patients who had received adjuvant chemotherapy alone. For patients with advanced EGFR-mutant lung adenocarcinoma, 23 patients who had received combined first-line EGFR-tyrosine kinase inhibitor and other treatments were compared to 15 patients who had received first-line EGFR-tyrosine kinase inhibitor alone. Disease-free survival, time to first-line treatment discontinuation, overall survival, clinicopathological characteristics and genomic alterations were evaluated.

Results: Among 76 patients with lung adenocarcinoma, there were 45 females (59.21%) with the median age of 57.28 ± 9.59 years. There were 21 patients in clinical stage I, 6 patients in stage II, 4 patients in stage IIIB and IIIC, and 45 patients in stage IV. Lobectomy is the commonest surgical procedure in early-stage lung adenocarcinoma (stage I-II, 23/27, 85.19%). Amplification of the MYC gene is the commonest compound mutation (11/76, 14.47%) with the median copy number of 4.1(range: 2.9 - 13.9). The median disease-free survival (mDFS) and 95% confidence interval (CI) of patients with early-stage lung adenocarcinoma receiving adjuvant targeted therapy were 5 (2.562 to 7.438) months, while 9 (1.799 to 16.201) months for patients with adjuvant chemotherapy (p = 0.354). 23 patients with advanced lung adenocarcinoma received first-line EGFR-tyrosine kinase inhibitor alone, while 15 patients received combined EGFR-tyrosine kinase inhibitor with other therapy including chemotherapy (10 cases), anti-angiogenesis therapy (2 cases) and chemotherapy plus anti-angiogenesis therapy (3 cases). The median progression-free survival (mPFS) and 95% confidence interval (CI) of those patients receiving combined targeted therapy were 14 (8.336 to 19.664) months, while 7 (2.658 to 11.342) months for patients receiving targeted therapy alone (p = 0.037). The median overall survival (mOS) and 95% confidence interval (CI) of patients with advanced lung adenocarcinoma received receiving first-line combined targeted therapy were 28 (12.423 to 43.577) months, while 21 (16.830 to 25.170) months for patients with targeted therapy alone (p = 0.123).

Conclusions: Patients with advanced EGFR-mutant lung adenocarcinoma harboring concurrent RB1/TP53 alterations benefit more from the compound treatment comprising EGFR-tyrosine kinase inhibitor and other therapy.

Keywords: EGFR, RB1/TP53, lung adenocarcinoma

EP.12A METASTATIC NON-SMALL CELL LUNG CANCER - TARGETED THERAPY - EGFR
SATURDAY, SEPTEMBER 7, 2024 - 11:58 - 11:59

EP.12A.26 Overall Survival of Advanced Non-Small Cell Lung Cancer Treated with First-Line Afatinib: A Multicenter Real-World Study in Vietnam

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Introduction: Afatinib, a second-generation tyrosine kinase inhibitor (TKI), has been approved for the treatment of non-small cell lung cancer (NSCLC) harboring epidermal growth factor receptor (EGFR) mutations in Vietnam since 2018. The previous largest multicenter study of first-line afatinib in Vietnamese NSCLC patients indicated that the median time-to-treatment failure was 16.7 months, but the overall survival (OS) data were not mature at that time. Here, we briefly present the updated OS data from the same cohort.

Methods: We retrospectively reviewed data from patients with EGFR-mutant NSCLC who were treated with first-line afatinib between April 2018 and June 2022 in nine cancer centers in Vietnam. Eligibility criteria included advanced NSCLC (inoperable stages IIIB-IIIC, recurrences, and stage IV), initial treatment with afatinib, and specific EGFR mutations (excluding de novo T790M mutations). A starting dose of afatinib ranging from 20 mg to 40 mg was determined by physicians and adjusted based on tolerability. Post-afatinib treatment strategies were guided by T790M mutation status, performance status, site of progression, and patient preferences. The OS was estimated using the Kaplan-Meier method, with univariate and multivariate analyses performed to identify prognostic factors.

Results: Out of 343 patients treated with first-line afatinib, EGFR exon 19 deletions (Del19) were detected in 46.9% of patients, L858R mutations in 26.3%, and other uncommon EGFR mutations, including compound mutations, in 26.8%. Brain metastases at baseline were present in 25.4% of patients. The predominant starting dose of afatinib was 30 mg (58.6%), followed by 40 mg (39.9%) and 20 mg (1.5%). Subsequent treatments post-afatinib failure included osimertinib (31.2%), doublet platinum-based chemotherapy with or without immunotherapy (24.6%), single-agent chemotherapy (5.4%), and best supportive care (31.5%), with 7.3% of treatments unknown. After a median follow-up of 36.8 months, 61.2% of the patients experienced events, with a median OS (mOS) of 31.1 months (95% CI: 29.4-32.9). Patients who received osimertinib after first-line afatinib had a mOS of 37.5 months. The mOS for patients with uncommon mutations was lower compared to those with the Del19 mutation (27.6 vs. 31.7 months, p=0.022) and the L858R mutation (27.6 vs. 35.2 months, p=0.040), using the Hochberg adjustment method. The mOS did not significantly differ between patients with and without brain metastases (31.5 vs. 29.9 months, p=0.130), between starting dose subgroups (40 mg vs. <40 mg: 32.6 vs. 30.0 months, p = 0.133), or based on the tolerance dose (40 mg vs. <40 mg: 31.5 vs. 30.6 months, p = 0.942). Multivariate analyses identified uncommon mutations, a poor performance status (PS score ≥2), and current smoking as adverse prognostic factors for OS.

Conclusions: The OS observed in patients treated with first-line afatinib in Vietnam was encouraging. In this real-world setting, the effectiveness of first-line afatinib treatment was evident across various patient subgroups, including those with or without brain metastases, those with common and uncommon mutations, and those receiving different starting doses.

Keywords: Overall survival, Vietnam, Afatinib

EP.12A METASTATIC NON-SMALL CELL LUNG CANCER - TARGETED THERAPY - EGFR
SATURDAY, SEPTEMBER 7, 2024 - 11:58 - 11:59

EP.12A.27 Targeting DDR Pathway Activates the TBK1-NF?B P65 Axis and Enhances the Killing Effect of CD8+ T Cells

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Introduction: Deficiencies in DDR signaling pathways have been linked to improved responses to immunotherapy. This study seeks to explore whether inhibiting the key mediator of DDR pathways, ATR, could enhance the function of CD8+ T cells and elucidate its underlying mechanism.

Methods: The CD8+ T cell-killing experiment was conducted in vitro to assess the effectiveness of ATR inhibitors. RNA Sequencing analysis was then performed to identify the regulatory mechanism following ATR inhibition. Subsequent investigations involved Western blotting, RT-qPCR, and immunofluorescence assays were utilized to evaluate the inflammatory signaling pathway in relation to the RNA sequencing results. Flow cytometry and ELISA were employed to detect downstream targets such as surface MHC-I expression and chemokine molecules within the network, in order to confirm our hypotheses.

Results: The ATR inhibitor (VX970) had been demonstrated to increase the cytotoxic impact of CD8+ T cells on tumor cells. RNA-seq analysis indicated the enrichment of pathways associated with inflammatory responses, along with pathways related to TNFκ signaling via NFκB. Accumulation of cytosolic dsDNA and increased κH2AX protein expression had been found, suggesting important roles of DNA damage in triggering inflammatory responses following ATR inhibition. Further increases in phospho-TBK1 (p-TBK1) and p-NFκB p65 proteins were observed as RNA-seq analysis indicated. Activated NF-κB then entered the nucleus and initiated the transcriptional response involving CCL2 and CCL20 to exert significant anti-tumor effects. Furthermore, the upregulation of active forms could enhance the expression of MHC-I molecules via TAP1 presentation, which partially explained the reason ATR inhibition could induce the recruitment of CD8+ T cells.

Conclusions: Targeting the DDR pathway results in the accumulation of stimulated CD8+ T cells, possibly through increased MHC-I surface expression and upregulation of CCL2 and CCL20. This accumulation may be attributed to the presence of cytosolic DNA and activation of the TBK1-NFκB/p65 signaling pathway. Ultimately, these mechanisms could enhance the efficiency of immunotherapy.

Keywords: ATR, immunotherapy, CD8+T cell

EP.12A METASTATIC NON-SMALL CELL LUNG CANCER - TARGETED THERAPY - EGFR
SATURDAY, SEPTEMBER 7, 2024 - 11:58 - 11:59

EP.12A.28 Overall Survival in a U.S. Asian Population with EGFR-Mutated Stage IV NSCLC Treated with Any Generation of TKIs as First-Line Treatment

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Introduction: Osimeritinib, a 3rd-generation EGFR tyrosine kinase inhibitor (TKI), was approved as first-line (1L) treatment for metastatic non-small-cell lung cancer (NSCLC) with EGFR mutations (ex19del or L858R) in 2018. This approval was based on the FLAURA trial, which showed improved progression-free survival and overall survival (OS) of 1L osimertinib compared to 1st-generation TKIs. Despite this, subgroup analyses revealed no OS difference in Asian or L858R patients. Observational studies such as GioTag and UpSwinG showed better median OS in Asian ex19del patients on sequential afatinib and osimeritinib treatment, prompting the question of whether sequencing treatment may also benefit L858R patients. We conducted this analysis of real-world outcomes in U.S. Asian patients with EGFR mutated NSCLC treated with 1L osimertinib, 1st- or 2nd- generation TKIs (TKIs-only), or sequential 1st- or 2nd- generation TKI followed by osimertinib (sequential-TKI-osi). This abstract was accepted by ASCO 2024 for online publication only.

Methods: We conducted a single-institution IRB-approved retrospective study at NYU, including Asian patients diagnosed with stage IV NSCLC with EGFR ex19del or L858R, who received any generation of TKIs from 1/1/2010 to 1/1/2024. We compared 3-year OS based on treatment groups, excluding patients with less than 3 years of follow-up. The analysis utilized the Cox proportional-hazards model to calculate hazard ratios (HR) and P values of OS. Survival curves were estimated using the Kaplan-Meier method. The log-rank tests were used to assess survival differences between treatment groups. Additionally, a multivariable Cox proportional-hazards model explored the association between patients' survival time and multiple predictor variables.

Results: We analyzed 139 cases: 103 (74%) females, 68 (49%) L858R, 113 (81%) never smokers, with age range of 31-96 years. The analysis revealed no significant difference in the OS among L858R patients who received TKIs-only (p=0.83) or sequential-TKI-osi (p=0.90), compared to 1L osimertinib (median OS not reached in all three groups). However, in ex19del patients, TKIs-only (HR 0.31, 95% CI 0.13-0.76) and sequential-TKI-osi (HR 0.30, 95% CI 0.11-0.85) treatments showed superior OS compared to 1L osimertinib, with a median OS of 24.7 months in 1L osimertinib vs. not reached in the other two treatments. Among all predictor variables (treatment, age, sex, EGFR subtypes, and smoking status), only age had a significant but small impact on OS (HR 1.03, 95% CI 1.01-1.06).

Conclusions: Our real-world analysis revealed that Asian stage IV NSCLC patients with L858R treated with 1L osimertinib had a similar 3-year OS compared to those treated with TKIs-only and sequential-TKI-osi. Whereas, 1L osimertinib was inferior to both treatments in OS for ex19del patients. This finding may be unique and significant in Asian ex19del patients, though our analysis is limited by the small cohort of a retrospective study. Larger cohorts from retrospective studies and real-world data sets are needed to investigate the response of Asian ex19del patients to either 1L osimertinib, and now the recently approved FLAURA2 1L regimen of Osimertinib and chemotherapy, while underlining the need for novel treatment options for L858R patients.

Keywords: NSCLC, Asian, Osimertinib

EP.12A METASTATIC NON-SMALL CELL LUNG CANCER - TARGETED THERAPY - EGFR
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EP.12A.29 Characteristics of Osimertinib Non-Responders vs Responders in EGFR Mutated Lung Cancer

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Introduction: Since the early 2000s the treatment options for Non-Small Cell Lung Cancer (NSCLC) have increased after the discovery of targetable 'driver mutations'. From the landmark FLAURA trial, third generation Osimertinib demonstrated improved median PFS and OS.

Methods: From electronic medical records, a database of patients with NSCLC with EGFR mutations. Inclusion criteria were EGFR Exon 19 or L858R mutations, available imaging for review and metastatic/recurrent disease. We excluded patients who discontinued osimertinib due to side effects or did not tolerate full dose of 80mg. Tumor burden at diagnosis was determined by initial PET/CT and MRI brain. Oligometastatic disease was defined as less than 3 regions while elevated tumor burden was determined by greater than 3 regions of disease. Lymph node regions and bone metastasis were separated into discrete anatomical regions; head/neck, thorax, pelvis, abdomen, and extremities.

Results: From over 400 patients with EGFR-mutated NSCLC, 125 patients met our eligibility criteria. With median follow up of 41.9 months, median PFS was 20.2 (95% CI 17.2-24.4) and median OS was 34.4 (95% CI 28.7, 45.9). The 28 patients (22.4%) with oligometastatic disease at diagnosis had longer PFS compared to non-oligometastatic disease at 26.1 months (95% CI 22.8-57.5) versus 18.2 months (95% CI 14.9-23.2) HR 1.75 (1.07-2.86, p=.025) and OS not reached (53.2 NE) vs 28.7 (95% CI 26.6-37.9) HR 4.00 (1.89-8.47, p=<.001). 38 patients received radiation after less than 3 months on Osimertinib and had worse survival compared to patients who received radiation after 12 months, OS 32.2 (95% CI 26.9-46.1) HR 2.60 (1.24-5.44, p=0.011) vs OS 52.3 (95% CI 38.1 NE) and PFS 19.9 (95% CI 15.2-34.4), HR 1.56 (0.89-2.73, p=.122) vs PFS 29.1 (95% CI 24.5-45.1). 73 patients had both hilar and mediastinal adenopathy (by PET/CT) at diagnosis with worse PFS/OS compared to single or no nodal disease PFS 17.1 (95% CI 11.8, 25.3) HR 1.53 (1.02-2.30 p=.041) versus PFS 23.2 (95% CI 18.5-38.0) and OS 28.7 (95% CI 26.0-45.7) HR 1.89 (1.15-3.11, p=0.012) versus 42.3 (95% CI 33.9-NE). 41 patients had CNS disease at diagnosis (22 received early radiation to the brain) without significant difference in survival, PFS 20.4 (95% CI 15.7-34.4) and OS 33.9 (95% CI 26.1-46.1) HR 1.29 (0.79-2.09, p=.308), compared to no CNS disease with PFS 19.5 (95% CI 16.5-26.1) HR 1.05 (0.69-1.59, p=.817), OS 37.9 (95% CI 28.2-53.9). 22 (17.6%) patients continued osimertinib with stable disease, 77 (61.6%) patients received second line therapy; the majority (51 patients) received platinum-based chemotherapy. The most common co-mutation was TP53 (73 patients) followed by EGFR amplification (17 patients). CCNE1 was more common in patients who progressed before 18 months, while MYC was more common in patients with stable disease.

Conclusions: From this retrospective evaluation of a single institution, oligometastatic disease at diagnosis, single or no hilar/mediastinal disease, late radiation were associated with improved PFS and OS. CNS disease at diagnosis had minimal change in PFS and OS. Novel RNA sequencing on the different cohorts is ongoing and results will be presented at the meeting.

Keywords: EGFR-Mutated, Osimertinib, Response

EP.12A METASTATIC NON-SMALL CELL LUNG CANCER - TARGETED THERAPY - EGFR
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EP.12A.30 Landscape of EGFR Mutations and Real-World Experience of Therapeutic Interventions - A Community Oncology Study

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Introduction: EGFR is the most commonly targeted mutation in lung cancer however the heterogeneity in these mutations has led to expansion of treatment options in metastatic settings. Herein, we comprehensively summarize the spectrum of EGFR mutations and co-mutations, clinical characteristics, treatment patterns, and survival outcomes in a real-world community oncology practice

Methods: This retrospective study included consecutive patients from community oncology centers diagnosed with metastatic EGFR mutant Non-small cell lung carcinoma (NSCLC) between March 2018 and December 2023. Clinical characteristics including the method of EGFR testing, spectrum of EGFR mutation and co-mutations, and treatment records were retrieved from the EMR. Progression-free survival and overall survival were calculated using the Kaplan-Meier analysis

Results: Out of 1068 patients with Non-small cell lung carcinoma (NSCLC), 871 were identified as adenocarcinomas, with EGFR mutations detected in 311/871 (35.7%). The median age of the cohort was 64 years (34-89) with 11 patients presenting at less than 40 years of age and the M:F ratio being 1:1.07. The majority of these patients were Stage IV (264/311) and the prevalence of EGFR was higher in females compared to males (37.3% v/s 23.1%, p<0.05). Detailed EGFR mutational testing records were available for 200 patients out of which comprehensive Next-generation sequencing (NGS) was done in 97/200 patients wherein 79.3% were tissue-based NGS, and 20.6% were liquid biopsy-based NGS while 103/200 patients were tested by Polymerase chain reaction (PCR). The Spectrum of EGFR mutations and frequency of co-mutations with EGFR are shown in Table 1. The majority of patients received tyrosine kinase inhibitors (TKIs) in the first-line (200/264, 75.7%) of which Gefitinib, Erlotinib, Afatinib, and Osimertinib were used in 55%, 7%, 22.5%, and 20.5% respectively. TKI in combination with Chemotherapy as first-line therapy was used in 64/200 patients. Median survival for the cohort was 35 months (95% CI 29.8-40.2) with a median follow-up time being 31 months (95% CI 26-36)

Conclusions: This study highlights the prevalence and spectrum of EGFR mutation and the use of NGS testing in identifying driver mutations along with co-mutations which can impact disease behavior, therapeutic interventions, and treatment outcomes. These real-world outcomes from community practice are consistent with the current literature

Keywords: EGFR Co-mutations, NGS testing, TKIs

EGFR with Exon details		EGFR with Co-mutants	
Exon records not available	111/311 (35.6%)	EGFR+ALK	9/200 (4.5%)
Exon records available	200/311 (64.3%)	EGFR+ROS	4/200 (2%)
Del 19	114/200 (57%)	EGFR+ALK+ROS	1/200 (0.5%)
Exon 21 L858R	56/200 (28%)	EGFR+TP53	4/200 (2%)
20 insertion	17/200 (8.5%)	EGFR+MET	2/200 (1%)
T790M as baseline	6/200 (3%)	EGFR+BRAF	2/200 (1%)
EGFR rare mutation	26/200 (13%)	EGFR+KARS	1/200 (0.5%)
		EGFR+RET	1/200 (0.5%)

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EP.12A.31 Clinical Characteristics and Outcomes of EGFR-Positive Non-Small Cell Lung Cancer with Acquired RET Fusions

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Introduction: Osimertinib has emerged as the standard of care for treatment-naïve patients with EGFR-mutant and EGFR T790M mutation-positive NSCLC. However, the development of resistance to osimertinib is nearly inevitable in most NSCLC patients over time. Acquired RET fusions represent one of the mechanisms of resistance to osimertinib. Selpercatinib, a highly selective RET inhibitor, has demonstrated significant and durable efficacy in NSCLC patients with RET fusion-positive tumors. However, there is limited information available regarding the clinical characteristics of patients who develop RET fusions after osimertinib failure, as well as the safety and efficacy of the combination therapy comprising osimertinib and selpercatinib.

Methods: Osimertinib has emerged as the standard of care for treatment-naïve patients with EGFR-mutant and EGFR T790M mutation-positive NSCLC. However, the development of resistance to osimertinib is nearly inevitable in most NSCLC patients over time. Acquired RET fusions represent one of the mechanisms of resistance to osimertinib. Selpercatinib, a highly selective RET inhibitor, has demonstrated significant and durable efficacy in NSCLC patients with RET fusion-positive tumors. However, there is limited information available regarding the clinical characteristics of patients who develop RET fusions after osimertinib failure, as well as the safety and efficacy of the combination therapy comprising osimertinib and selpercatinib.

Results: During the study period, 523 patients with EGFR mutations received osimertinib, and 45 patients underwent NGS testing after osimertinib treatment. Among these patients, 3 (7%) were found to have acquired RET fusions. All three patients were female and presented with clinical stage IVB adenocarcinoma. Two patients had EGFR exon 19 deletion, and one had the L858R mutation. All patients initially received osimertinib as first-line treatment. NGS testing after osimertinib failure were underwent with biopsy from liver metastasis and revealed non-KIF5B fusions (ANKRD26-RET, CCDC6-RET, CGNL1-RET) in all three cases. Two patients received selpercatinib 80 mg twice daily in combination with osimertinib 80 mg daily, while the remaining patient received selpercatinib 160 mg twice daily. The median duration of treatment was 3.7 months (range; 1.1-4.5), and one patient is still undergoing treatment. Initial treatment response was stable disease in two patients who underwent at least one CT scan. Notably, although lesions with detected RET fusions responded, other lesions progressed by the 4-month follow-up evaluation. The combination therapy of osimertinib and selpercatinib was generally well tolerated, with adverse events consistent with the known profiles of each drug alone. None of the three patients experienced grade 3 or higher adverse events during treatment.

Conclusions: The combination therapy of osimertinib and selpercatinib demonstrated feasibility and showed effectiveness to a certain extent. However, selpercatinib following osimertinib resistance resulted in a mixed response, suggesting heterogeneous resistance mechanisms that warrant further investigation.

Keywords: EGFR-mutant, Acquired RET fusions, NSCLC

EP.12A METASTATIC NON-SMALL CELL LUNG CANCER - TARGETED THERAPY - EGFR
SATURDAY, SEPTEMBER 7, 2024 - 11:58 - 11:59

EP.12A.32 Discontinuation of EGFR-TKI in NSCLC During COVID-19 Infection: Assessing Unvaccination, Low BMI, and Comorbidities

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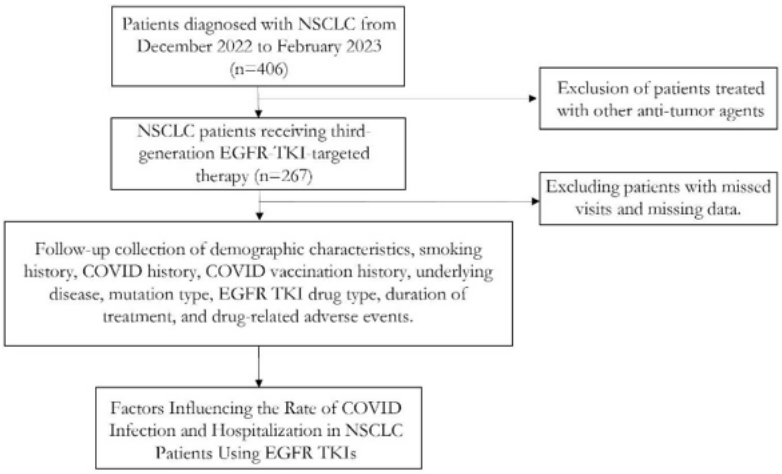
Introduction: Although the COVID-19 emergency prevention and control phase has been over since May 2023, there is still a positive rate of 1% to 42.5% of monthly influenza-like illness in China. Whether targeted therapy with epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) affects the severity of illness from COVID-19 in patients with non-small cell lung cancer (NSCLC) is unknown. Hence, we conducted a retrospective study to determine the rate of COVID-19 infection and the factors influencing the hospitalization and prognosis of patients receiving EGFR TKI-targeted therapy at our hospital within one month after the onset of the COVID-19 pandemic.

Methods: Patients with a diagnosis of NSCLC who were receiving treatment with third-generation EGFR TKIs were included in the study. We collected and analyzed data on patients' demographic and clinical characteristics and the varieties of EGFR TKIs they received. Factors influencing the hospitalization of COVID-19-infected patients were also determined.

Results: Overall, 267 patients with NSCLC who were treated with third-generation EGFR TKI-targeted therapy were included in the analysis. Their mean age was 62.6 years, and 64.8% of them were females. Among them, 37.5% (100/267) received targeted therapy with osimertinib, 36.3% (97/267) with furmonertinib and 26.2% (70/267) with almonertinib. After a mean follow-up of 30 days, 80.5% (215/267) of the patients were infected with COVID-19, 12.6% (27/215) were hospitalized for COVID-19 treatment and 1.4% (3/215) died of COVID-19 infection. No effect of age, gender, education, smoking status, alcohol intake, gene mutation, type of targeted therapy, variety of EGFR TKI or duration of medication was found. Compared to patients who were vaccinated, had a BMI ≥ 22.3 kg/m2 and no comorbidities, those with no COVID-19 vaccination (hazard ratio [HR] = 2.072, 95% confidence interval [CI]: 0.914 to 4.696, p = 0.059), a BMI < 22.3 kg/m2 (HR = 2.287, 95%CI: 1.054 to 4.963, p = 0.036) and comorbidities (HR = 3.439, 95%CI: 1.463 to 8.083, p = 0.004) had higher rates of infection and hospitalizations. However, targeted therapy during hospitalization was not significantly correlated with the infection rate of COVID-19 among patients with a different vaccination status, BMIs and comorbidities.

Conclusions: NSCLC patients with unmet COVID-19 vaccination, low BMI, or comorbidities may need to suspend EGFR-TKI therapy after COVID-19 infection.

Keywords: COVID-19, EGFR TKI, non-small cell lung cancer



EP.12A METASTATIC NON-SMALL CELL LUNG CANCER - TARGETED THERAPY - EGFR
SATURDAY, SEPTEMBER 7, 2024 - 11:58 - 11:59

EP.12A.33 A Comparative Analysis of Outcomes in Patients with Single EGFR Muations for Concurrent Gene Alterations

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Introduction: Epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) administered as initial therapy enhance the quality of life for individuals diagnosed with EGFR mutation-sensitive non-small cell lung cancer (NSCLC). Our investigation focused on evaluating treatment outcomes among patients with EGFR-mutant NSCLC who exhibit concurrent gene alterations, aiming to ascertain their predictive significance regarding response to EGFR-TKIs treatment.

Methods: A retrospective cohort study was conducted the next gene sequencing (NGS) data from January 2019 to Jun 2023. All patients were categorized into two groups: one comprising individuals with a single EGFR mutation (group 1), and the other consisting of patients with concurrent EGFR mutations (group 2). A total of 109 patients with sequencing data prior to first-generation/second-generation EGFR TKI therapy were enrolled in the study. Progression-free survival (PFS) and overall survival (OS) of EGFR-TKIs therapy were assessed using Kaplan-Meier methods and compared between different patients using the log-rank tests.

Results: Among 109 patients with EGFR mutation showed 72 patients had partial responses (66.1%), one had complete response (0.9%) and 17 patients had stable disease (15.6%); 19 patients had progressive disease (17.4%). The ORR was 67% and DCR was 82.6%. The PFS in the group with single EGFR mutation and concurrent gene alterations group were 15.03 months (CI 95%: 13,17-16,89) and 11.00 months (CI 95%: 9,95-12,05) (P= 0.001). Among the 43 patients with concomitant mutations, patients with ALK mutation had the longest PFS (13.43 months), followed by other PIK3CA (11.00 months) and the lowest PFS was MET application (4.77 months).

Conclusions: This study has demonstrated the concurrent gene alterations in some patients with EGFR mutations, which leads to reduced outcome of EGFR-TKIs. NGS should be performed regularly in patients to determine genetic mutation status before targeting treatment.

Keywords: Epidermal growth factor receptor (EGFR), concomitant gens, treatment outcomes

EP.12A METASTATIC NON-SMALL CELL LUNG CANCER - TARGETED THERAPY - EGFR
SATURDAY, SEPTEMBER 7, 2024 - 11:58 - 11:59

EP.12A.34 Chemotherapy and/or Immunotherapy after Progression on Tyrosine Kinase Inhibitors in EGFR Mutant Non-Small Cell Lung Cancer Patients.

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Introduction: Tyrosine kinase inhibitors (TKIs) have shown promising efficacy in the treatment of metastatic non-small cell lung cancer (mNSCLC) in patients with actionable genetic aberrations (AGA). However, most patients experience progression, because previous trials have shown efficacy with the use of chemotherapy (CHM) plus immunotherapy (IMN) in treating patients without AGA, many of these patients with resistance to TKI therapy have been treated with CHM alone, chemoimmunotherapy (CHM+IMN) or IMH alone with most of the doctors favoring the first two modalities. This retrospective review evaluates the use of CHM and/or IMH as subsequent therapy for patients who progressed on targeted therapy.

Methods: This study was a retrospective review of patients with advanced NSCLC who progressed on a TKI and received either CHM or IMH alone, or a combination of both at a community cancer center between Jan 1, 2015, to October 12, 2023. Data was collected and reviewed from electronic health records of 229 patients until data cutoff on January 19, 2024. All time-to-event data were estimated using the Kaplan-Meier method and compared using Cox proportional hazard models with alpha level set to 0.05. Progression free survival (PFS) and overall survival (OS) were reported in months and compared across patients who received CHM, IMH, or CHM+IMN. Measurement data was expressed in medians and standard deviations. All statistical analyses were performed with SPSS. The primary endpoint was PFS defined as the time from therapy initiation after TKI failure to disease progression as defined by the RECIST criteria. The secondary endpoint was OS defined as time from therapy initiation to death from any cause. Other secondary endpoints include PFS of patients with non-EGFR mutated NSCLC. This will include patients with ROS, ALK, and other AGA.

Results: A total of 37 patients met criteria for inclusion of which 26 patients received both CHM+IMN (mainly IMPOWER 150 regimen), 9 patients received CHM alone and only 2 patients received IMH alone. Within 29 patients who expressed EGFR mutations, exon 19 deletions and L858R mutations accounted for nearly half of the group. All patients had progressed beyond an EGFR TKI before starting study therapy with 35% of patients failing at least two EGFR TKIs prior to data collection. The overall median PFS was 5.6 months. The median PFS for the CHM+IMN cohort was 6.3 months compared to 3.4 months and 0.4 months for the CHM and IMH cohorts respectively. The median OS was 12.8 months for patients who received CMH+IMN versus 3.4 months and 0.6 months for the CHM and IMN cohorts respectively. Survival analysis in the non-EGFR mutation populations showed no statistically significant differences between treatments.

Conclusions: Addition of immunotherapy to chemotherapy in patients with EGFR mutated mNSCLC prolonged PFS and OS in comparison to patients who received chemotherapy or immunotherapy alone. This was consistent with the results reported by the IMpower150 study group. The survival analysis result, however, was not statistically significant. due to probably the sample size. More information is needed in this field in view of other trials with challenging results.

Keywords: EGFR, Immunotherapy, NSCLC

EP.12A METASTATIC NON-SMALL CELL LUNG CANCER - TARGETED THERAPY - EGFR
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EP.12A.35 A Phase I Open-label Study Ofnimotuzumab with Nivolumab in Advanced Non-Small Cell Lung Cancer or Head and Neck Squamous Cell Cancer

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Introduction: Nimotuzumab (Nimo) is a monoclonal antibody (mAb), which targets the epidermal growth factor receptor (EGFR) and is used in Asia for the treatment of head and neck squamous cell cancer (HNSCC). Nivolumab (Nivo) is an anti-programmed death 1 (PD-1) mAb, which overcomes immune checkpoint inhibition and is approved for advanced non-small cell lung cancer (NSCLC) and HNSCC. Due to preclinical studies linking EGF to PD-L1 signaling, this trial aimed to evaluate the recommended phase II dose (RP2D) as well as the safety, tolerability and efficacy of combination treatment.

Methods: This was a single-center, single-arm, non-randomized study utilizing a 3+3 dose-escalation design. Nimo was planned to be given intravenously (IV) at escalating doses of 200mg, 300mg, and 400mg after Nivo infusion at 240mg IV every two weeks in a 28-day cycle. RP2D and dose-limiting toxicities (DLT) were determined. Treatment was continued until disease progression, unacceptable toxicity or withdrawal from the trial. Serial EKG and troponin checks were performed.

Results: Seven patients were enrolled across the 200mg and 300mg Nimo dose levels. The median age was 64.1 years. Four patients (57.1%) were males. Five (71.4%) had NSCLC and the predominant histology was pure adenocarcinoma (n=4, 57.1%). Four patients (57.1%) had KRAS mutation. All patients had disease progression after platinum-based and anti-PD1 therapy prior to enrollment except two NSCLC who were enrolled to receive this treatment after initial platinum-based chemotherapy only. Four patients (two from each dose level) had troponin elevation (median 0.1 ng/ml, range 0.07 to 0.3 ng/ml) lasting at least 24 hours which normalized next week without any associated chest pain except for one patient (HNSCC) with potential treatment-related DLT. Disease control rate was 42.9% (stable disease as best response, n=3).

Conclusions: Asymptomatic troponin elevation was seen with this combination treatment. While there were no clinically significant adverse cardiac outcomes, further development was terminated due to competitive landscape.

Keywords: Advanced non-small cell lung cancer, Targeted therapy, Immunotherapy

EP.12A METASTATIC NON-SMALL CELL LUNG CANCER - TARGETED THERAPY - EGFR
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EP.12A.36 Early Experience with the FLAURA2 Regimen in Patients with NSCLC and EGFR Mutations in Latin America

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Introduction: Clinical guidelines advise Osimertinib (Osi) as the preferred 1st-line treatment for advanced EGFR-mutated non-small cell lung cancer (NSCLC) with exon 19 deletions (del19) or L858R mutation. Recently, results from the FLAURA2 trial demonstrated better progression-free survival (PFS) at 24 months in the Osi/chemotherapy (CT) group compared with the Osi-only group (57%vs. 41%, respectively). It also found a favorable trend toward overall survival (OS) improvement at 2-years of follow-up in post-progression outcomes. However, the incidence of adverse events (AEs) >G3 from any cause was higher with the combination than with Osi alone (the percentage of AEs with an outcome of death was 6.5% and 2.9%, respectively). This study aims to collect and analyze the early outcomes of a cohort of Hispanic patients with EGFR-mutated NSCLC treated with the FLAURA2 study regimen in Latin America.

Methods: A retrospective analysis was conducted on 38 patients from five countries in Latin America who had EGFR-mutated NSCLC and were treated in 1st-line with the FLAURA2 study regimen. Patient demographics, tumor characteristics, and early treatment outcomes were analyzed. Survival analyses assessed progression-free survival (PFS) and overall survival (OS), considering the limited follow-up. Clinicobiological features, reasons for choosing the combination with Osi/CT, and perspectives on tolerance and quality of life were also evaluated.

Results: The mean age of the included patients was 62 years (+/- 7), 73% were men, 89% were never smokers, 71% had baseline cerebral involvement, and 8% had meningeal involvement. The mutational profile showed that 52.6% and 47.4% had del19 or the L858R mutation, respectively. The main reasons for choosing the FLAURA2 regimen (by treating physicians) were central nervous system (CNS) involvement (19/50%), disease burden and symptoms (11/29%), and the L858R mutation in the presence or absence of commutations (7/18.4%). The overall response rate (ORR) was 84.3%, and 5 patients (13.2%) achieved an early complete response (CR). After a median follow-up of 9.8 months, PFS (early data analysis) was 7.9 months (95%CI 7.0-8.7), and OS (immature) was 11.3 months (95%CI 10.4-14.1). At this moment, 84.2% of patients maintain the response with a >G3 toxicity of 52.6%. One patient (2.6%) died from complicated febrile neutropenia. Overall, the perspective of the treatment was that tolerance appeared to be adequate in 63.2% of cases, toxicity was more significant than expected in 18.4%, and toxicity negatively affected the quality of life vs. monotherapy in 18.4%.

Conclusions: EGFR-mutated NSCLC is more significant in Latin America; hence, the estimated impact derived from the regular use of Osi alone or in combination with CT. The findings from this multinational cohort of patients are early but demonstrate an ORR comparable to the phase III clinical trial. The reasons for choosing the FLAURA2 regimen are associated with poor prognostic factors, including CNS disease, a higher tumor burden, and the presence of the L858R mutation (especially if there are TP53 commutations). Given the increase in toxicity, a longer follow-up time and number of patients are required to estimate the real impact of using the FLAURA2 regimen.

Keywords: FLAURA, EGFR, Real world evidence

EP.12A METASTATIC NON-SMALL CELL LUNG CANCER - TARGETED THERAPY - EGFR
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EP.12A.37 Erlotinib: A Beacon of Hope in EGFR TKI-Progressed Lung Cancer, A Real-World Experience from a Tertiary Care Cancer Centre in South India

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Introduction: There are studies on the use of Osimertinib post progression on first line epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) in patients with non-small cell lung cancer (NSCLC). However, Osimertinib is expensive and beyond the reach of most patients in low-and-middle-income countries (LMICs). Currently, there is no established standard of care for patients who experience progression on Osimertinib. Here, we present our experience with Erlotinib in patients with EGFR-mutated NSCLC who have progressed on previous EGFR TKI.

Methods: We conducted a retrospective analysis of all patients with metastatic NSCLC who presented to our center between 2011 and 2024 and had experienced progression on Gefitinib and/or Osimertinib, and subsequently received Erlotinib upon progression. Patients who tested negative for EGFR receptor mutation and those who had taken Erlotinib for less than a week were excluded from the analysis. Data were extracted from the medical records. The disease control rate (DCR) was calculated as the sum of complete response (CR), partial response (PR), and stable disease (SD). Progression-free survival (PFS) and overall survival (OS) were estimated using the Kaplan-Meier method.

Results: The study included 32 patients, with a median age of 52 years, among whom 53% (n=17) were male. Most patients were non-smokers (n = 28, 87.5%), had adenocarcinoma (n=30, 94%), and exhibited a performance status (PS) of less than 3 (n=29, 90%). The most common mutation observed was EGFR exon-19 deletion (n=17, 53%), followed by Exon-21 L858R mutation (n=8, 25%), both exon 19 and 21 mutations in 3% (n=1), and others (n=6). Prior therapy included Gefitinib (n=31, 97%), Pemetrexed/Platinum-based chemotherapy (n=23, 72%), Docetaxel (n=8, 25%), and Osimertinib (n=12, 37.5%). Erlotinib was initiated as second-line treatment in 9 (28%) patients, third-line in 11 (34.5%), fourth-line in 10 (31.5%), and fifth-line in 2 (6.3%) patients. Liquid biopsy for T790M mutation testing was conducted after progression on Gefitinib in 11 (34%) patients, among whom it tested positive in 3 patients, all of whom received Osimertinib. Response assessment was performed on twenty-six patients, revealing 6 with PR (23%), 9 with SD (34.6%), and 11 (42.4%) with progressive disease. The DCR was 57.6%. The median duration of response was 8.2 months. The median PFS was 73 days (95% CI 27-118 days), while the median OS was 247 days (95% CI 107-387 days). Patients with exon 19 deletion exhibited a median PFS of 173 days compared to 53 days in patients with exon-21 L858R mutation (P=0.008). The median PFS in patients who received Erlotinib post-progression on Osimertinib was 63 days. Grade-2 or higher skin rash and diarrhea were observed in 28% (n=9) and 3% (n=1) of patients respectively.

Conclusions: This is the first study to report on rechallenge with Erlotinib in patients who have received prior EGFR TKI. Erlotinib shows activity in EGFR-mutated NSCLC patients who progress on EGFR TKIs (especially those with an exon-19 deletion) and can be considered as a treatment option when no other standard treatment is available, especially in LMICs where access to Osimertinib is limited.

Keywords: Erlotinib, EGFR Mutated metastatic NSCLC, Post Osimertinib

EP.12A METASTATIC NON-SMALL CELL LUNG CANCER - TARGETED THERAPY - EGFR
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EP.12A.38 Durable Response to Savolitinib in Advanced EGFR-WT NSCLC with MET Amplification: Case Series

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Introduction: MET amplification plays a vital role in NSCLC development, either de novo or resistance to TKI. It's an emerging biomarker in NSCLC. MET TKI is widely used in MET-aberrant NSCLC. However, the efficacy of savolitinib monotherapy in primary MET amplification as 1st line therapy or as salvage therapy in MET-amplified patients without EGFR mutation is still unknown.

Methods: Medical records from January 2023 to November 2023 were searched to collect consecutive cases diagnosed with advanced MET amplified NSCLC without EGFR/ALK/ROS1 mutation, who received savolitinib and had subsequent disease assessment. Clinicopathological characteristics, treatment response, duration, and safety were analyzed, with a data cutoff on February 29, 2024.

Results: Four patients with stage IVb EGFR-wt NSCLC and MET amplification (detected by NGS) were treated. Two patients started with savolitinib as first-line therapy, while one received it after entrectinib failure. All patients achieved a partial response (PR) within one month and maintained it until data cutoff. Patient 1, a 52-year-old male smoker, with MET amplification (CN: 14), achieved PR after 1 month of savolitinib. Patient 2, a 75-year-old male smoker with MET amplification (CN: 17.1), also achieved PR within 1 month and maintained it for 11 months. Patient 3, a 67-year-old female non-smoker with brain metastases, received entrectinib monotherapy for CHSY1-NTRK fusion and MET amplification. Disease progressed after 1 month with a pulmonary embolism, requiring ICU care. A re-biopsy showed a MET CN of 4.1. Subsequently, she received a second-line therapy of savolitinib, which rapidly improved her PS scores and achieved PR in 1 month. Then, tumor response was observed both in the brain and lung after 3 cycles. Five months later, anlotinib was added, resulting in a PFS of 7 months with consistent safety profile. Patient 4, a 67-year-old male smoker with MET amplification, received initial combination therapy followed by second-line savolitinib with PR after 5 months. However, he developed interstitial pneumonia, so savoratinib was discontinued and steroid treatment was given. One month later, a reexamination showed improvement compared to before. (Detailed information in Table)

Conclusions: Savolitinib demonstrated a quick and durable response in EGFR-wt NSCLC patients with MET amplification regardless of lines and concomitant mutations in this case series. Meanwhile, the safety profile was tolerable. Further data from larger cohorts and longer follow-up are needed to confirm these findings.

Keywords: Savolitinib, MET amplification, NSCLC

Patient case	Sex	Age	Smoking history	TNM stage	Metastases	*MET* CN	IHC	Concurrent mutation	Prior treatment	Regimen	Response	Adverse events
1	Male	52	Yes	cT4N3M1c	Bones, adrenal gland	14	*MET* IHC 3+ (90%), *PD-L1* positive(TPS:60%+)	*TP53* mutation	None	Savolitinib monotherapy	PR, ongoing	None reported
2	Male	75	Yes	cT1cN0M1c	Bone	17.1	*MET* IHC 2+ (100%), *PD-L1* positive(TPS:80%+)	*TP53* mutation;*ARID1A* mutation;*KMT2D* mutation;*RICTOR* amplification; *RICTOR* mutation	None	Savolitinib monotherapy	PR, ongoing	None reported
3	Female	67	No	cT4N3M1c	Brain	1.6(1st-line) 4.1 (re-biopsy)	Re-biopsy:*MET* IHC 3+ (100%), *PD-L1* positive (TPS:45%+)	*NTRK* fusion; *TP53* mutation;*PIK3CA* mutation;*FGFR1* amplication; *ATM* mutation;*RICTOR* mutation;	Entrectinib	Savolitinib with Anlotinib	PR, ongoing	None reported
4	Male	67	Yes	cT2N3M1c	Thoracic vertebral, brain	3.3	PD-L1(TPS:85%)	*TP53* mutation;BRCA2 mutation;NF2 mutation;	Combined immunochemotherapy	Savolitinib, with sindilimab	PR, ongoing	Interstitial pneumonia

EP.12A METASTATIC NON-SMALL CELL LUNG CANCER - TARGETED THERAPY - EGFR
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EP.12A.39 MET Point Mutations as the Mechanism of Resistance to EGFR-TKI Therapy: A Case Report of MET H1094Y-Mediated Resistance to Osimertinib Overcome by Capmatinib and a Systematic Review.

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Introduction: The EGFR tyrosine kinase inhibitors (TKIs) are the frontline standard in the treatment of metastatic EGFR-mutant NSCLC. Although response rates are impressive, most patients develop resistance through secondary EGFR mutations, upregulation of alternate signaling pathways, and histological transformation. Activation of the MET signaling pathway by means of amplification is a common resistance mechanism to EGFR-TKIs, but activation caused by point mutations in MET has only been rarely described. Here we describe MET H1094Y as the mechanism of resistance to EGFR-TKI therapy that was overcome by combination therapy with osimertinib and capmatinib.

Methods:

Results: Our patient is a 69-year-old male who has metastatic EGFR-mutant exon 19 deletion lung adenocarcinoma. Molecular profiling done on the tissue showed EGFR exon 19 deletion with EGFR amplification, and alterations in MDM2, AXIN1, and PRKDC. He received osimertinib monotherapy and achieved a partial response. Seven months later, he came off osimertinib due to progressive disease in the thorax. Blood-based next-generation sequencing (NGS; Guardant) showed no detectable genomic alterations including the EGFR mutation. As second-line treatment, he received combination immune checkpoint inhibitor therapy for seven months. Blood-based NGS (Guardant) done around the time of progressive disease showed a significant increase in the allele frequency (AF) of the EGFR mutation (nondetectable to 12.6%) along with EGFR amplification. He started third-line treatment with a novel EGFR-TKI in a clinical trial in May 2023. Due to progressive disease manifesting as rapidly accumulating pleural effusion, he was taken off the trial in October 2023 and required supplemental oxygen usage and indwelling pleural fluid catheter placement. Repeat blood-based NGS (Guardant) showed that the EGFR mutant variant AF decreased from 12% to 2%, but there was a new MET mutation (MET H1094Y). He started osimertinib with capmatinib on 10/28/23. He had rapid and dramatic reduction in his pleural effusions, with symptomatic improvement in cough and dyspnea. The indwelling pleural fluid catheter stopped draining in December 2023 and he no longer requires supplemental oxygen. He is tolerating the combination well except for grade 2 creatinine elevation from a baseline of 1.3 to 1.7 which is attributed to capmatinib and grade 2 lower extremity edema requiring dose reduction of capmatinib. Repeat blood-based NGS was done on 12/18/23 and 2/29/24 and there was disappearance of both the EGFR exon 19 deletion and MET H109Y mutation. The literature review revealed singular reported cases of MET H1094Y (treated with gefitinib and crizotinib), L1195F, D1228N/H, P97Q, I865F, Y1003N, along with a case of simultaneous D1228N/H, Y1230H and D1231Y mutations after EGFR-TKI therapy. The details of these cases will be presented.

Conclusions: Our patient's case is the first reported usage of osimertinib and capmatinib for MET H1094Y after EGFR-TKI. This case demonstrates several clinical pearls. At disease progression, molecular profiling plays a critical role in identifying resistance mechanisms. Our patient's clinical improvement suggests that the MET H1094Y point mutation can mediate resistance to EGFR-TKI therapy, which can be overcome by simultaneously targeting both EGFR and MET. Further research is needed to comprehensively catalogue actionable MET alterations beyond MET amplification.

Keywords: EGFR-TKI resistance, Capmatinib, H1094Y

EP.12A METASTATIC NON-SMALL CELL LUNG CANCER - TARGETED THERAPY - EGFR
SATURDAY, SEPTEMBER 7, 2024 - 11:58 - 11:59

EP.12A.40 Savolitinib Plus Osimertinib for Previously Untreated NSCLC Patients with EGFR Mutations and Met-Amplification: A Case Series

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Introduction: Rarely (2-4%) observed in untreated advanced NSCLC patients, primary MET amplification (METamp) may be slightly common in NSCLC patients with EGFR mutations (m), which may induce primary resistance to EGFR tyrosine kinase inhibitors (TKIs) used as primary therapy. Preclinical data have suggested that EGFR TKIs plus MET TKIs are a possible subsequent therapy for EGFRm NSCLC patients who developed acquired resistance to EGFR TKIs. Here, we present a case series highlighting the clinical activity of savolitinib plus osimertinib as first-line therapy in previously untreated NSCLC patients with both EGFRm and METamp.

Methods: Previously untreated advanced NSCLC patients with EGFRm and METamp detected by next-generation sequencing (NGS) received concomitant oral savolitinib 400 mg QD and oral osimertinib 80 mg QD. Investigators assessed the objective response based on RECIST v1.1, and progression-free survival (PFS) was analyzed.

Results: Three patients were retrospectively reviewed: 1) A 55-year-old female patient was diagnosed with stage IVA poorly-differentiated lung adenocarcinoma. NGS revealed an EGFR L858R mutation and METamp. The patient was administered concomitant savolitinib plus osimertinib orally. After 24 days of treatment, the CT scan showed that the volume of the primary lesion was significantly reduced, and the clinical evaluation was partial response (PR). By the time of manuscript submission, the patient was still in response with a PFS of more than 22 months. The safety profile was good. 2) A 67-year-old male patient was diagnosed with stage IIIB poorly-differentiated lung adenocarcinoma. NGS identified 18 gene variations, including three driver alterations of EGFR p.L861Q, PIK3CA p.R88Q, and METamp. The patient received savolitinib plus osimertinib treatment. The CT scan after 45 days of treatment showed obvious tumor shrinkage, and the clinical evaluation was PR. As of the last follow-up visit, the patient was still in response with a PFS of over 13 months. There were no other drug-related side effects except Grade 1 nausea. 3) A 60-year-old female patient was diagnosed with stage IVA lung adenocarcinoma. NGS revealed EGFR 19del and EGFR20 p.T790M mutations, and this patient also harbored MET amplification (copy number: 4.4). The patient received a combination therapy of savolitinib and osimertinib. CT images on Day 19 of the treatment showed significant shrinkage of the primary tumor, and the clinical evaluation was PR. Up to now, the patient was still receiving treatment with no sign of progression, and the PFS is 34 months. No intolerable adverse event was observed.

Conclusions: Savolitinib plus osimertinib first-line treatment showed rapid and durable antitumor activity in previously untreated advanced NSCLC patients with EGFRm and METamp, and the safety profile was acceptable. However, the clinical activity of this combination therapy in first-line settings still requires further investigation and validation in larger cohorts.

Keywords: NSCLC, EGFR, MET

EP.12A METASTATIC NON-SMALL CELL LUNG CANCER - TARGETED THERAPY - EGFR
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EP.12A.41 First-Line Treatment of EGFR-Mutant NSCLC: TKI Alone or Combinations - What I Use Today and Why in the Latin America vs the World

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Introduction: Lung cancer has the highest lethality among all cancers in Latin America (LATAM), settling a huge health issue as the Continent faces a limited access to diagnosis and treatment. Non-small cell lung cancer (NSCLC) accounts for about 80% of all lung cancers. Concerning this histological type, mutations of the epidermal growth factor receptor (EGFR) are the most frequent ones, determining tumor growth and progression. Tyrosine kinase inhibitors (TKIs) represent today the first-line treatment for advanced NSCLC containing activating EGFR mutations. Despite that, it is related to acquired resistance, which suggests that maybe combinations with a different agent may improve clinical outcomes. Although, due to impaired accessibility for other agents in LATAM, TKI alone still remains the primary treatment for this disease. Therefore, there is a crescent need for more knowledge around the outcome of TKI alone or in combination in the treatment of NSCLC in LATAM and how it compares to the rest of the World.

Methods: This consists on a review study of articles available in databases PubMed and Lilacs about the treatment with EGFR-TKI for NSCLC in Latin America. Using the keywords “EGFR”, “TKI” and “NSCLC” with the Boolean operator “AND” and filtering between years 2018 - 2022, there were found 1.680 articles; by adding the marker “Latin America”, the number rechead was only 3. Then, thirty articles were selected to guide this study. Then all data was noted in a document and analyzed.

Results: Based on the findings of the articles, there is a paucity of data evaluating the scenario around EGFR-Mutant NSCLC treatment in Latin America. Although, over the world, combined therapy appears to be favored over monotherapy with EGFR - TKIs for the treatment of this kind of tumor. Studies highlighted that combining platinum-based chemotherapy with TK-inhibitors evidenced conflicting overall survival (OS) compared to monotherapy, besides greater results of progression free survival (PFS) and overall response rates (ORR). One of those shared resembling OS, but significant PFS and ORR for pacients receiving combination therapy compared to the group that got monotherapy (PFS: 5.6 vs 2.8 months, ORR: 32.1% vs 13.2%, respectively). Other studies, on the other hand, showed a significant difference of OS between the use of TKI combined or alone (OS= 25,8 months [CI,16.27-35.33] vs 19,8 months [CI, 18.60-21.00]), as well as greater PFS (PFS = 7.9 months vs 5.9 months [p = 0.015], respectively). Still, combined therapy may be related to increased toxicity and a second or third-generation EGFR-TKI may be a preferable treatment for patients with advanced disease. In LATAM, the first-line treatment is yet based on isolated TKI without emphasys on the combination regimens, mainly due to limited resources of the countries’ health systems.

Conclusions: Although some data suggesting that combination therapy may offer significant advantages over TKI monotherapy in EGFR-mutant NSCLC, poor accessibility to diagnosis and treatment in Latin America represents a barrier to overcome lung cancer within the continent.

Keywords: NSCLC, EGFR-TKI, Latin America

EP.12A METASTATIC NON-SMALL CELL LUNG CANCER - TARGETED THERAPY - EGFR
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EP.12A.42 Savolitinib Plus Osimertinib in EGFR-Mutant NSCLC with MET Overexpression and Acquired Resistance to Previous EGFR Inhibitor

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Introduction: Aberration of MET (overexpression or amplification) is one of the primary mechanisms of acquired resistance to EGFR-TKIs. Preliminary data from TATTON and SAVANNAH trials indicated encouraging activity of savolitinib, an oral, potent, and highly selective MET-TKI, in combination with osimertinib in patients with MET-amplified/overexpressed, EGFRm advanced NSCLC with disease progression on a prior EGFR-TKI. Here, we present 6 patients with EGFR-mutant MET-overexpressed NSCLC receiving savolitinib plus osimertinib outside of clinical trials.

Methods: The medical record was accessed and reviewed retrospectively. Patients with EGFR-mutant advanced NSCLC, who experienced disease progression after prior EGFR-TKI therapy, with tissue re-biopsy indicating acquired MET overexpression (MET IHC; 3+ in ≥50% of tumor cells, MET IHC 3+) and subsequently received savolitinib plus osimertinib regimen, were included. Clinicopathological characteristics, treatment response and duration and adverse events (AEs) were analyzed. The data cut-off date was March 5, 2024.

Results: Six patients diagnosed with EGFR-mutant MET-overexpressed NSCLC, following disease progression on EGFR-TKI, were treated with savolitinib 400mg daily and osimertinib 80 mg once daily, as detailed in the table. Patients were aged 51-74 years, four were male, three had smoking history, all were adenocarcinoma and two had brain metastases at diagnosis (patient 2 and 5). Five patients were harboring EGFR L858R mutation (patient 1 had EGFR 19 exon deletion). Among all patients, three of them also observed acquired MET amplification (in re-biopsy tissue, 2 by NGS, 1 by FISH testing), with MET gene copy number ranged from 4.8 to 8.3. Five patients previously treated with third-generation EGFR-TKI and three had prior chemotherapy. The median prior lines of therapy were 2 (range, 1-5). All patients achieved a partial response as per physician assessment. Till data cutoff date, treatment was ongoing for three patients, while the remaining three discontinued due to disease progression. Median follow-up duration was 20.5 months (range, 19.3-24.9) and median progression-free survival of 13.7 months (range, 8.8-23.2), two patients are currently alive while patient 1 died on February 11, 2024. Median treatment duration was 13.3 months (range, 8.8- 23.3). The most common AEs are edema (6/6, 100%), nausea (3/6, 50%) and fatigue (3/6, 50%), mostly grade 1 or 2.

Conclusions: In this case series, savolitinib and osimertinib showed promising clinical benefit in patients with MET-overexpressed, EGFR mutation-positive, advanced NSCLC, who had disease progression on previous EGFR-TKI. Safety profile was acceptable . Meanwhile, the tissue re-biopsy could help identify resistance mechanism to guide subsequent therapy.

Keywords: MET, Savolitinib, NSCLC

EP.12A METASTATIC NON-SMALL CELL LUNG CANCER - TARGETED THERAPY - EGFR
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EP.12A.43 Savolitinib and Third-Generation EGFR-TKI Therapy in EGFRm, MET-Altered NSCLC Patients: A Case Series

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Introduction: The efficacy of EGFR-TKIs plus MET-TKIs in EGFRm lung cancers with primary/acquired MET alterations is still controversial. We aimed to assess the response of savolitinib plus third-generation EGFR-TKI in advanced or metastatic NSCLC patients with EGFRm and MET alterations in real-world setting.

Methods: Medical records were reviewed for three NSCLC patients with MET alterations and EGFRm who received savolitinib plus EGFR-TKI from July 2022 to February 2024. A retrospective analysis was conducted on the patient's symptoms, diagnosis, and the efficacy and safety of combination therapy. Progression-free survival (PFS) was calculated from the start of combination therapy.

Results: Patient 1 is a 70-year-old male smoker who has been diagnosed with advanced lung sarcomatoid cancer (cT4N2M1c, Stage IVB). EGFR L858R and MET 14 exon skipping mutations were detected by DNA-based NGS in tumor tissue. The patient was subsequently treated with savolitinib and osimertinib, and achieved PFS of 16 months, and was still in remission. The patient had only mild adverse reactions (increased aminotransferase, grade 2; edema, grade 2), which were resolved after symptomatic treatment. Patient 2 was a 50 years old non-smoking woman with lung adenocarcinoma (pT3N3M0, Stage IIIC) with EGFR L858R mutation. Brain metastases developed without symptoms during adjuvant platinum-containing chemotherapy. After 20 months of gefitinib treatment, the patient developed a central nervous system progression. EGFR T790M mutation was detected by NGS in blood and the patient was subsequently treated with osimertinib, but the effect was poor. After consultation of the Lung Cancer MDT Team, we considered that the patient had progressive aggravation of intracranial cerebral edema, obvious midline displacement, and a high risk of cerebral hernia. Brain surgery was recommended. The patient subsequently underwent two surgeries with brain metastases. Postoperative pathology suggested metastatic lung adenocarcinoma, and EGFR L858R and MET overexpression were detected by DNA-based NGS and IHC (SP44, ++-+++) respectively in tumor tissue. Then the patient received savolitinib and third-generation EGFR-TKI, improving left lower limb muscle strength. However, self-with drawing savolitinib for 1 month led to a decrease in muscle strength. Fortunately, recovery of combination therapy restored muscle strength. The patient achieved PFS of 19 months and was still in remission. No adverse events were observed in relation to the treatment. Patient 3, a 35-year-old male smoker with advanced lung adenocarcinoma (cT1N2M1c, Stage IVB) with EGFR 19Del mutation, responded initially to osimertinib, but after 13 months, the disease progressed. DNA-based NGS testing revealed EGFR 19Del and MET amplification. Chemotherapy and anti-angiogenic therapy were given for 5 months, but disease progressed. Fourth-line therapy with savolitinib and osimertinib resulted in partial response (PR) with 7-month PFS. When progressed, the patient was diagnosed as small cell neuroendocrine carcinoma with biopsy of lower abdominal. Currently, the patient was receiving albumin-paclitaxel monotherapy (7th line).

Conclusions: Combination therapy of savolitinib and third-generation EGFR-TKI shows potential in treating advanced or metastatic NSCLC patients with EGFRm and MET alterations. A comprehensive test of MET should be conducted by various ways. Dual-targeted therapy may be effective in EGFRm and MET-altered patients.

Keywords: EGFRm, MET-altered, Savolitinib

EP.12A METASTATIC NON-SMALL CELL LUNG CANCER - TARGETED THERAPY - EGFR
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EP.12A.44 Short-course Immunotherapy Prior to Targeted Therapy in EGFR-Mutated Metastatic Non-Small Cell Lung Cancer: A Retrospective Study

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Introduction: Despite epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) being the standard treatment for patients with EGFR-mutated (EGFRm) metastatic non-small cell lung cancer (mNSCLC), the extended duration required for genetic mutation testing and the urgency to treat patients with rapidly progressing disease often lead to the initiation of immunotherapy (IO) before obtaining mutation testing results in clinical practice. This study evaluates the efficacy and safety of a sequential treatment regimen, transitioning from a short course of IO to targeted therapy upon confirmation of EGFR mutations (including exon 19 deletions or L858R mutations) in NSCLC patients.

Methods: We conducted a retrospective analysis of EGFRm mNSCLC patients who received first-line (1L) IO±chemotherapy (CT) (1-4 cycles) ± anti-angiogenesis therapy (AAT) followed by EGFR TKI (first, second, or third generation)±CT±AAT at our center from June 17, 2019, to June 17, 2023. Follow-up continued until March 28, 2024. The primary endpoints were objective response rate (ORR), disease control rate (DCR), and safety, with progression-free survival (PFS) evaluated through Kaplan-Meier analysis.

Results: The study included 22 patients, with an average age of 59.27±9.57 years, of whom 86.36% were diagnosed with adenocarcinoma, and 36.36% were female. Thirteen patients were carriers of EGFR exon 19 deletions, and nine had the L858R mutation. Prescriptions for IO were all issued before the results of EGFR mutation testing were available. The sequential strategy yielded an ORR of 77.27%, with an ORR of 44.44% (4/9) and a DCR of 100% assessed after the short-course IO. Adverse events of grade ≥3 were documented in 2 patients (9.09%), including hepatic dysfunction and myelosuppression, both of which were manageable. Sixteen patients were included in the survival analysis, with a median PFS estimated at 879.125 days (95% CI: 638.139-1120.111).

Conclusions: This study reveals that the compelling sequential treatment strategy initiated by clinical necessity, with short-course IO followed by targeted therapy, demonstrated manageable safety without significant adverse reactions. However, the impact of short-course IO on subsequent targeted therapy, whether positive or negative, requires further clarification. Based on an in-depth analysis of existing clinical data, our findings allow us to explore strategies for the effective combination of IO with targeted therapy to address complex clinical challenges within the framework of personalized treatment, especially over larger patient cohorts and longer follow-up periods.

Keywords: EGFR-mutant mNSCLC, targeted therapy, immunotherapy

EP.12A METASTATIC NON-SMALL CELL LUNG CANCER - TARGETED THERAPY - EGFR
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EP.12A.45 Study of the Mutational Profile of EGFR-Mutated Lung Cancer in the Russian Population on the Example of the City of Moscow

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Introduction: EGFR-mutations are the most common driver mutations in patients with non-small cell lung cancer. This paper investigates the mutational profile and survival of patients with EGFR-positive lung cancer in the Russian population using the example of Moscow city.

Methods: We analyzed databases of the State budgetary health care institution “Moscow City Oncology Hospital No. 62”. We analyzed 1113 cases of non-small cell lung cancer with EGFR mutation in the period from 2013 to 2021. Statistical analysis of the results was performed using GraphPad Prism 9.5.1 (GraphPad Software, San Diego CA, USA). Quantitative and qualitative features were evaluated, and the nonparametric log-rank test was used to compare survival curves. Differences were considered statistically significant at $p<0.05$.

Results: The majority of the sample patients (74%) were female. The age range was from 29 to 94 years, with a median age of 66 years. Most frequently the mutation was found in exons 19 and 21 (55.6% and 37.4%, respectively), less frequently in exons 18 and 20 (4.6% and 1.9%, respectively). The T790M mutation was detected in 89 patients (8.0%), more commonly in patients with a mutation in exon 19 (55.6%). The median progression-free survival of patients with locally advanced or metastatic lung cancer was 13.3 months, and overall survival was 28.8 months. No correlation between the localization of mutation in the EGFR gene and patient survival was found.

Conclusions: The data on the sex and age structure of the sample, the distribution of occurrence of various EGFR mutations in patients with EGFR-positive lung cancer are consistent with the data of the world literature. The results of survival analysis of patients with EGFR-positive locally advanced or metastatic lung cancer are comparable to the results of the randomized phase III clinical trial FLAURA.

Keywords: EGFR-mutated NSCLC, targeted therapy

EP.12A METASTATIC NON-SMALL CELL LUNG CANCER - TARGETED THERAPY - EGFR
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EP.12A.46 Age, Health Utility Scores (HUS), and Survival Outcomes in EGFR-Mutated Lung Cancer Patients Receiving 1L TKI Treatment

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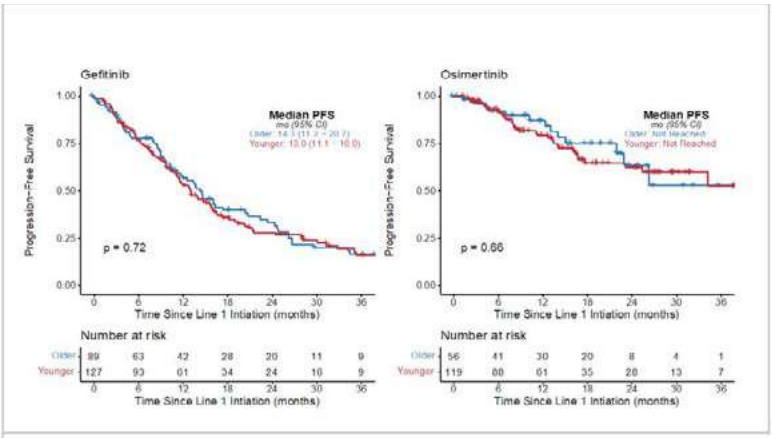
Introduction: EGFR-mutated cancers span a broad age-range. We evaluated whether there were differences in HUS, treatment course and survival while on first-line (1L) tyrosine kinase inhibitor (TKI) therapy, by age.

Methods: Patients with EGFR-mutated lung cancers were recruited prospectively (2015-2023; CARMA-BROS-real-world-observational study; NCT:04151342). Clinico-demographic, treatment, outcome data, and patient-reported EQ-5D-5L questionnaires were collected. Health Utility Scores (HUS) were derived from Canadian population norms. Older group was defined as age 70+ years. Younger group was defined as <70 years at time of diagnosis of advanced/metastatic EGFR-mutated lung-cancer.

Results: Among 233 older (median age 77 [IQR:73-82] years) and 396 younger patients (median 59 [IQR:52-64] years), major demographics were similar (64% female, among known-ethnicity, 62%/Asian, 25%/White; 70%/never-smoker) except for performance-status (ECOG-PS), where older patients had worse ECOG-PS (p<0.001). Among all EGFR-mutations, 87% were common; 9% were exon-20-insertions (p>0.05 between younger/older). Among common mutations, older patients were more likely to have L858R mutation (56% older vs 39% younger) than exon 19-deletion (p<0.001), and had greater number of comorbidities by modified-Charlson-comorbidity-index (mCCI) scores (11% mCCI=3+ and 34% mCCI=0 in older versus 8% mCCI=3+/ 54% mCCI=0 in younger; p<0.001). The table shows mean-HUS at initiation of, on, and progression on 1L-TKI by age-group; the main difference between older versus younger groups was the larger drop in HUS at progression on 1L-TKI in older adults. Median PFS on 1L-gefitinib/1L-osimertinib in older versus younger patients are presented in the Figure; PFS appears similar between age-groups, with caveat of short median-follow-up for Osimertinib patients.

Conclusions: Older patients with EGFR-mutated advanced/metastatic lung cancers derive similar benefit (in efficacy and quality-of-life) while on monotherapy TKIs, despite older patients having more comorbidities, worse ECOG-PS, and more EGFR-L858R-mutations at baseline. However, at progression on 1L-TKI, older patients suffer greater decreases in quality-of-life, signifying an unmet need to improve 1L PFS in such patients.

Keywords: EGFR-mutated, 1L-TKI, older adults



Age Group	Disease State (First-line)	Any TKI N	Any TKI Mean HUS (95% CI)	Gefitinib N	Gefitinib Mean HUS (95% CI)	Osimertinib N	Osimertinib Mean HUS (95% CI)
70+ years	At TKI initiation	57	0.78 (0.74 – 0.83)	25	0.79 (0.74 – 0.85)	32	0.77 (0.70 – 0.84)
	Stable on TKI	80	0.82 (0.78 – 0.85	64	0.83 (0.79 – 0.87)	16	0.78 (0.67 – 0.88)
	At Progression on TKI	20	0.58 (0.47 – 0.69)	15	0.54 (0.42 – 0.66)	5	0.70 (0.42 – 0.99)
<70 years	At TKI initiation	82	0.72 (0.67 – 0.77)	31	0.79 (0.74 – 0.83)	51	0.68 (0.61 – 0.75)
	Stable on TKI	145	0.81 (0.79 – 0.84)	97	0.84 (0.81 – 0.86)	48	0.77 (0.72 – 0.83)
	At Progression on TKI	26	0.77 (0.69 – 0.84)	15	0.81 (0.73 – 0.88)	11	0.71 (0.56 – 0.87)

EP.12B METASTATIC NON-SMALL CELL LUNG CANCER - TARGETED THERAPY - FUSIONS: ALK / ROS1 / RET / NTRK
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EP.12B.01 Weight Gain and Metabolic Changes Associated with Alectinib Use in ALK-Positive Lung Cancer

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Introduction: Alectinib is a widely used ALK tyrosine kinase inhibitor (TKI) and thought to be generally well tolerated. However, weight gain and other adverse metabolic effects associated with alectinib may be under-reported and the real-world prevalence of these metabolic changes with potential impact on cardiovascular health and long-term quality of life is unknown.

Methods: In this single-institution retrospective analysis, we analyzed clinical data for 72 patients with advanced ALK-positive NSCLC treated with first-line alectinib. Additionally, 59 patients with advanced EGFR-mut NSCLC treated with first-line osimertinib were also analyzed as a comparator cohort with similar demographics and performance status as ALK-positive patients and with usage of a comparably well tolerated and highly effective TKI. Clinical data analyzed included patient demographics, cardiovascular and endocrine comorbidities, duration of TKI therapy, and changes in weight during therapy. Chi-square analyses and t-tests assessed differences in metabolic changes between ALK-positive and EGFR-mut groups during TKI therapy. Univariate and multivariate logistic regression assessed metabolic and genomic factors associated with weight gain.

Results: Median follow-up time for the alectinib and osimertinib group was 27.7 months and 19.4 months, respectively, with no significant difference in baseline performance status (p=0.33). Treatment-emergent weight gain was observed at 23.2% Grade 1, 29.0% Grade 2, 5.8% Grade ≥ 3 for alectinib and 23.6% Grade 1, 9.0% Grade 2, 1.8% Grade ≥ 3 for osimertinib. Relative weight gain (%) in patients treated with alectinib was significantly greater than those treated with osimertinib at 6, 12, and 18 months (all timepoints $p < 0.001$), with increasing magnitude of difference at each time point. After 12 months on TKI, patients treated with alectinib had a mean weight gain of 7.3% and 1.61-fold increase in BMI compared to a 0.8% weight decrease and 0.12-fold BMI decrease in patients treated with osimertinib ($p < 0.001$). After controlling for comorbidities including diabetes, hypertension, pre-treatment dyslipidemia, and smoking status, patients on alectinib were significantly more likely to have a grade 2 or higher (≥ 10% increase) weight gain relative to patients on osimertinib (OR 7.07, 95% CI 2.12-29.09). Among patients with baseline and on-treatment LDL results (alectinib n=20, osimertinib n=7) and Hemoglobin A1c results (HbA1c; alectinib n=11, osimertinib n=4), there was no significant treatment-related changes in LDL (mean LDL change +10.9 points for alectinib, +15.1 points for osimertinib, p=0.87) or HbA1c (mean HbA1c change -0.1 points for alectinib, -0.4 points for osimertinib, p=0.23).

Conclusions: First-line alectinib in a real-world cohort is associated with >30% incidence of G1-G2 weight gain, more than 3-fold higher than previously reported in Phase 3 clinical trial results and significantly increased relative to a similar EGFR-mut cohort treated with a comparably well tolerated and highly effective TKI. Prospective evaluation of weight and potential long-term metabolic complications related to alectinib and other ALK TKIs is warranted.

Keywords: alectinib, TKI, osimertinib

EP.12B METASTATIC NON-SMALL CELL LUNG CANCER - TARGETED THERAPY - FUSIONS: ALK / ROS1 / RET / NTRK
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EP.12B.02 Real-World Treatment Patterns and Effectiveness in Patients with ALK+ Advanced NSCLC Treated with 1L ALK TKIs

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Introduction: This retrospective cohort study described real-world treatment patterns and effectiveness in patients with anaplastic lymphoma kinase positive (ALK+) advanced non-small cell lung cancer (NSCLC) treated with first-line (1L) ALK tyrosine kinase inhibitors (TKIs).

Methods: Data for adults with ALK+ advanced NSCLC initiating 1L alectinib, brigatinib, lorlatinib, or crizotinib monotherapy (index date: initiation of 1L ALK TKI) were extracted from the US Flatiron EMR-derived database (Jan 2011-Sept 2023). First subsequent treatment (2L) after 1L ALK TKI, real-world time to treatment discontinuation (rwTTD) and time to next treatment (rwTTNT) of 1L ALK TKI were evaluated. A multivariate Cox proportional hazard model to compare rwTTD and rwTTNT for 1L brigatinib or 1L alectinib vs. crizotinib, adjusting for relevant covariates (age, sex, race, ECOG-PS, smoking, baseline brain metastasis, time from advanced diagnosis to index) was performed. To further compare the real-world effectiveness of 1L brigatinib vs. 1L alectinib or 1L crizotinib, propensity score matching using an inverse probability of treatment weighting (IPTW) method was applied.

Results: The study included 832 patients: 1L alectinib, 643; 1L brigatinib, 28; 1L lorlatinib, 17; 1L crizotinib, 144; mean age: 62, 61, 61, 70 years; % male: 44%, 57%, 35%, 45%; ECOG-PS 0-1 at index: 69%, 50%, 65%, 60%. In the 1L alectinib cohort, 2L lorlatinib was the most common ALK TKI (17%) followed by 2L brigatinib (6%). In the 1L brigatinib cohort, 2L lorlatinib was the most common ALK TKI (18%). 1L alectinib and 1L brigatinib were associated with improved rwTTD or rwTTNT vs. 1L crizotinib (Table). IPTW analysis showed similar effectiveness for 1L alectinib and 1L brigatinib and improved effectiveness for 1L brigatinib vs. 1L crizotinib (Table).

Conclusions: In patients with ALK+ advanced NSCLC, 1L alectinib and 1L brigatinib had similar rwTTD and rwTTNT. These real-world findings mirror and support the Phase 3 ALTA-1L trial data demonstrating the efficacy of 1L brigatinib vs. crizotinib in patients with ALK+ advanced NSCLC.

Keywords: Brigatinib, Real-world data, ALK+ NSCLC

Table: rwTTD and rwTTNT

1L ALK TKI[a]	Unadjusted median[b] months (95% CI)	Adjusted median[c] months (95% CI)	Adjusted HR[d] (95% CI)	*P* value
rwTTD				
Alectinib (n=643)	23.2 (18.2–29.2)	23.5 (18.6–34.2)	0.304 (0.241–0.384)	<0.0001
Brigatinib (n=28)	23.9 (8.4–NR)	23.9 (8.4–NR)	0.357 (0.199–0.641)	0.0006
Crizotinib (n=144)	4.1 (3.0–5.0)	6.7 (3.0–15.7)	-	
rwTTNT				
Alectinib (n=643)	25.5 (20.5–31.6)	28.9 (22.8–36.9)	0.321 (0.254–0.405)	<0.0001
Brigatinib (n=28)	23.9 (10.8–NR)	23.9 (10.8–NR)	0.377 (0.210–0.675)	0.001
Crizotinib (n=144)	5.3 (4.1–7.4)	12.5 (NR–NR)	-	

[a]1L lorlatinib was not assessed due to small sample size. [b]Estimated using Kaplan-Meier survival analysis. [c]Post IPTW (conducted separately for brigatinib vs. alectinib and brigatinib vs. crizotinib. [d]Cox proportional hazard model with crizotinib as control.

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EP.12B.03 Cognitive Impact of Lorlatinib Administration in Advanced Non Small Cell Lung Cancer with ALK and ROS1 Fusions

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Introduction: Lorlatinib is a third-generation ALK and ROS1 tyrosine kinase inhibitor (TKI) recently been approved in Italy for the treatment of ALK and ROS1 rearranged Non-Small-Cell Lung Cancer. Compared with first and second-generation ALK and ROS1 TKI, lorlatinib has a specific Adverse Events (AEs) profile including neuropsychological effects. Lorlatinib neurotoxicity has been partly attributed to pharmacokinetics, specifically its ability to penetrate the blood-brain barrier and accumulate in the central nervous system (CNS) and partial inhibition of trkB. Since many patients do not experience cognitive AEs during treatment, it is possible that different and non-characterized factors beyond drug concentration in the CNS, could influence susceptibility to neuropsychological AEs of lorlatinib. Moreover, the exact prevalence of cognitive sequelae in "real-life" setting is unclear. The aim of our preliminary experience, based on patients' initial report of subjective cognitive deficits, was to evaluate the neuropsychological impact of lorlatinib treatment.

Methods: A battery of neuropsychological tests, tapping: learning (L); short and long-term memory (STM; LTM); executive functions (EF); reasoning (R); attention (ATT) and visuo-constructional abilities (CA) was administered to each patient. We furtherly collected demographic and clinical data: sex, age at diagnosis, education, Performance status, histology, smoking history, dose reduction, presence of brain metastases and previous local treatment (surgery or RT).

Results: We included 15 never or ex light smoker lung adenocarcinoma patients (12 males) with median age at diagnosis of 64 years (range 25-84), 14 harboring alk fusion and 1 ros 1 positive. At therapy initiation, 10/15 (66%) were PS:0, 4/15 (26%) and 1 (6%) PS:2. 9/15 (60%) had BM at baseline, 1/15 (6%) had previous WBRT and 2/15 (13%) SBRT. Among the 9 patients with BM, 2 had brain complete response, 3 stable disease, 3 partial response, 1 was not evaluable. Interestingly, all the 3 patients who achieved brain PR were pretreated with RT while complete response was observed in no RT patients. 3 patients with brain metastases (20%) presented with at least one cognitive deficit (range 0-2), while 12 (80%) showed no impairment. Deficits affected EF (n=3), LTM (n=1), STM (n= 1), L (n=1) and CA (n=1). A subgroup of 9 patients underwent a follow-up test session at a median time of 12 months (range: 6-15). Adverse events of grade ^{3}2 leading to dose reduction were experienced in 4 patients (26%), 1 for dizziness, 1 for psychotic reaction, 1 for severe peripheral edema, 1 for hypercholesterolemia and hypertriglyceridemia. 3 patients showed a stable and impaired cognitive status, with deficits affecting EF (n=2), LTM (N=2), L (n=1) and CA (n=1). Neuropsychological functions in the remaining 6 patients was preserved and, in 2 of them, tests scores (memory and attention) slightly improved.

Conclusions: Our preliminary data seem to indicate that cognitive functions in these patients are influenced by a set of factors rather than by administration of lorlatinib alone. Despite the small sample size, this is one of the first studies performing an in-depth neuropsychological assessment on a long time-span.

The study is currently ongoing to prospectively follow treatment naïve patients in first line.

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EP.12B.04 BMF Deficiency Leads to an Increase of Drug Tolerant Persister Cells in ALK-Positive Lung Cancer

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Introduction: ALK-rearranged non-small cell lung cancer (NSCLC) often shows remarkable tumor shrinkage by the treatment with ALK inhibitors (ALKi) with long-lasting efficacy. However, acquired resistance inevitably leads to tumor relapse, and a small fraction of patients experience relapse within a short period. Pre-existing drug-resistant cells harboring genetic alterations in ALK or other oncogenes, and drug tolerant persister (DTP) cells have been implicated as the cause of the development of resistant tumors. However, the mechanism by which these tumor cells survive exposure to ALKi has not been fully elucidated. To identify this mechanism, we performed a genome-wide CRISPR/Cas9 knockout screening using ALK-positive patient-derived cell lines (PDCs) that are sensitive to ALK-TKIs. Recently, we found and reported that loss of ERRFI1 (MIG6) causes ALKi resistance induced by low-dose EGF ligand-mediated EGFR activation (JCI Insight 2023). In addition, we have identified several factors that can induce DTP phenotypes in the ALK-TKI naïve cells. In the current study, we identified that loss of Bcl-2 modifying factor (BMF), a pro-apoptotic protein, increased DTP cells, and analyzed the detailed mechanisms how BMF loss induces the DTP cells and how to overcome these DTP phenotypes.

Methods: A genome-wide sgRNA library was introduced Cas9 overexpressed ALK-TKI sensitive ALK-positive NSCLC cells, and cultured in alectinib or lorlatinib containing medium for 9 days. Genomic DNA from the remaining DTP cells was purified for sgRNA sequences analysis by NGS. Identified candidate sgRNA target genes were knocked out by creating additional sgRNA in ALK-TKI sensitive cells, and DTP phenotypes were confirmed by various assays. Regarding the BMF, the mechanisms of gene expression regulation and the effect of mitochondria-mediated apoptosis were investigated by quantitative PCR, and immunoblot of related proteins. To overcome the DTP phenotypes by BMF loss, knockdown of pro- and anti-apoptotic proteins or inhibitor treatments were performed.

Results: BMF loss was identified as one of the top hits in the CRISPR/Cas9 screening. Since BMF is known to induce mitochondria-mediated apoptosis by inhibiting anti-apoptotic proteins, deletion of BMF in ALK-positive NSCLC cell lines resulted in a decrease in apoptosis induction and an increase in the number of DTP cells under ALKi treatment. BMF protein levels significantly increased within 24 hours of ALK-TKI treatment, and the increase was also observed upon co-inhibition of both ERK and PI3K. In BMF knockout cells treated with ALKi, apoptosis was effectively induced by knocking down or inhibiting MCL-1. Concurrent knockdown of MCL-1 and BCL-XL further enhanced the induction of apoptosis by ALKi.

Conclusions: BMF deficiency increases DTP cells by attenuating apoptosis induction during ALKi therapy, which reduces the therapeutic effect. Combination therapy with MCL-1 inhibitors may overcome this attenuation. BMF loss has been observed in approximately 1% of NSCLC cases in the cBioportal database, but further evaluation of clinical significance is needed using pre- and post-TKI treated samples. Additionally, preclinical in vivo studies are needed to assess the efficacy and toxicity of the potential combination therapy for depleting DTP cells after ALK-TKI treatment.

Keywords: ALK-positive lung cancer, Drug tolerant persister, BMF

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EP.12B.05 Drivers of Treatment Choice in ALK-Positive Metastatic Non-Small Cell Lung Cancer from Patients' and Caregivers' Perspectives

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Introduction: With the emergence of NSCLC treatments tailored to ALK rearrangement (ALK+), patients and caregivers face a choice between multiple targeted therapies, requiring them to weigh benefits and risks. We aimed to identify drivers of treatment choice from patients' and caregivers' perspectives.

Methods: Ten adults with ALK+ Stage IV NSCLC and ten informal caregivers in the US participated in semi-structured qualitative interviews. Participants 1) ranked four benefit measures by meaningfulness to evaluate efficacy, 2) rated adverse events (AEs), and 3) selected two most important AEs to avoid. Interview data were analyzed using descriptive and content analysis.

Results: Patients were 35 years old on average (range 23-56), mostly female (n=7) and White (n=6) and diagnosed with NSCLC on average 2 years (range: 1-5) ago, with 4 patients also reporting brain metastasis. The study included 8 patient-caregiver dyads and 2 non-dyads. Patients and caregivers surveyed stated that progression free survival (n=16) was more meaningful than overall survival (n=11) as a measure of benefit. They valued quality of life with less or no symptoms, but many ultimately hoped to buy time until a new treatment becomes available. Patients and caregivers ranked prevention of brain metastasis 3rd (n=9) and symptom relief 4th (n=11) as they translated metastasis-free and symptom-free to progression-free. Among the prespecified treatment-associated AEs, lung complications (n=17), abnormal lab results (n=9) and cognitive/mood effects (n=6) were most frequently selected as the most important AEs to avoid. The top 4 AEs that were rated high by degree of concern by patients were lung complications, cognitive/mood effects, myalgia and weight gain, while caregivers cited lung complications, hypertension, abnormal lab results and cognitive/mood effects as the most concerning AEs (Table). Lung complications were frightening due to the lack of management options and their potential impact on future clinical trial eligibility and on the existing lung cancer. Abnormal lab results were alarming as they may imply treatment discontinuation and dose reduction. Patients and caregivers were concerned about the impact of cognitive/mood effects on their relationship.

Conclusions: Patients and caregivers generally consider PFS as the most meaningful benefit measure and lung complications, abnormal lab results, cognitive/mood effects, myalgia and weight gain as concerning AEs. A subsequent study is planned to quantify the extent to which these attributes drive treatment choice.

Mean Rates of AE by Degree of Concern on a Scale of 0 (Not Concerning) to 10 (Extremely Concerning)

Keywords: NSCLC, ALK inhibitors, Patient and caregiver perspectives

	Patient (n=10)	Caregiver (n=10)
Lung complications	8.3	8.3
Cognitive/mood effects	6.8	6.5
Myalgia	6.3	5.6
Weight gain	6.1	4.5
Nausea	6.0	6.1
Fatigue	5.8	5.5
Abnormal lab results	5.6	6.7
Diarrhea	5.3	5.8
Hypertension	4.9	6.9

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EP.12B.06 Efficacy of Lorlatinib in Advanced ALK-Positive Non-Small Cell Lung Cancer Patients in Thailand: A Multicenter Study

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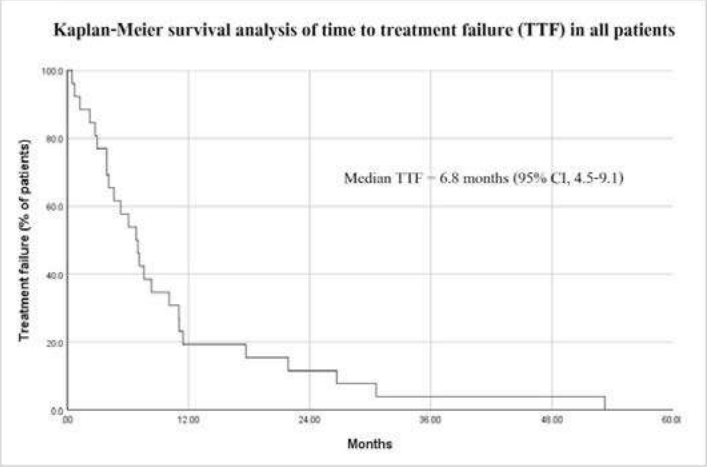
Introduction: Anaplastic lymphoma kinase (ALK) translocation is an uncommon driver alteration in non-small lung cancer (NSCLC). This study aimed to evaluate the efficacy of lorlatinib as a subsequence treatment in ALK-positive NSCLC in a real-world, multi-center observational study.

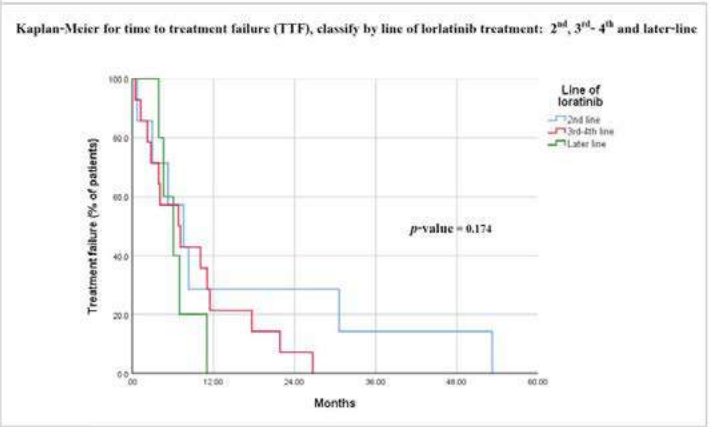
Methods: Retrospective cohort of 26 ALK-positive advanced NSCLC patients in 5 centers of Thailand who received lorlatinib under Named Patient Use program between April 2019 and February 2021 was conducted by Thai Lung Cancer Group (TLCG) under Thai Society of Clinical Oncology. Demographic characteristics, treatment response, and toxicity were collected. The primary endpoint was time to treatment failure (TTF). The secondary endpoints were overall survival (OS), and toxicity profile.

Results: The median follow-up was 51.2 months (range, 11.8-122). The median age was 61 years. Majority of the patients were female (69.2%), never smoker (76.9%), and ECOG PS 0-1 (84.6%). Initial and subsequent brain metastasis were reported in 23.1 and 65.4% of patients, respectively. Median OS was 90.6 months (95% CI, 51.7 - 90.6) and 5-year OS was 70.3%. Lorlatinib was used in 26.9%, 26.9%, and 46.2% as second-, third- and later-line treatment, respectively. The median TTF of lorlatinib in overall cohort was 6.8 months (95% CI, 4.5-9.1). In detail, median TTF of lorlatinib in second-line, third-line, and later-line were 7.6 months (95% CI, 1.7-13.5), 6.8 months (95% CI, 1.3-12.4), and 6.1 months (95% CI, 3.0-9.2), respectively which was not affect TTF by regression analysis. Fifteen patients (57.7%) experienced all grade treatment-related toxicities. The most common grade 3/4 toxicities were dyslipidemia (30.7%), weight gain (3.8%), and mood-cognitive effect (3.8%). Dose interruption and/or dose reduction was observed in 30.7%.

Conclusions: Lorlatinib demonstrated clinical benefits in ALK-positive NSCLC with good tolerability. The efficacy was consistent with the reported clinical trials.

Keywords: ALK, lorlatinib, advanced NSCLC





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EP.12B.07 Identification of Candidate Therapeutic Targets Using Single Cell RNA Sequencing in ALK-Positive Lung Cancers

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Introduction: Oncogenic ALK fusion proteins in lung cancer (LC) cells are not expressed on cell surfaces, except as HLA-bound peptides following ALK intracellular domain proteolysis. Consequently, development of surface-targeting therapeutics for treatment of ALK+ LC cells, such as antibody-drug conjugates (ADCs), bi- and tri-specific antibodies, CAR-T cells, and vaccines, has been limited. To identify potential cell surface targets in ALK+ LC cells, we developed a computational pipeline to analyze publicly available single cell RNA sequence (scRNAseq) data from LC tumor samples.

Methods: Analysis of scRNAseq data from 11 ALK+ LC patients (Maynard et al 2020, Bischoff et al 2021, Wu et al 2021) versus 107 normal lung samples (Sikkema et al 2023) identified candidates for such therapies. The CellXGene VIP visualization interface we employed enables assessment of gene expression in a cell cluster format, in relation to over 18,000 genes expressed among the 61 cell types enumerated in the Human Lung Cell Atlas (Sikkema et al 2023), as well as on a cell-by-cell basis.

Results: We compared computationally identified genes transcribed in ALK+ AT2 cells (Figure 1) that encode FDA-registered/IND-approved drug targets, regardless of their disease area of approval. First, we identified expressed candidate targets from FDA-registered/IND-approved lists of antibody-drug conjugates (16), bi- and tri-specific antibodies (11), CAR-T cell therapies (10) and cancer vaccines (11). Second, we found support for clinical trials of solid tumor vaccines like BNT116 for ALK+ and EGFR+ LC patients because 70% of ALK+ patients and 59% of EGFR+ patients sampled express one or more among the six proteins in this mRNA vaccine. Third, our analysis of gene ensembles relevant to ALK-driven carcinogenesis identified genes within ALK signaling and ALK TKI bypass resistance pathways (24) and the epithelial-mesenchymal transition pathway (52) and among immune checkpoints (18). We are currently analyzing additional tumor RNA datasets for additional drivers from publicly available sources for comparison.

Conclusions: Taken together, we believe these types of data offer opportunities to expedite therapeutic development of improved treatments for ALK+ and other oncogene-driven LC patients. We will extend this work to include validation of transcriptome-nominated targets in tumor cells using immunohistochemistry, mass spectrometry and other protein expression assays, and in vitro and in vivo models.

Keywords: ALK, Single cell RNA sequencing, Drug targets

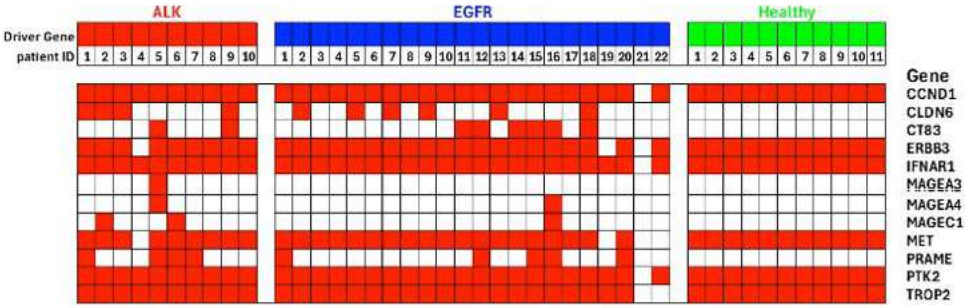

Figure 1. Binary heatmap displays the presence of gene expression for 12 target genes across 43 individuals, categorized into ALK+ (N=10), EGFR+ (N=22), and Healthy (N=11) groups. Columns represent individual patients; rows correspond to the genes. Red squares indicate detectable expression of a gene in at least one cell within a patient sample, based on single cell transcriptomics data. The distribution of red across the heatmap provides insight into the gene expression landscape, highlighting differences and similarities in the expression profiles of patients with different driver genes and healthy individuals.

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EP.12B.08 Characterizing the Severity and Timing of Real-World ALK-Inhibitor Associated Weight Gain in Non-Small Cell Lung Cancer

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Introduction: As second and third generation Anaplastic Lymphoma Kinase (ALK) tyrosine kinase inhibitors (TKIs) extend progression-free survival beyond 3 years in ALK-fusion positive NSCLC, long-term toxicities are increasingly recognized. ALK-Inhibitor associated Weight Gain (AIWG) is a described toxicity in first-line registrational trials; in the CROWN trial of lorlatinib, rates of grade 2 (10 to <20%) and grade 3 (>=20%) weight gain were 17% and 20% respectively. Improved understanding of real-world severity, timing and risk factors for AIWG is important for clinician-patient decision making.

Methods: We performed a retrospective review of ALK-fusion positive metastatic NSCLC patients receiving FDA-approved ALK TKIs at our institution from 1/1/2020-12/31/2023. Demographics and treatment history were gathered. Clinic-measured weight (kg) was noted at 12-24 week intervals (as available) from baseline until progression on each TKI. Descriptive statistics were summarized with mean (range) or frequency. TKI-specific weight gain (mean % change from baseline [95% CI], or grade per CTCAE v5.0) was compared via ANOVA (p<0.05).

Results: Our cohort included 89 patients receiving 158 total treatment lines of TKI; 23 patients received crizotinib (100% first line [1L]), 2 received ceritinib (100% 2L - excluded from analyses for small N), 25 received brigatinib (20% 1L, 60% 2L, 20% 3/4L), 68 received alectinib (80.9% 1L, 13.2% 2L, 5.9% 3/4L), and 40 received lorlatinib (17.5% 1L, 47.5% 2L, 22.5% 3L, 12.5% 4/5L). Mean age at first TKI was 55yrs (range 25-88), 74% were female, 76% were never-smokers. At first TKI, mean weight was 73.7kg (42.2-127), 32% of patients were overweight (BMI 25 to <30 kg/m2), 13% were obese (BMI >=30 kg/m2). Shown in Table 1, mean maximum weight gain was highest for patients on lorlatinib versus other TKI (+13.3% from baseline, p<0.001), as was mean weight gain by 6 months (+5.8% from baseline, p=0.02). Lorlatinib weight gain did not significantly vary by line of therapy (p=0.19). 11 patients received a weight loss-associated medication; excluding these patients did not alter findings (not shown). 29% of lorlatinib weight gain was grade 3 (p<0.001 versus other TKIs). Time to maximum gain was similar between TKIs (p=0.24), ranging from 16-24.6 months on treatment. Further analysis to follow.

Conclusions: These data help characterize real-world AIWG, demonstrating >10% weight gain (grade 2-3) for a significant portion of patients. Real-world weight gain was most common with lorlatinib and more severe than in its registrational trial. Future investigation of optimal prevention and management of weight gain is encouraged.

Keywords: NSCLC, ALK Tyrosine Kinase Inhibitors, Weight Gain

	Crizotinib	Brigatinib	Alectinib	Lorlatinib	p-value
Mean Max Weight Gain (% baseline) [95% CI]	+4.2% [1.9-6.7]	+4.5% [2.3-6.6]	+6.4% [4.4-8.5]	+13.3% [9.3-17.4]	<0.001
Mean Time to Max Weight Gain (mo) [95% CI]	20.0mo [12.4-27.6]	24.6mo [14.0-35.2]	16.0mo [11.8-20.1]	22.2mo [13.7-30.8]	0.24
Mean Max Weight Gain by 6 mo (% baseline) [95% CI]	-1.4% [-4.0-1.2]	+0.9% [-1.2-3.0]	+3.2% [1.3-5.1]	+5.8% [2.9-8.7]	0.02
% Grade 2-3 Weight Gain [% Grade 3]	11.8% [0%]	13.0% [0%]	30.2% [3.9%]	61.3% [29.0%]	<0.001

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EP.12B.09 Real-World Efficacy and Toxicity Comparison Between the RET Inhibitors (RETi) Pralsetinib and Selpercatinib in Patients with Stage IV NSCLC

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Introduction: RET fusions occur in 1-2% of patients with NSCLC, with 2 US-FDA approved RETi for patients with stage IV NSCLC harboring it. Due to recent approvals, there is limited data of their real-world outcomes and adverse events (AEs). We aimed to compare the utilization of pralsetinib and selpercatinib in this population.

Methods: We performed a retrospective chart review of the electronic medical records of all patients with stage IV NSCLC treated with RETi between the date of FDA-accelerated approval of these drugs, 09/04/2020 for pralsetinib and 05/08/2020 for selpercatinib, and 02/15/2024. All patients were treated at the Mayo Clinic Health System. We collected data about baseline characteristics, diagnosis, AE, and outcomes. Chi-squared test was used to compare AEs frequency, while Kaplan-Meier method was used to calculate median progression free survival (mPFS), and Cox proportional hazards regression for hazard ratio (HR).

Results: Thirty-four patients were treated with RETi. Pralsetinib was used in 23 patients, selpercatinib in 17, while 2 received pralsetinib after selpercatinib, and 4 received selpercatinib after pralsetinib. In the pralsetinib group, median age of diagnosis was 63 years, 43.48% were male, and median number of previous lines of therapy (mPLT) was 1. In the selpercatinib group, median age of diagnosis was 62 years, 52.94% were male, and mPLT was 1. For both groups, median ECOG at time of diagnosis was 0. KIF5B-RET fusion was present in 78.26% of those treated with pralsetinib and 70.59% with selpercatinib. The mPFS was not reached in neither group. 2-year PFS was 73.6 % (95% CI 56.1-96.6) for pralsetinib, and 53.3% (95% CI 29.8-95.4). HR was 1.12 (95% CI 0.27-2.91). Most common AEs are reported in table 1. Pralsetinib was discontinued in 30.43% of patients, and selpercatinib in 5.88%. Temporary drug hold occurred in 21.74% and 41.18% of cases with pralsetinib and selpercatinib, respectively, while dose reduction happened in 43.48% of cases with pralsetinib, and 41.18% with selpercatinib.

Conclusions: We observed similar efficacy with both RETi, but relevant AEs differences. These may guide treatment in patients with underlying comorbidities. Selpercatinib may be favored in patients with underlying respiratory comorbidities, due to significantly lower incidence of pneumonitis. Despite no statistical difference, pralsetinib may be preferred in those with renal diseases, and selpercatinib in cases with hepatic dysfunction. Nonetheless, over 40% of cases required dose reductions, stressing the need for close treatment monitoring. Prospective multi-centric studies would provide further information regarding differences between these drugs.

Keywords: RET fusion, Pralsetinib, Selpercatinib

	Pralsetinib	Selpercatinib	p-value
Peripheral edema (%)	4.35	17.65	0.17
Hypertension (%)	34.78	35.29	0.97
Creatinine elevation (%)	26.09	41.18	0.31
Liver function tests abnormality (%)	60.87	47.06	0.39
Pneumonitis (%)	21.74	0.0	0.04

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EP.12B.10 Patterns and Clinical Impact of Alectinib Dose Reduction in Patients with ALK-Positive Non- Small Cell Lung Cancer (NSCLC)

B. To, S. Farid, S. Zhao, M. Li, N. Amirmokhtari, L. Wei, R. Memmott,, A. Alahmadi, K. He, J. Kaufman, L. Roof, P. Shields, D. Carbone, G. Otterson, C. Presley, D. Owen, The Ohio State University Medical Center, Columbus/OH/USA

Introduction: The second generation ALK inhibitor alectinib is a standard treatment for patients with advanced ALK positive NSCLC, and has substantial CNS efficacy. In the landmark phase 3 ALEX clinical trial, adverse events led to dose reductions in 16% of patients. However, the frequency of dose reduction and impact on outcomes including CNS disease and overall progression has not been well characterized outside of clinical trials.

Methods: We conducted a single-institution retrospective study of non-small lung cancer patients who were treated at The Ohio State University Comprehensive Cancer Center (OSUCCC) between 2005-2022. Data was extracted from patient's electronic medical records (EMR) and collected in REDCap. Patients with ALK positive NSCLC who received alectinib were included in this study. Fischer's exact test was used to compare incidence of general progression or CNS progression between reduced and non-reduced groups. Kaplan-Meier survival analysis was used to evaluate survival outcomes. Statistical analysis was done in SAS 9.4.

Results: We identified 73 patients whose tumors harbored an ALK rearrangement; 57 of these patients received alectinib either as their first (59.7%), second (31.6%) or third (8.8%) line targeted therapy. The median age at diagnosis was 55 years (IQR 48-64); 55.4% were female. The predominant ethnic group among patients was Caucasian (78.6%), followed by African American (16%), with the remainder categorized as " Asian and Other" (5.4%). 37% of patients had CNS disease prior to initiation of alectinib. 22.8% of patients underwent dose reduction during their treatment with the majority of those patients decreasing from 600 mg alectinib BID to 450 mg BID. The median time to dose reduction was 3 months (IQR 0.9-15.4). The most common reasons for dose reduction include fatigue (25%), elevated creatine kinase (15%), myalgia (15) and liver toxicity (15%). Other less common causes include muscle weakness, lower extremity edema, bradycardia, rash and vision changes. The median time on treatment with alectinib was 13.3 months (IQR 10.8-15.4) in patients who underwent dose reduction compared to 5.7 months (IQR 1.7-20.1) in patients without dose reduction. New or progressive CNS disease was observed in 30% of patients who underwent dose reduction compared to 13.6% in those who did not undergo dose reduction (p-value=0.94). There were no significant differences in progression-free survival or overall survival between patients with and without dose reduction (log-rank p-values of 0.5724 and 0.7854, respectively).

Conclusions: In this single institution retrospective study, there was no significant difference in the rate of new or progressive CNS disease in patients with or without drug reduction. There was also no significant difference in overall survival in both groups. Overall, findings from this study suggest that when dose reduction is needed, it does not appear to negatively impact patient outcomes including CNS disease control, however further studies are needed to confirm findings and to determine whether the same holds true for other ALK inhibitors.

Keywords: alectinib, dose reduction, CNS disease

EP.12B.11 Clinical Treatment Selected by Patient-Derived Organoid in a Patient with Stage IV Lung Adenocarcinoma with Unique ALK Alternation

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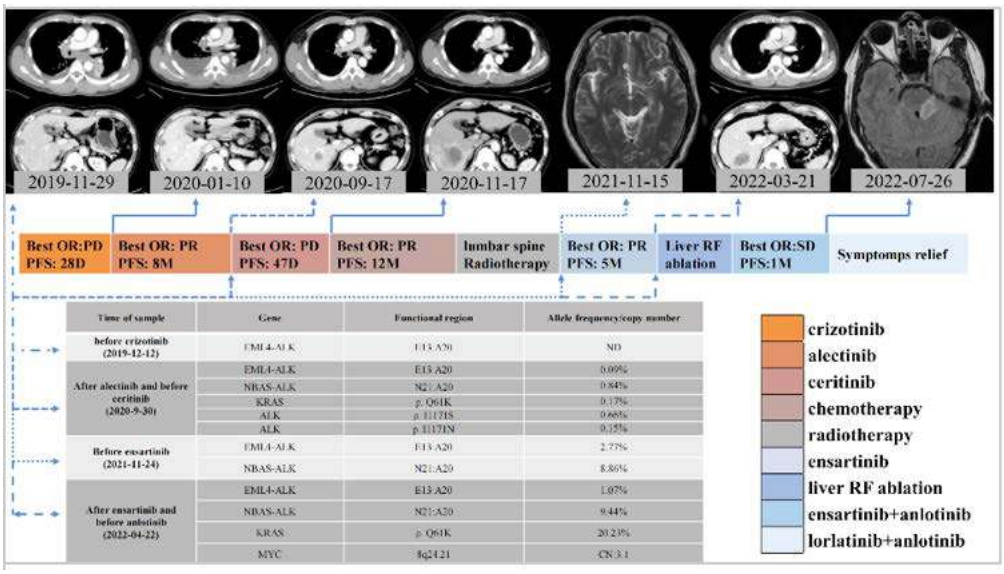
Introduction: Anaplastic lymphoma kinase (ALK) fusion is prevalent in 3-5% of non-small cell lung cancers (NSCLC) and represents a crucial molecular target in this disease. Apart from the common EML4-ALK fusions, novel fusion variants are continuously being identified, but their response to ALK tyrosine kinase inhibitors (ALK-TKIs) remains uncertain. The use of patient-derived organoids (PDOs) for drug screening to offer personalized treatment options for cancer patients is gaining attention.

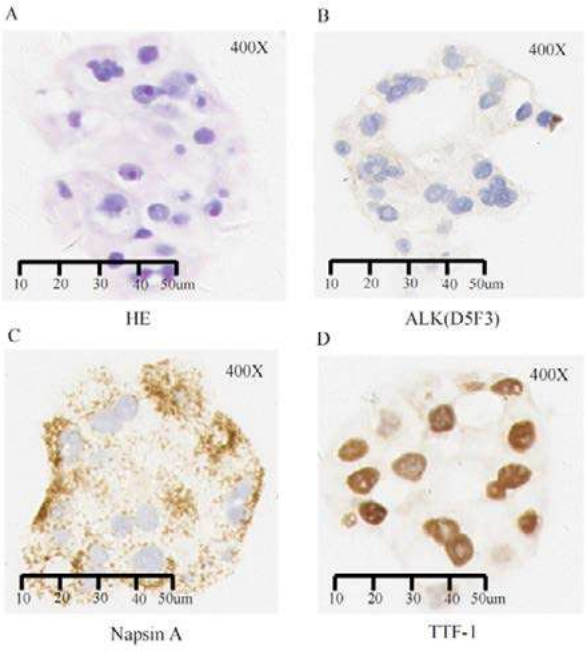
Methods: We report a case of stage IV lung adenocarcinoma harboring a unique combination of non-reciprocal/reciprocal ALK translocation (EML4-ALK and NBAS-ALK), ALK 1171N and ALK 1171S mutations, and establish a corresponding PDOs model. PDO-based drug sensitivity testing was compared to clinical efficacy to evaluate their potential in clinical practice.

Results: The treatment process is detailed in Figure 1. H&E staining and IHC (Figure 2)indicated that PDOs maintained the histopathologic characteristics of the original tumor tissue, while gene detection results showed consistent expression of EML4-ALK and NBAS-ALK with the primary tumor. The drug sensitivity tests accurately predicted the patient's clinical response to treatment.

Conclusions: This study validates the use of organoids as predictive preclinical models for lung cancer treatment development especially for the rare and uncommon mutations.

Keywords: patient-derived organoids, lung adenocarcinoma, ALK alternation





EP.12B METASTATIC NON-SMALL CELL LUNG CANCER - TARGETED THERAPY - FUSIONS: ALK / ROS1 / RET / NTRK
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EP.12B.12 Intrinsic ALK-TKI Resistance Due to Met-Coamplification in ALK+ NSCLC, Effectively Treated by Alectinib-crizotinib Combination

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Introduction: The vast majority of advanced ALK-rearranged (ALK+) NSCLC patients experience prolonged response to second generation (2G) ALK-TKIs. Yet, to our knowledge, we present herein the first case of ALK+ NSCLC rapidly progressing on 1st line Brigatinib treatment due to de novo MET-amplification. This represents an underrecognized mechanism of intrinsic resistance to ALK-TKIs.

Methods: A 46-year-old female, never-smoker, without comorbidities, in performance status 2, was diagnosed with T4N3M1c pulmonary adenocarcinoma. NGS analysis of DNA (Oncomine Comprehensive Assay v.3; ThermoFisher Scientific) and RNA (Archer FusionPlex® Lung panel v1.0; ArcherDX, Inc.) extracted from the diagnostic biopsy detected EML4-ALK fusion variant 1 (EML4-ALK v.1) and a TP53 co-mutation (p.G245S). The patient was treated with 1st line Brigatinib.

Results: Unexpectedly, we observed modest mixed response after three months and highly symptomatic progression after six months of treatment with this 2G ALK-TKI. A rebiopsy from new hepatic metastasis showed maintained adenocarcinoma histology without phenotypic transformation to SCLC, squamous carcinoma or sarcomatoid carcinoma (EMT). DNA- and RNA-NGS analysis of the rebiopsy displayed persistence of the original EML4-ALK v.1 fusion and TP53 mutation, without any additional variants or copy number variations. Supplementary IHC for MET receptor (CONFIRM anti-MET, clone ID, SP44 rabbit mAb; Ventana Medical Systems, Inc.) and FISH analysis for MET gene (dual-color Zyto-Light SPEC MET/CEN7 probe; Zytovision GmbH) revealed MET receptor overexpression (3+ in 80% of tumor cells) and heterogeneously increased MET gene copy number (CN) in tumor cells, including 20% with MET clusters (≥15 gene copies, thus uncountable) and the other 80% with median MET CN of 8.3, indicating high-level MET amplification. To investigate whether MET amplification was intrinsic or acquired, we retrospectively performed MET-IHC and -FISH on the diagnostic biopsy from the primary lung tumor. Thereby, we revealed increased MET receptor expression (2+ in 100%) and MET amplification (median MET CN 6.1), which otherwise had not been detected by NGS. Thus, given the well-documented efficacy of Alectinib towards EML4-ALK v.1, combined 2nd line treatment with Alectinib and the MET-TKI, Crizotinib, was implemented. This resulted in a very pronounced objective response (RECIST v.1.1.) without adverse events and with significantly improved quality of life so far (5 months).

Conclusions: Intrinsic ALK-TKI resistance is rare in patients with ALK+ NSCLC. Yet, our case advocates for more awareness of de novo co-alterations which may cause primary treatment failure on ALK-TKIs. MET-amplification is a frequent form of acquired resistance to 2G ALK-TKIs, whereas to our knowledge, this is the first reported case of intrinsic resistance to a 2G ALK-TKI due to de novo MET-amplification. Our case also demonstrates that the combination of Alectinib and Crizotinib is a feasible and effective treatment for ALK+ NSCLC with de novo MET amplification. The recognition of this mechanism of ALK-TKI resistance by FISH, especially in NGS-negative cases, should be considered before initiating 1st line treatment. This is of clinical importance, as effective combined therapy with ALK-TKI and MET-inhibitor is feasible.

Keywords: de novo MET-amplification, intrinsic ALK-TKI resistance, TKIs combination

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EP.12B.14 Platinum-Pemetrexed Chemotherapy and Lorlatinib Combination in Advanced ALK Positive NSCLC Progressing to Lorlatinib: A Case Series

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Introduction: Advanced, anaplastic lymphoma kinase ALK positive (ALK+) non-small cell lung cancer (NSCLC) is currently treated with a 2nd generation ALK tyrosine kinase inhibitor (TKI) followed by the potent, brain-penetrant, third-generation TKI lorlatinib, with broad coverage of ALK mutations, or upfront lorlatinib. Currently, subsequent treatment to overcome lorlatinib resistance remains an unmet clinical need. After failure of targeted therapies, platinum and pemetrexed-based chemotherapy (PT/pem-based-CT) might still be a valid option, albeit with modest effectiveness (Lin JJ et al. J Thorac Oncol. 2020;15(2):258-265.) and frequent brain metastasis (BM) progression.

Methods: This retrospective analysis investigated the clinical effectiveness and safety of the PT/pem-based-CT and lorlatinib combination after lorlatinib failure in second- or later-line setting in six advanced consecutive ALK+ NSCLC patients (pts). Clinical-pathological data collected at our institutional database between June 2020 and November 2023 were used. Kaplan Meier's survival curves for progression-free survival (PFS) (defined as the time from starting combination therapy to progression or death) and intracranial-PFS (defined as the time from starting combination therapy to brain progression or death) were performed.

Results: 4/6pts had BM at disease onset. The average of treatment lines prior to lorlatinib was of two 1st/2nd generation ALK-TKI. Progression site on lorlatinib were: lymph nodes (2/6), lung (2/6), liver (2/6), brain (2/6). Regarding BM, one patient received SBRT immediately before starting induction phase, the other was clinically asimptomatic. Available tissue biopsy after lorlatinib progression, did not demonstrated ALK resistance mechanisms/ histology transformation. Treatment monitoring with liquid biopsy was negative for both on-target and off-target resistance mutations in all six patients. Following multifocal progression, therapy with lorlatinib was continued and all pts were added a PT/pem-based-CT with the association of pembrolizumab in half of the cases. In 3/6pts four induction cycles were administered, one patient stopped treatment after only two cycles and 2/6pts received six total platinum cycles. Subsequently a maintenance with pemetrexed +/- pembrolizumab was carried out. In half of the cases, a reduction in chemotherapy dose was necessary, in two cases for hypercreatininemia grade 2 and in one for transaminase increase grade 2. All dose reductions occurred during maintenance and the drug concerned was pemetrexed. No lorlatinib dosage reduction occurred. PT/pem-based-CT and lorlatinib combination was found to be active in 5/6pts, bringing the best response to partial response (PR) in 2pts and stability (SD) in 3/6pts. Analyzing pts with CT dose reduction, 2 PR and 1 SD were recorded. Only one patient, who had not even completed induction phase, recorded systemic disease progression as best response and was a solely clinical progression. In only one case BM progression occurred. Median PFS was 5.5 months (interquartile range 3.5 - 9.0) and intracranial median PFS 7.7 months (interquartile range 5.5 - not reach).

Conclusions: This is the first proof of efficacy and safety of PT/PEM-based-CT and lorlatinib combination after lorlatinib failure in advanced in ALK+ NSCLC. To confirm this evidence, we developed a prospective, multicenter, phase II trial combining PT/PEM-based-CT and lorlatinib for the treatment of ALK+ NSCLC pts extracranially progressed on lorlatinib

Keywords: ALK+ NSCLC, lorlatinib, chemotherapy and lorlatinib combination

EP.12B METASTATIC NON-SMALL CELL LUNG CANCER - TARGETED THERAPY - FUSIONS: ALK / ROS1 / RET / NTRK
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EP.12B.15 ALK-Fusion Positive NSCLCs: Diversity in Mutations and Co-Mutations with Therapeutic Perspective and Clinical Outcomes

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Introduction: ALK-positive lung cancers are known to have aggressive biology, and advanced disease at presentation which further gets complicated by concurrent co-mutations and makes therapeutic interventions challenging. This study describes ALK mutations and co-mutations, clinical presentations, treatment, and survival outcomes from a community oncology practice in India

Methods: A retrospective analysis was conducted for ALK-fusion-positive NSCLCs treated between March 2018 and December 2023 from a community oncology setup. Clinical and molecular data was extracted from electronic medical records, highlighting ALK mutation types, treatment modalities, and clinical outcomes

Results: A total of 1068 patients of Non-small cell lung carcinoma (NSCLC) were assessed and ALK mutations were found in 50 of these patients (4.7%). The median age was 56.5 years (30-82) with 2 patients presenting at less than 40 years of age and the M:F ratio being 1:1.08. The majority of these patients were Stage IV (46/50) and adenocarcinomas (48/50) with a baseline brain metastasis seen in 15/50 patients. ALK mutations were tested by NGS in 17/50 patients, IHC in 9/50, and FISH in 1/50 patients. NGS test further elucidated EML-ALK fusions in 10 patients, point mutation in 2 patients, and G1202R in 2 patients. Co-mutations were seen in 14/50 (28%) patients where EGFR was co-mutated in 9/14, followed by TP53 in 4/14 and ROS, PIK3CA, and BRAF in 1 patient each. The treatment landscape constituted of 1st line Tyrosine kinase inhibitors (TKIs) used in 37/50 (74%) patients where 1st, 2nd, and 3rd generation TKI was used in 34%, 38%, and 2% respectively. Chemotherapy as 1st line therapy was used in 8/50 patients while chemotherapy + TKI was used in 1/50 patients. 3rd Generation TKI was used in 7/50 patients wherein more than 70% of cases it was used in 3rd line and beyond. Median survival for the cohort was 35 months (with 95% CI 13.5-56.5) with a median follow-up time being 36 months (with 95% CI 18.7-53.5)

Conclusions: ALK-directed therapies have changed the treatment paradigms in NSCLCs. Easy availability of testing, cost-effectiveness of 1st generation TKIs, and encouraging patient assistance programs have led to the increased usage of these drugs in first-line settings leading to better outcomes. ALK co-mutations especially with EGFR are common and may affect the treatment decisions and survival

Keywords: ALK-fusion positive NSCLCs, ALK Co-mutations, 3rd Generation TKIs

EP.12B METASTATIC NON-SMALL CELL LUNG CANCER - TARGETED THERAPY - FUSIONS: ALK / ROS1 / RET / NTRK
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EP.12B.16 Effectiveness of Alectinib in ALK Rearrangement NSCLC: Real World Data of Peru

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Introduction: Non-small cell lung cancer (NSCLC) with ALK rearrangement represents approximately 5% of cases. Tyrosine kinase inhibitor therapy has improved the survival of this group of patients. We describe the clinical features and survival outcomes in a developing country.

Methods: Retrospective study based on case review of patients with metastatic NSCL with ALK rearrangement who received alectinib at Instituto Nacional de Enfermedades Neoplasicas (INEN), Lima- Peru. Descriptive analysis was conducted for clinical and epidemiological characteristics. PFS was calculated from the date of started treatment until the first documented progression and OS was calculated with Kaplan Meier curve.

Results: 23 patients were included for this analysis. Median age at diagnosis was 51 yo (range 31-68), 47.8% (n=11) of patients were female, 25% (n=6) were smokers and 16.6% (n=4) were exposed to wood smoke. The most common histology subtype was adenocarcinoma (87%), and 13% was NOS carcinoma. 21.7% (n=5) of patients had only intrathoracic disease, 34.7% (n=8) had systemic metastasis without brain metastasis and 47.8% (n=11) brain metastasis. 17.4% (n=4) started alectinib as second line of therapy, 78% (n=18) presented with ECOG 1-PS and 22% (n=5) presented with ECOG 2-PS at the beginning of treatment. ORR were reached in 74% (RC=4 + RP=13), 13 % had EE (n=3), 8.7% had PD (n=2) and 4.3% (n=1) was not evaluated yet. Regarding CNS response, 18.2% (n=2) achieved CR, 27.3% (n=3) PR, 45% (n=5) SD and 9% (n=1) was not evaluated yet. Median PFS and median OS was not reached. PFS rate at 4 year was 66.7% and OS rate at 4 year was 64.1%. Finally, 13% (n=3) presented grade 2-3 hyperbilirubinemia.

Conclusions: Tyrosine kinase inhibitor therapy, such as alectinib, has shown significant improvement in the survival outcomes of patients with ALK rearrangement NSCLC. Alectinib demonstrated high ORR, even favorable responses in patients with CNS metastasis, which is often a challenging site of management. Median PFS and median OS were not reached, suggesting a potentially durable benefit from alectinib therapy in this patient population.

Keywords: ALK rearrangement, metastatic NSCLC, alectinib

EP.12C METASTATIC NON-SMALL CELL LUNG CANCER - TARGETED THERAPY - KRAS
SATURDAY, SEPTEMBER 7, 2024 - 11:58 - 11:59

EP.12C.01 Sotorasib vs Adagrasib: Matching-adjusted Indirect Comparison in Prior Treated KRAS G12C Advanced Non-Small Cell Lung Cancer

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Introduction: Sotorasib and adagrasib are two approved KRASG12C inhibitors with demonstrated efficacy in previously treated patients with KRAS G12C advanced non-small cell lung cancer (NSCLC). However, comparative efficacy data is unavailable. A matching-adjusted indirect comparison (MAIC) was hence performed to assess their relative efficacy using patient-level data for sotorasib and aggregate data for adagrasib.

Methods: Systematic literature reviews identified CodeBreaK 100, CodeBreaK 200 trials for sotorasib and KRYSTAL-1 for adagrasib. CodeBreak 100 and KRYSTAL-1 phase 2 trials were determined as the most comparable trials for this analysis due to similarities in trial design, inclusion criteria and distribution of key baseline patient characteristics. A set of five covariates identified as prognostic for NSCLC outcomes were used for adjustment in the base-case model based on clinical expert guidance: gender, race, Eastern Cooperative Oncology Group performance score, metastatic disease and brain metastases. An additional 4 covariates were included in the sensitivity model (bone metastases, liver metastases, smoking status, prior treatment with anti-programmed cell death (ligand)-1 (anti-PD-[L]1) and platinum-based chemotherapy). Further scenario analyses limiting patients from CodeBreaK 100 to North America ensuring comparability with the US population of KRYSTAL-1 was conducted. Hazard ratios (HRs) were used for overall survival (OS) and progression-free survival (PFS). Odds ratios (ORs) were estimated for objective response rates (ORRs).

Results: CodeBreaK 100 included 126 patients receiving sotorasib, with 62.7% from North America whereas all 116 patients enrolled in KRYSTAL-1 were from the US. After matching on key covariates in the base-case model, an effective sample size of 80.6 from CodeBreaK 100 was obtained. The adjusted results suggested that in the overall population subjects receiving sotorasib had an 8% lower risk of death during the study period compared with patients receiving adagrasib (Hazard Ratio [HR] 0.92; 95% Confidence Interval [CI] 0.61-1.38; p=0.69); however, the results were not statistically significant. Restricting the CodeBreaK 100 population to patients enrolled in North America, produced similar results suggesting a 13% non-significantly lower risk of death with sotorasib compared to adagrasib (HR 0.87 [95% CI 0.55-1.36]; p=0.54). The risk of progression was not significantly different for subjects receiving sotorasib compared to adagrasib in either the overall (HR 1.20 [95% CI 0.86-1.68]; p=0.28) or North American subgroup (HR 1.13 [95% CI 0.78-1.63]; p=0.52). The likelihood of achieving an ORR was similar between the two treatment groups in the overall population (OR 0.99 [95% CI 0.59-1.66]; p=0.97) and was 18% higher for sotorasib in the North American subgroup (OR 1.18 [95% CI 0.66-2.11]; p=0.58); the results did not achieve statistical significance. Robustness of findings was confirmed in sensitivity analyses (crude analysis, alternative model with additional covariates and exclusion of outliers).

Conclusions: Using an MAIC approach, comparable efficacy was estimated between sotorasib and adagrasib in treating patients with KRAS G12C advanced NSCLC. The results are specifically relevant for informing clinical practice and payer decisions in the 2L+ treatment setting.

Keywords: Non-small cell lung cancer, sotorasib, matching-adjusted indirect comparison

EP.12C METASTATIC NON-SMALL CELL LUNG CANCER - TARGETED THERAPY - KRAS
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EP.12C.02 5-Azacytidine DegradedKRAS By Recruiting E3 Ubiquitin Ligase UBE3C

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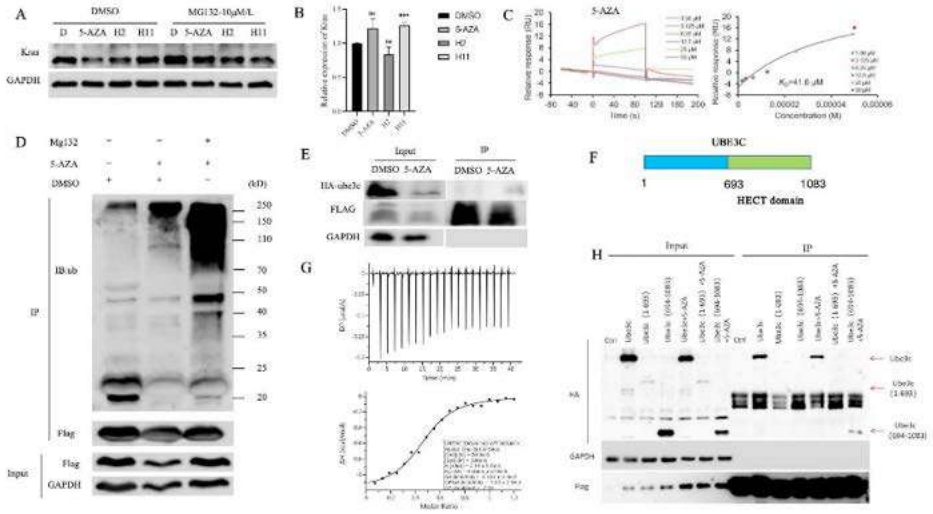
Introduction: KRAS mutations promote tumorigenesis, invasion, drug resistance and poor prognosis in lung cancer. Development of degradation agents targeting KRAS may help target tumors and alleviate chemotherapy resistance.

Methods: A compound screening system for the lentivirus infected RFP-KRAS-EGFP-FLAG monoclonal cell line was constructed, and identified candidate compound 5-Azacytidine through compound library screening. Clarify the molecular mechanism of compound degradation of KRAS. Various techniques and methods such as computational simulation and molecular biochemical experiments to further optimize and modify 5-Azacytidine, and conduct in vivo and in vitro pharmacological activity and safety evaluations.

Results: Study showed that compound 5-Azacytidine can degrade both wild-type and mutant KRAS proteins, and its degradation could be inhibited by MG132. Immunoprecipitation results showed that compound 5-Azacytidine promoted the ubiquitination of KRAS, and MG132 can protect KRAS from degredating. Compound 5-Azacytidine exhibited time- and concentration-dependent degradation of KRAS protein. We performed protein profiling of compound 5-Azacytidine-treated KRAS protein and found that the E3 ligase UBE3C could bind to KRAS.

Conclusions: Compound 5-Azacytidine can act as a molecular glue between KRAS and UBE3C protein and induce KRAS degradation via ubiquitin-proteasome system.

Keywords: Lung cancer, 5-Azacytidine, Degradation



(A) Compound 5-Azacytidine can reduce the level of KRAS protein, and the level of KRAS protein increases after treatment with MG132. (B) qPCR detection was used to verify the expression changes of KRAS mRNA after treatment with compound 5-Azacytidine. (C) SPR experiment verifies the affinity of compound 5-Azacytidine with KRAS mutant protein. (D) Compound 5-Azacytidine promotes ubiquitination of KRAS. (E) By constructing HA labeled ube3c plasmid, exogenous IP showed that after 5-AZA treatment, KRAS can bind to ube3c. (F) The protein structure of UBE3C, 693-1083aa, contains the HECT domain region. (G) The ITC results showed that 300 umol UBE3C was dropped into 300 umol KRAS+20umol 5-AZA, and the results showed binding between 5-AZA, UBE3C, and KRAS. (H) Western blot experiments showed that grouping ctrl, ube3c, ube3c (1-693), ube3c (694-1083), ube3c+5-AZA, ube3c (1-693)+5-AZA, ube3c (694-1083)+5-AZA was performed, and the above plasmids were transferred into stable flag kras PC-9 cell lines and IP was performed using flag beads. The results showed that ube3c (694-1083) is a functional segment that binds to kras, and 5-AZA promotes the binding of ube3c (694-1083) to kras.

EP.12C METASTATIC NON-SMALL CELL LUNG CANCER - TARGETED THERAPY - KRAS
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EP.12C.03 Toxicities Associated with Immune Checkpoint Inhibitors Followed by KRAS G12C Inhibitors in Patients with Metastatic NSCLC

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Introduction: KRAS G12C inhibitors are approved for KRAS G12C mutated non-small cell lung cancer (NSCLC) following progression on first line systemic treatment, which typically includes an immune checkpoint inhibitor (ICI). KRAS G12C inhibitors are associated with an increased risk of hepatotoxicity and pneumonitis. Sequential treatment with ICI followed by KRAS G12C inhibitors has previously been associated with an increased risk of hepatotoxicity. In this study, we evaluated whether ICI exposure prior to KRAS G12C targeted therapy was associated with an increased risk of hepatotoxicity and pneumonitis.

Methods: This is a single center, retrospective review of the electronic medical records of patients with KRAS G12C mutated metastatic NSCLC who received a KRAS G12C inhibitor in the second or later line between June 2021 and November 2023. Patients were stratified based on timing of exposure to ICI prior to KRAS G12C initiation (< 3 months, ≥ 3 months, or no exposure to ICI). We collected data on the development of treatment-related hepatotoxicity and pneumonitis. Adverse events were graded based on the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.

Results: Twenty-eight patients were included in the analysis. Of the twenty-three patients with prior ICI exposure, 16 (70%) received ICI <3 months before receiving a KRAS G12C inhibitor. All patients received sotorasib. Of these, 8 (50%) experienced any grade hepatotoxicity i.e. transaminitis. Four patients (25%) experienced ≥ Grade 3 transaminitis and 4 patients (25%) experienced Grade 1-2 transaminitis. Two patients discontinued treatment and two patients required dose reduction due to hepatotoxicity. Only one (14%) patient who had exposure to ICI ≥ 3 months prior and one patient (20%) without any prior exposure to ICI experienced Grade 1-2 transaminitis. No grade ≥ 3 hepatotoxicity was noted. Across all patients, only one patient (4%) experienced pneumonitis (Grade 3) after starting a KRAS G12C inhibitor. This patient had ICI exposure ≥3 months prior. The pneumonitis occurred shortly after the KRAS G12C inhibitor was discontinued due to disease progression. The patient had received radiation to the mediastinum and right lung three years before developing pneumonitis.

Conclusions: Sequential treatment with ICI and KRAS G12C inhibitors is associated with an increased risk of hepatotoxicity. The risk appears highest if patients received a KRAS G12C inhibitor within 3 months of ICI. The risk for pneumonitis was much lower. More studies are needed to elucidate the mechanism and optimal timing of KRAS G12C inhibitors following exposure to ICI.

Keywords: KRAS G12C Inhibitors, Pneumonitis, Hepatotoxicity

Patient Cohort	Patients (n)	Age in years (Mean)	Sex (Male %)	Patients with two/ ≥ two lines of prior treatment (%)	Grade transaminitis n (%)	Grade 3-4 transaminitis n (%)	Any grade pneumonitis n (%)
KRAS G12C Inhibitor without prior immunotherapy	5	73.8	71.4%	80/20	1 (20%)	0	0
Immunotherapy <3 months before KRAS G12C	16	68.7	31.3%	75/25	8 (50%)	4 (25%)	0
Immunotherapy ≥ 3 months before KRAS G12C	7	70.3	0%	57/43	1 (17%)	0	1 (17%)

EP.12C METASTATIC NON-SMALL CELL LUNG CANCER - TARGETED THERAPY - KRAS
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EP.12C.04 Location of Metastases and Prognosis of Patients with Metastatic KRAS-Mutant Non-Small Cell Lung Cancer

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Introduction: KRAS is the most frequently mutated oncogene in Non-Small Cell Lung Cancer (NSCLC), occurring mostly at codon 12. KRASG12C is present in 10 to 13% of patients with NSCLC and KRASG12V in 5% of patients. KRAS status as a prognostic factor or predictor of response to immunotherapy in NSCLC remains a topic of debate.

Methods: In this study, we carried out a retrospective analysis including all patients with metastatic KRAS-mutant NSCLC diagnosed at La Paz University Hospital from May 2022 to September 2023. KRAS status was determined by the Oncomine precision assay and/or the Oncomine comprehensive assay V3, using the Genexus Integrated Sequencing System (Thermo fisher scientific). PD-L1 expression was analyzed by immunohistochemistry (22C3).

Results: : A total of 49 patients with metastatic KRAS-mutant NSCLC were identified throughout this period. The majority (n=27, 55.1%) were males with a median age of 66 years old. 47 patients (95.9%) had smoking history. Most patients had adenocarcinoma (n=44, 89.8%). Regarding KRAS mutations, around one third of the patients (32.7%) had G12C, 24.5% G12V, 10.2% G12D, 8.2% Q61L and 24.4% had other less frequent mutations. The most frequent co-mutations found were TP53 (14.3%) and CDKN2A (10.2%). The most frequent locations of metastases were the bone (38.8%), the brain (36.7%), the lungs (36.7%), the liver (20.4%) the pleura (26.5%) and the adrenal glands (26.5%). The presence of bone metastases was significantly less frequent in patients with KRASG12V mutation (8.3% vs 48.6%, p:0.01). The median progression-free survival (PFS) after first-line (1L) and overall survival (OS) were 9.02 (95%CI:2.69-15.34) and 14 months (95%CI:0.00-37.00), respectively. KRASG12C and KRASG12V-mutant patients had non-significantly longer PFS after 1L with chemoimmunotherapy and OS than other patients with other less frequent KRAS mutations. On the other hand, KRASG12D-mutant patients had non-significantly shorter PFS after 1L.

Conclusions: In our cohort, KRAS-mutant patients appear to have a different metastatic pattern depending on their KRAS mutation subtype. In addition, KRASG12C and KRASG12V-mutant patients seem to have better prognosis and response to chemoimmunotherapy than KRASG12D-mutant patients.

Keywords: Non-small cell lung cancer, KRAS mutations, Location of Metastases and Prognosis

EP.12C METASTATIC NON-SMALL CELL LUNG CANCER - TARGETED THERAPY - KRAS
SATURDAY, SEPTEMBER 7, 2024 - 11:58 - 11:59

EP.12C.05 KRASG12c-Mutant NSCLC Under Targeted Therapy in China: Lessons from Eight Cases

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Introduction: KRAS mutations are one of the commonest oncogenic driver mutations of non-small cell lung cancer (NSCLC), while KRASG12C mutation is the most prevalent subtype in Chinese population. Only until recently, two selective KRASG12C inhibitors (KRASG12Ci), called sotorasib and adagrasib, have been approved under fast-track by the U. S. Food and Drug Administration (FDA) for patients with NSCLC harboring KRASG12C mutation. However, there are limited data regarding the efficacy of selective therapy for KRASG12C-mutant NSCLC in real world. To our knowledge, this is the first study to characterize the clinicopathological features, genomic characteristics, and clinical outcomes of patients with KRASG12C-mutatant NSCLC under KRASG12Ci treatment in Chinese patients.

Methods: Patients with KRASG12C-mutatant NSCLC under KRASG12Ci treatment, identified by next-generation sequencing from January 2019 to March 2023 were enrolled. Time to KRASG12C inhibitor discontinuation, progression-free survival, overall survival, clinicopathological features and genomic alterations were evaluated.

Results: All the 8 KRASG12C patients were male (100%) and 7 of them were smokers (87.5%), with the median age 64.5 years (range 52 to 70 years). Current cohort enrolled 2 patients with stage IIIB (25%) and 6 patients with stage IV (75%) at initial diagnosis. One patient in stage IIIB developed stage IV disease (brain metastasis) at 5 months after surgery. 3 cases (37.5%) presented with ECOG score 0-1, and 5 cases (62.5%) with ECOG score 5. The most common metastatic sites were bone (6/8, 75%), contralateral lobe (3/8, 37.5%), brain (2/8, 25%), pleura (2/8, 25%), adrenal gland (2/8, 25%). The histologic types of these patients were all lung adenocarcinomas (8/8, 100%). The prevalence of concurrent type I mutation in these patients was MET (1/8, 12.5%). For concurrent type II mutations, there were TP53 (5/8, 62.5%), MYC (1/8, 12.5%), EGFR (1/8, 12.5%), STK11(1/8, 12.5%). The median overall survival (OS) was 19.0 months (95% confidence interval [CI] 2.77-35.23) and median progression-free survival (PFS) was 8.0 months (95%CI 2.22-13.78). Only 1 patient (12.5%) received G12Ci as first-line therapy. This patient was initially diagnosed with clinical stage IV lung adenocarcinoma at 64 years old, the OS was 3 months and PFS was 1 months. While the median OS was 19.0 months (95%CI 3.32-34.68) and median PFS was 8.0 months (95%CI 4.29-11.71) for patients who had received KRASG12Ci as second/later-line therapy.

Conclusions: Our survival data reinforce the view that the efficacy of KRASG12Ci is inferior to what has been reported for targeted therapy in other oncogene-addicted subsets of NSCLC (e.g. EGFR mutations, reported median OS was 40.5 months (95%CI 27.1-54.0) and median PFS was 19.4 months (95%CI 14.3-24.4) for advanced EGFR-mutated patients who had first-line EGFR targeted therapy). Clinical outcomes with KRASG12Ci vary widely among patients. Additionally, patients with KRASG12C have a predilection to bone metastasis, which is consistent with the current literature. Larger prospective study on efficacy of KRASG12Ci will be needed to validate our findings and clarify the markers for further patient classification and stratification.

Keywords: KRAS, G12C, NSCLC

EP.12D METASTATIC NON-SMALL CELL LUNG CANCER - TARGETED THERAPY - BRAF/ HER2 / MET
SATURDAY, SEPTEMBER 7, 2024 - 11:58 - 11:59

EP.12D.01 Clinical Outcomes of Patients with HER2-Mutant NSCLC in Real-World Settings: A Systematic Literature Review

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Introduction: The identification of oncogenic drivers led to several approved therapies for NSCLC, and a new wave of investigational agents. HER2 mutations account for 2% to 4% of NSCLC and were first described 20 years ago. Developing effective therapies for this molecularly-defined patient population presents specific challenges. To gain further insight into the unmet medical need for patients with HER2-mutant NSCLC, we conducted a global systematic literature review (SLR) to identify and analyze real-world studies published in the last 5 years describing clinical outcomes among patients with advanced NSCLC harboring such mutations.

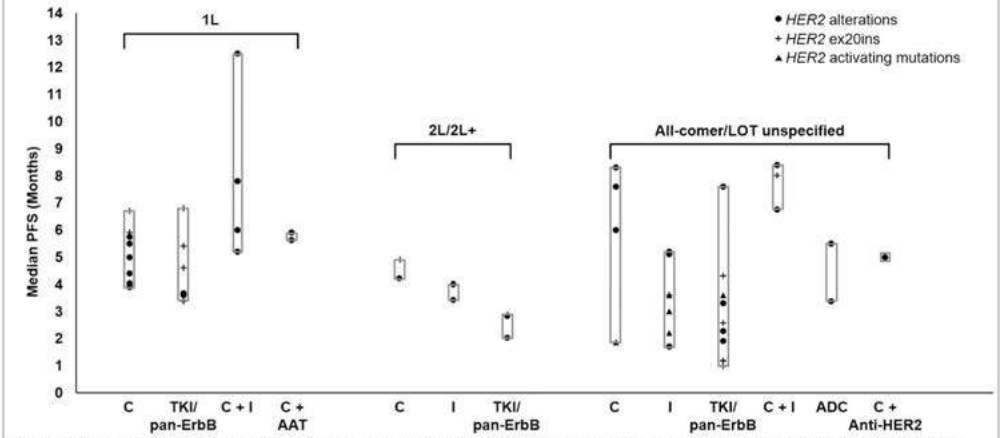
Methods: The SLR covered English language articles published between January 2019 and November 2023 and followed PICOS (Population, Patient, or Problem; Intervention; Comparison; Outcome; Study) design elements recommended by the Centre for Reviews and Dissemination (CRD) guidance for conducting reviews in healthcare. The review window aimed to capture outcomes of interest from studies that reflect modern molecular testing practices and standard of care in NSCLC.

Results: The SLR identified 66 studies, including studies describing the frequency of HER2 alterations, activating mutations, and/or ex20ins (n=38), PFS outcomes (n=32), tumor response outcomes (n=30), and OS outcomes (n=27). The reported frequency of HER2 activating mutations and ex20ins in patients with NSCLC ranged from 0.8-5.4% and 0.8-5.77%, respectively. HER2 mutation frequencies trended numerically higher among East Asian populations, including China. Median PFS reported across included studies ranged from 1.7-15.67 months, but were typically in the 2-6-month range. ORRs reported across included studies were typically in the 10-35% range. Median PFS and ORR outcomes were primarily from studies evaluating HER2/EGFR targeted therapies, followed by those evaluating single-agent immunotherapy or immunotherapy plus chemotherapy, or chemotherapy alone. Reported median OS among patients with advanced NSCLC ranged from 5.9-23 months in those harboring HER2 activating mutations, and from 1.3-35 months in those harboring ex20ins.

Conclusions: Excluding amplifications, HER2 ex20ins mutations are the most common HER2 genomic alteration in advanced NSCLC. Patients with NSCLC harboring HER2 ex20ins mutations tended to have poorer treatment outcomes compared to those with non-ex20ins mutations. Notable evidence gaps include lack of studies reporting prognostic impact of HER2 activating mutations in comparison to the general advanced NSCLC population, treatment duration outcomes, and HER2 mutational frequencies from large epidemiologic studies, especially in European countries. Future studies to validate reported associations as well as the lack of observed associations in larger patient cohorts and in more general settings are needed.

Keywords: HER2-mutant NSCLC, Systematic literature review, Progression-free survival

Figure. Median PFS (Months) among Patients with NSCLC Harboring *HER2* Alterations, Ex20ins, and/or Activating Mutations by Treatment Regimen and Line of Therapy



Abbreviations: AAT, anti-angiogenesis therapy; ADC, antibody-drug conjugate; C, chemotherapy; I, immunotherapy; LOT, line of therapy; PFS, progression-free survival; TKI, tyrosine kinase inhibitor.

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EP.12D.02 Treatment Strategies and Survival Outcomes of Advanced NSCLC with HER2 Mutation and BM: A Multicenter Retrospective Study

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Introduction: Human epidermal growth factor receptor 2 (HER2) mutation occur in 1-4% of non-small-cell lung cancer (NSCLC). Approximately 10-47% of HER2-mutant NSCLC will develop brain metastasis (BM) which is a poor prognostic factor, while chemotherapy alone yielded limited benefits for patients with BM. Fortunately, novel HER2-TKIs and antibody drug conjugates (ADCs) have shown certain efficacy; in particular, HER2-ADCs represented by T-DXd demonstrated promising intracranial efficacy. However, no available real-world data on such patients have been reported. We thus conducted this retrospective study to investigate the treatment regimens and clinical outcomes of advanced HER2-mutant NSCLC with BM.

Methods: From July 2018 and June 2023, this multicenter retrospective study included 178 patients with advanced HER2-mutant NSCLC who had received at least two cycles systemic antitumor therapy. The primary endpoint was overall survival (OS), measured from the diagnosis of BM until death or the last follow-up. Secondary endpoints included objective response rate (ORR), intracranial objective response rate (iORR), progression-free survival (PFS), and intracranial progression-free survival (iPFS).

Results: The study included 85 patients with HER2-mutant NSCLC with BM; 54.1% was female, median age was 60 years (range 31-88), 68.2% was nonsmokers, and 80.0% had a ECOG PS 0-1. The median OS after BM diagnosis was 15.7 months (95% CI: 13.5-17.9). In the first line (1L) treatment setting, patients were stratified into four groups based on the treatment regimens: chemotherapy (N=23), chemotherapy combined with immune checkpoint inhibitors (ICIs) (N=27), chemotherapy combined with anti-angiogenesis agents (N=28), and HER2-TKIs (N=7). The ORR for the above groups was 21.7/29.6/35.7/28.6%; the iORR was 18.2/25.9/26.9/28.6%, respectively. Patients who received chemotherapy plus antiangiogenic agents had a longer median PFS than those who received chemotherapy alone or combined with ICIs (6.8 months vs. 5.9 months vs. 4.9 months, P=0.032); while no significant differences were found in either median iPFS (4.3 vs. 5.2 vs. 5.8 months, p=0.088) or OS (14.4 vs. 17.4 vs. 16.0 months, p=0.880). In the second-line or later line (≥2L) setting, 25 patients who received next-generation HER2-ADCs treatment had the ORR and iORR of 52.0% and 27.3% respectively; the median PFS and iPFS were 7.2 months (95% CI: 4.7-9.7) and 6.7 months (95% CI: 5.2-8.2), respectively. Further analysis of patients who received with ADCs showed a longer median OS than those without ADCs (18.7 vs. 12.0 months, p=0.028). Besides, cranial radiotherapy significantly prolonged OS in patients with BM (17.9 vs. 9.0 months, p=0.0014). Inferior ECOG PS (HR=4.27, 95% CI: 2.02-9.05, P<0.001), undergoing intracranial radiotherapy (HR=0.49, 95% CI: 0.26-0.92, P=0.027), and receiving ADC treatment (HR=0.47, 95% CI: 0.24-0.93, P=0.030) were independent predictors for OS.

Conclusions: For HER2-mutated NSCLC and BM, 1L chemotherapy combined with anti-angiogenesis therapies brings greater survival benefits than chemotherapy alone; besides, next-generation HER2-ADCs and cranial radiotherapy could improve OS.

Keywords: brain metastasis, human epidermal growth factor receptor 2 mutations, non-small cell lung cancer

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EP.12D.03 Characterization of HER2Alterations in 23,321 NSCLC Cases and Real-World Therapeutic Pattern in Chinese HER2-Mutant NSCLC the CHAPTER Study

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Introduction: The FDA has granted approval for fam-trastuzumab deruxtecan-nxki (Enhertu) in the treatment of non-small cell lung cancer (NSCLC) harboring ERBB2 activating mutations, although it is yet to receive approval in China. The studies on treatment pattern and the clinical efficacy of different regimens among Chinese population in the real-world setting are scare.

Methods: We analyzed the comprehensive genomic profiling results of tissue samples from 23321 NSCLC patients through Lung Cancer Big Data Precise Treatment Collaboration Group (LANDSCAPE) project (Cohort I). Samples of ERBB2 alterations (alt) and sequencing data covered the following genes, including EGFR, MET, KRAS, BRAF, ALK, RET, ROS1, ERBB3, PIK3CA, PTEN, CCNE1, IGF1R, were used for ERBB2 co-occurrent analysis. We also retrospectively collected clinical and survival data of 236 NSCLC patients who had ERBB2 alt from Peking University Cancer Hospital and Institute between December 2015 and March 2024 (Cohort II).

Results: Pathogenic/likely pathogenic alterations in ERBB2 were identified in 5.0% (n = 1174) of NSCLC tissue samples. Among these, ERBB2 mutations (mut) accounted for 3.8% (snv, indel) and amplification for 1.5%. ERBB2 alt were significantly more prevalent in patients under 45 years old compared to those ERBB2 wild type (WT) (12.8% vs. 4.4%, p<0.001), and also exhibited significant more female patients (55.5% vs. 44.5%, p<0.001). ERBB2 alt were more common in lung adenocarcinoma (89.1% vs 82.5%, p<0.01). ERBB2 mutations occur mainly in the kinase domain (KD, 85%, 91% of which were exon20ins), followed by the extracellular domain (ECD, 11%) and transmembrane domain (TMD,3%). ERBB2 mutations (n=519) were relatively mutually exclusive with other known oncogenic drivers (EGFR, KRAS, BRAF, MET, ALK, ROS1, RET; each p<0.01). Notably, as many as 83% of ERBB2 pathogenic/likely pathogeinc mutations in our data were observed in the DESTINY-Lung01 trial. Meanwhile, in Cohort II, of 236 NSCLC patients who had ERBB2 alt, 44.1% (104/236) were ERBB2 exon20ins. For unresectable locally advanced or metastatic patients received first-line treatment (N=195), the median progression-free survival (PFS) of chemotherapy/bevacizumab/immunotherapy (N=7), chemotherapy/immunotherapy (N=63), chemotherapy/bevacizumab (N=32), chemotherapy (N=32), EGFR-TKIs (N=52), and anti-ERBB2 inhibitors (N=9, mostly pyrotinib) was 13.0 months (95%CI: 6.5-19.5), 8.5 months (95%CI: 6.5-10.5), 6.0 months (95%CI: 4.7-7.3), 6.5 months (95%CI: 5.4-7.6), 10.0 months (95%CI: 7.0-13.0), and 6.0 months (95%CI: 3.4-8.6), respectively (P=0.42). For patients received subsequent-line Enhertu (mostly third-line or fourth-line), the objective response rate (ORR) was 54.5%, which is higher than other anti-HER2 inhibitors (pyrotinib, ORR=9.1%; afatinib/dacomitinib, ORR=27.8%; trastuzumab, ORR=0%; others, ORR=22.2%, P=0.077). A numerically longer mPFS was also observed with Enhertu (N=14, mPFS 7 months, 95%CI: 3.3-10.7) versus pyrotinib (N=33, mPFS 4.0 months, 95%CI: 2.6-5.4), afatinib/dacomitinib (N=19, mPFS 3.3 months, 95%CI: 1.7-4.9), trastuzumab (N=7, mPFS 3.0 months, 95%CI: 2.1-3.9), and other therapy regimens (N=11, mPFS 2.6 months, 95%CI: 1.2-4.0) (P=0.34)

Conclusions: A comprehensive analysis of the molecular characteristics and real-world treatment patterns in patients with ERBB2-mutated NSCLC can aid in optimizing the treatment of these patients, ultimately enhancing their prognosis. The more favorable efficacy benefit demonstrated by Enhertu compared with all other anti-HER2 regimens indicates the optimal treatment choice for Chinese NSCLC patients with ERBB2 alterations.

Keywords: NSCLC, ERBB2, Enhertu

EP.12D METASTATIC NON-SMALL CELL LUNG CANCER - TARGETED THERAPY - BRAF/ HER2 / MET
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EP.12D.04 Treatment Pattern and Clinical Outcome in Chinese NSCLC Patients with MET Alterationwho Had Disease Progressionon EGFR-TKIs

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Introduction: Dysregulation of the MET signaling pathway, including MET amplification/over-expression (amp/OE), is one of the most common acquired resistance mechanism to EGFR-TKIs in patients (pts) with advanced EGFRm NSCLC. Previous studies indicated the combination of MET-TKIs and EGFR-TKIs had shown encouraging clinical efficacy and a tolerable safety profile in these pts with MET amp/OE. However, the data of treatment pattern and clinical outcome for these patients in real-world setting is still limited.

Methods: We performed a retrospective, real-world study to analyze treatment pattern and clinical outcome in advanced or metastatic EGFRm NSCLC pts with MET amp/OE who progressed on EGFR-TKIs between Feb. 2022 and Oct. 2023 in China. MET amp was detected by fluorescence in situ hybridization (FISH; MET copy number ≥5 and/or MET:CEP7 signal ratio ≥2), and MET OE by immunohistochemistry (MET IHC; 3+ in ≥50% of tumor cells). Data of patient characteristics, treatment pattern, clinical outcome and safety were collected and analyzed. The objective response rate (ORR), time to treatment failure (TTF) were evaluated.

Results: 32 advanced EGFRm NSCLC pts with MET amp/OE who progressed on EGFR-TKIs were included this study. 93.5% pts had adenocarcinoma histology, 56.3% pts were ECOG 0~1, and 40.6% pts had brain metastases. Overall, 31.3% pts received the combination therapy of MET-TKI and EGFR-TKI, 46.9% pts received chemotherapy(chemo)-based regimen and 21.8% pts received other regimens as subsequence therapies. The ORR of pts who received MET-TKI plus EGFR-TKI was 61.5%. The median TTF (mTTF) of these pts was 9.5 months(m). Of these pts, the ORR of the pts who received savolitinib plus osimertinib was 77.8%, the mTTF was 10.2m. However, the mTTF of the pts who received chemo-based therapies was only 4.4m. The ORR of the pts who received MET-TKI plus EGFR-TKI as second-line(2L) was 75% and the mTTF was 12.8m. The ORR of the pts who received chemo-based regimen as 2L was only 33.3%, the mTTF only was 5.5m. The safety profile of the combination therapy of MET-TKIs plus EGFR-TKI and chemo-based therapy were similar to previously reported data.

Conclusions: Chemo-based therapy remained most common treatment regimen for these advanced NSCLC pts with MET amp/OE who have progressed on EGFR-TKIs in the real-world setting. The combination of MET-TKI and EGFR-TKI showed encouraging clinical benefit in these pts with acceptable safety. Future prospective studies are warranted to confirm the benefit of MET-TKIs plus EGFR-TKIs in these pts.

Keywords: post EGFR- TKI, MET amp/OE, treatment pattern

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EP.12D.05 MAIC of OS and TRAE Comparing Capmatinib with Other MET Inhibitors for Treatment of Ansclc with MET Exon 14 Skipping Mutations

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Introduction: Highly selective mesenchymal-epithelial transition (MET) inhibitors are preferred treatments for advanced non-small cell lung cancer (aNSCLC) with MET exon 14 skipping mutations1. At the time of this analysis (Aug 2023), 4 MET inhibitors (Capmatinib (CAP), savolitinib (SAV), glumetinib (GLU), and tepotinib (TEP)) had clinical data published based on respective single arm trials. In the absence of head-to-head studies, unanchored matching-adjusted indirect comparison (MAIC) of overall survival (OS) in first-line (1L) setting and treatment related adverse events (TRAE) in overall population was performed to adjust differences in clinical trial settings and estimate relative efficacy and safety of CAP vs other MET inhibitors.

Methods: The baseline characteristics of CAP treatment patients from the GEOMETRY mono-1 study were weighted to match aggregate data from published comparator trials (NCT02897479 for SAV, NCT04270591 for GLU, NCT02864992 for TEP). Cox proportional hazard regression analysis was used to identify the matching variables that had a significant association with OS. Post-MAIC, the CAP weighted Kaplan Meier OS curves was compared against comparator's curves to estimate hazard ratio (HR) in treatment naive patients. For TRAEs, baseline characteristics of both the overall population and the Asian population were adjusted and then recalculated.

Results: In the 1L setting, CAP was found to have numerically better OS than SAV (HR 0.532, 95%CI 0.265-1.068), TEP (HR 0.870, 95%CI 0.579-1.307), and the comparison with GLU was not able to be performed due to OS immaturity of GLU. The rate of any grade TRAEs for CAP were significantly lower than SAV and GLU in the overall population (Risk difference CAP vs SAV: -9.3%, GLU: -7.1%), and numerically lower than TEP (Risk difference CAP vs TEP: -1.1%). In the Asian population, CAP showed the lowest rate of any grade TRAEs against all comparators (Risk difference CAP vs SAV: -11.4%, GLU: -12.6%, TEP: -11.1%).

Conclusions: Considering all comparators, CAP showed numerical OS advantage trend in the first line setting and a lower incidence of TRAEs in both the overall population and the Asian population.

Reference: 1. NCCN Clinical Practice Guidelines in Oncology. Non-Small Cell Lung Cancer (Version 2. 2023). National Comprehensive Cancer Network.

Keywords: MAIC, Capmatinib, MET

EP.12D METASTATIC NON-SMALL CELL LUNG CANCER - TARGETED THERAPY - BRAF/ HER2 / MET
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EP.12D.06 Real-World Cases on Efficacy and Safety of Savolitinib for Elderly Patients with NSCLC Harbouring METex14 Skipping Mutations

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Introduction: Savolitinib is an oral targeted agent that selectively inhibits MET tyrosine kinase. Limited real-world data have been reported on the long-term survival of elderly (≥75 years) NSCLC patients with METex14 skipping. We reported three elderly NSCLC patients with METex14 skipping who were treated with savolitinib to explore the efficacy and safety of savolitinib.

Methods: Three patients with advanced METex14 skipping NSCLC between 2022 and 2024 were retrospectively reviewed (the database cut-off date was March 20, 2024). All the patients received savolitinib in the first-line therapy. The data analyzed by investigators included objective response (RECIST1.1), progression-free survival (PFS), and safety.

Results: The median age of the three patients was 81.6 (76-86) years. Case 1) An 83-year-old man complained of cough was diagnosed of lung adenocarcinoma with the stage of T3N0M0. Computed tomography (CT) scan showed a mass in the posterior upper lobe of the right lung, with right visceral pleural invasion. Lung tissue biopsy confirmed lung adenocarcinoma, and METex14 skipping was confirmed by NGS. The patient received savolitinib at a standard dose of 600 mg once daily (Qd). The patient achieved partial response (PR) after three months and subsequently achieved stable disease (SD), who continued to receive savolitinib until now. The PFS was 15 months. He experienced Grade 1 fatigue and pruritus sequentially. Case 2) An 86-year-old woman presented with chest distress was diagnosed with stage IVa NSCLC with cervical lymph node metastases. CT showed left upper lobe mass and lymph node metastases in the left hilar region, mediastinum, left supraclavicular region, left side of the neck, and left axillary region. NSCLC was confirmed by cervical lymph node biopsy (Not Otherwise Specific), and METex14 skipping was confirmed by NGS. She started savolitinib 400 mg Qd based on the weight of 45kg. After two months of treatment, the dosage was reduced to 300mg because of Grade 3 hepatic dysfunction, then further reduced to 200 mg Qd because of Grade 2 hepatic dysfunction after 2 days. The patient developed grade 2 hypoproteinemia after 6 months of savolitinib. Hypoproteinemia improved after diet adjustment. The PFS was 22 months. Case 3) A 76-year-old man presented with cough was diagnosed of adenocarcinoma with stage IV NSCLC (T3N1M1)from a thoracoscopic biopsy. He started savolitinib 600 mg Qd for a month and reduced to 300 mg because of grade 4 hepatic dysfunction, then further reduced to 200mg because of grade 2 hepatic dysfunction after 3 days. After 17 months of treatment with savolitinib, he was added radiotherapy (PTV 60Gy/30f) on the residual lesions in the left hilar region. The PFS exceeded 25 months. He also experienced Grade 2 limb edema and rash.

Conclusions: From the case series, savolitinib showed a favorable clinical benefit and safety profile, which may make it one of the best treatment options for elderly NSCLC patients with METex14 skipping. It provides long-term survival and is tolerable.

Keywords: NSCLC, METex14 Skipping, Savolitinib

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EP.12D.07 Efficacy and Safety of Savolitinib for MET-Altered Non-Small Cell Lung Cancer (NSCLC) In First-Line Setting: A Case Series

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Introduction: Recognition and detection of MET alterations, including MET exon14 skipping mutation (METex14), MET amplification (METamp), and overexpression, have fueled the clinical development of MET tyrosine kinase inhibitors (TKIs). In METex14 NSCLCs, MET TKIs have become a standard therapy, but the clinical data is limited for METamp EGFR wild-type (EGFRw) patients. Here, we present a case series of MET-altered EGFRw NSCLCs receiving savoltininb in the first-line setting.

Methods: Four patients with stage IV NSCLCs were retrospectively reviewed, including three with primary METamp (cases 1-3) and one with METex14 (case 4). Cases 2-4 had brain metastasis. All patients received savolitinib 600mg once daily in a first-line setting. Objective response by investigators and progression-free survival (PFS) were analyzed based on RECIST v1.1; the safety profile was evaluated according to CTCAE v5.0.

Results: The MET gene copy numbers of case1-3 were 2.46, 8, and 5, respectively, and all of these patients also harbored PD-L1 high expression (60%-80%). For cases 1, 2, and 4, the overall tumor response was PR after approximately one month of therapy. At the time of cut-off, they were receiving continuous treatment, and the primary lesions were still in response with a PFS of 17 months, 26 months, and 19 months, respectively. In the brain metastasis subgroup, case 2 and case 4 received stereotactic radiotherapy (SRT) and achieved a PR in brain lesions; the intracranial PFS was 26 months and 19 months. In case 3, a male patient also accompanied by 34 other gene mutations, the primary lesion achieved PR after therapy, but brain metastatic lesions showed a disease progression despite multiple therapies (including surgery, radiotherapy, and laser interstitial thermal treatment), with overall survival (OS) of only nine months. Three patients experienced peripheral edema (grade 2 for cases 1 and case 2, grade 1 for case 4), leading to savolitinib dose reduction to 400mg once daily. Still, the edema was manageable after dose reduction and diuretic therapy. No other serious adverse events were observed.

Conclusions: MET-altered EGFRw NSCLCs treated with savolitinib in the first-line setting showed promising primary tumor shrinkage and a durable response, regardless of brain metastatic status. For the brain lesions, savolitinib plus local radiotherapy could cause a prominent intracranial PFS. The safety profile was manageable. The mechanism of MET TKI resistance needs further study, especially in brain metastatic lesions. This study was supported by the grants from Beijing Natural Science Foundation (NO. 7242007)

Keywords: NSCLC, MET, savolitinib

Patient case	Sex	Age	TNM stage	Brain metastasis	EGFR	Met alteration	PD-L1 score	Primary tumor response	PFS	Intracranial response	Intracranial PFS	Adverse events
1	Male	67	T4N3M1	No	wild-type	METamp	60%	PR(ongoing)	17mo	NA	NA	Grade 2 PE
2	Male	81	T1N3M1	Yes	wild-type	METamp	80%+	PR(ongoing)	26mo	PR(ongoing)	26mo	Grade 2 PE
3	Male	64	T3N2M1	Yes	wild-type	METamp	<1%(lung), 65%(brain)	PR	4mo	PD	4mo	-
4	Male	85	T3N2M1	Yes	wild-type	METex14	-	PR(ongoing)	19mo	PR	19mo	Grade 1 PE

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EP.12E.01 OBX02-011, a Novel Oral ALK and EGFR Dual-target Tyrosine Kinase Inhibitor for the Treatment of Advanced NSCLC Patients, S. Heo[1], S. Lee[2], T. Ha[2], M. Baek[2], M. Kim[2], K. Jung[2], S-E. Kim[2], [1]ONCOBIX CO., LTD., Gyeonggi-Do,/KR,[2]ONCOBIX CO., LTD., Gyeonggi-Do/KR

Introduction: Multiple ALK and EGFR TKIs have been developed for patients with ALK-positive and EGFR-positive non-small-cell lung cancer. Despite the outstanding efficacy of inhibitors in the current market, resistance is inevitable. Both on-target and off-target mechanisms of resistance have been identified in patients who have progressed disease after prior treatment with ALK or EGFR TKIs. To address the limitations of existing targeted therapies, Oncobix is developing OBX02-011, a novel, synthetic, orally administered TKI.

Methods: OBX02-011 was evaluated for selectivity by testing its in vitro activity against more than 450 human kinases and disease relevant mutant variants using a binding assay. Kinase assays were also performed to investigate kinase selectivity. To confirm selectivity from the kinase assays, OBX02-011's potency in cell-based assays was compared to other ALK and EGFR TKIs. OBX02-011 was evaluated for in vivo anti-tumor activity in mice implanted with tumor cell lines expressing fusions with EML4-ALK_G1202R, EGFR sensitizing mutations, and EGFR acquired mutations. In addition, OBX02-011 was also evaluated for in vivo anti-tumor activity in the intracranial NCI-H2228-luc brain metastasis model.

Results: OBX02-011 showed high potency against ALK and EGFR, as well as a panel of acquired ALK and EGFR mutations that developed resistance to the marketed ALK or EGFR inhibitors. In the kinase assays, OBX02-011 inhibited ALK wild type and a panel of crizotinib, alectinib, and brigatinib resistant ALK mutations, including G1202R and L1196M. OBX02-011 inhibited EGFR as well as sensitizing mutations (exon 19 deletion and L858R) and acquired resistance (exon 19 deletion/C797S, L858R/C797S, exon 19 deletion/T790M/C797S, and L858R/T790M/C797S). In cell-based assays, OBX02-011 showed similar inhibition to lorlatinib in the ALK wild-type. In addition, OBX02-011 demonstrated superior inhibition compared to lorlatinib in ALK_C1156Y, G1202R, and L1196M mutations associated with clinical resistance to the first generation ALK inhibitor crizotinib and/or the second generation ALK inhibitors alectinib, brigatinib, and ceritinib. In the in vivo studies, OBX02-011 demonstrated tumor regression in EML4-ALK_G1202R, EGFR_exon 19 deletion, EGFR_L858R, EGFR_exon 19 deletion/C797S models, EGFR_L858R/C797S models. OBX02-011 also demonstrated tumor regression in the osimertinib-resistant lung cancer patient-derived xenograft model with EGFR_exon 19 deletion/T790M/C797S. OBX02-011 also demonstrated potency in the ALK wild-type brain metastasis model.

Conclusions: Non-clinical studies have shown that OBX02-011 is a potent inhibit of ALK and EGFR, including the respective ALK G1202R mutation and EGFR sensitizing and acquired mutations. In vitro cell-based assay results showed that OBX02-011 does not inhibit NTRK2 (TRKB), which causes neurological toxicity, and there were also no significant findings for OBX02-011 in the CNS safety pharmacology study. Based on these studies, a first-in-human study will be conducted in 2024 to address the current resistance mechanisms in ALK-positive or EGFR-positive NSCLC patients and prolong progression free survival.

Keywords: ALK, EGFR, TKI

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EP.12E.02 Landscape, Management & Outcome of Real-World Fusion-positive Non-Small Cell Lung Cancer (NSCLC)

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Introduction: The discovery of oncogenic driver genes in NSCLC and subsequent development of targeted therapies has dramatically changed the management and prognosis of these malignancies. For patients with NSCLC driven by kinase fusions or oncogenic isoforms, barriers persist with regards to diagnostic confirmatory testing, histology-restricted genomic sequencing algorithms, and reimbursement restrictions of molecularly targeted therapies. We aim address a current knowledge gap in the understanding of the characteristics, real world treatment, and outcomes of fusion- or isogenic isoform-positive NSCLC.

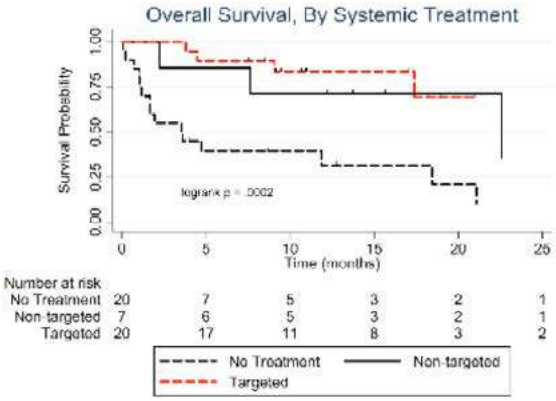
Methods: Alberta patients with advanced/metastatic (M1) NSCLC, meeting the criteria for funded provincial genomic sequencing between April 2022 and May 2023, received reflexive (SNV-hotspot driver negative) RNA next-generation sequencing (NGS) by Alberta Precision Laboratories. Testing was performed by Archer FusionPlex (IDT) with sequencing on Genexus (ThermoFisher). Demographic, clinical, treatment, and outcome details were extracted from a province-wide, real-world outcomes registry of patients treated in routine practice.

Results: Forty-seven individuals with an oncogenic fusion or isoform were identified. Median age at diagnosis was 70 years, 62% female, 51% never-smokers, 57% ECOG ≤ 1; 87% adenocarcinoma histological subtype. Alterations identified in this cohort were: MET exon 14 skipping (38%), BRAF oncogenic isoform (2%), and fusions: ALK (34%), RET (11%), ROS1 (9%), and FGFR2/3 (6%). Alterations were identified/reported a median 1.1 months following histological diagnosis of M1 lung cancer. Twenty-seven individuals (57%), predominantly with ECOG ≤1 (81%), received some form of systemic therapy, comprised of n=7 (26%) receiving a non-targeted systemic therapy (chemotherapy and/or immune checkpoint inhibitors), and n=20 (74%) receiving a targeted therapy. Median time-to-progression was 8.4 and 15.8 months, respectively. Targeted therapy availability, use, and survival outcomes (data cut-off: March 15, 2024) are described in Figure 1.

Conclusions: The advent of precision medicine relies on identification of both an effective therapy and amenable target. This analysis provides evidence of the number and variety of oncogenic fusions and isoforms in NSCLC identified in the era of NGS-testing, and encountered in routine clinical practice. These findings also reveal the low uptake of approved targeted therapies when self-funding is required for access. Inclusion of NGS-based genomic profiling and targeted therapies as part of standard of care within the public healthcare system supports appropriate clinical management to optimize patient outcome among those with actionable oncogenic fusions.

Keywords: genomic testing & targeted therapies, fusion-positive NSCLC, real-world management and outcomes

Figure 1: Systemic Treatment and Survival Outcome



Alteration	Systemic Therapy Received	Targeted Therapy Approved & Funded*	Targeted Therapy Received	Survival Analysis Post- Metastatic Disease◊
ALK Fusion (n=16)	94%	Approved + *Funded*	94%	NR (median time since systemic therapy initiation: 9.8 months)
BRAF Oncogenic Isoform (non-actionable) (n=1)	0%	No	N/A	NR
FGFR2/3 Fusion (n=3)	33%	No	N/A	3.5 months
MET Exon 14 Skipping (n=18)	33%	Approved Unfunded	6%	10.5 months
RET Fusion (n=5)	20%	Approved Unfunded	20%	1.2 months
ROS1 Fusion (n=4)	75%	Approved + *Funded*	75%	NR (median time since systemic therapy initiation: 9.5 months)
Survival Analysis Post- Metastatic Disease	22.6 months [2.2 – NR]	-	Not reached [17.4 – NR]	18.4 months [95% CI: 7.6 – 22.6]

* Targeted options approved and funded in Alberta, as of May 31, 2023, date of cohort testing cut-off.
◊ Data cut-off March 15, 2024
NR: Not reached

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EP.12E.04 Understanding the Dynamics of TKI Induced Changes in the Tumor Immune Microenvironment for Improved Therapeutic Effect

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Introduction: Understanding the functional dynamics and resistance mechanisms of tyrosine kinase inhibitors (TKIs) is pivotal for advancing non-small cell lung cancer (NSCLC) therapeutics

Methods: Multiplex Immunofuorescence and Immunohistochemistry (IHC) staining to explore the features of immune cell composition in the TME. Cell viability assay, Western blot analysis, Enzyme-Linked Immunosorbent Assay and T cell-mediated cancer cell killing assay to assessed the impact of TKI treatment on T-cell function. Animal experiments used to assessed aspirin potential role in overcoming TKI resistance by modulating the TME.

Results: In this study, we examined the influence of TKI interventions on the tumor immune microenvironment (TME) in NSCLC. Short-term TKI application enhanced T cell-mediated tumor clearance, reduced immunosuppressive M2 macrophage infiltration, and downregulated laminin subunit γ-2 (LAMC2), a key protein involved in tumor immune evasion. In contrast, long-term TKI treatment led to an immunosuppressive TME, fostering drug resistance and signifying a shift toward immune escape over time. Additionally, we observed differential TME responses to epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) mutations, with ALK-targeted therapies eliciting stronger anti-tumor immunity. Notably, aspirin emerged as a promising adjunct in combating TKI resistance, modulating the TME and enhancing T cell-mediated tumor clearance.

Conclusions: These findings provide new insights into the dynamics of TKI-induced changes in the TME, improving the understanding of NSCLC-related challenges and opening up new avenues for strategies to overcome TKI resistance.

Keywords: tumor immune microenvironment, tyrosine kinase inhibitor, non-small cell lung cancer

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EP.12E.05 Exploring Clinical Characteristics and Treatment Outcomes of Squamous Cell Lung Cancers Harboring EGFR and ALK Mutations: A Case Series

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Introduction: Squamous cell carcinoma (SCC) of the lung accounts for approximately 30% of non-small cell lung cancer (NSCLC) cases and is the second most common histological type of lung cancer. The Cancer Genome Atlas project and similar studies have detected a significant number of somatic gene mutations/amplifications in lung SCC (5-20%), mostly in TP53, CDKN2A, KMT2D, PIK3CA, and NFE2L2. In comparison with lung adenocarcinoma, EGFR/ALK mutations in SCC are relatively rare, with a reported prevalence of 3% to 18% and thus testing for these mutations is not commonly performed.1 Prior case reports have described ALK/EGFR mutations in SCC lung cancer patients with limited smoking history and worse prognosis despite treatment with targeted therapies.2,3 This case series presents three patients diagnosed with Stage III/IV squamous cell lung cancer and rare EGFR/ALK mutations, examining their demographics, smoking status, mutational profiles, and treatment outcomes.

Methods: This case series retrospectively analyzed three patients diagnosed with locally advanced/metastatic SCC and EGFR/ALK alterations at Sylvester Comprehensive Cancer Center between 2019 and 2024. Data on patient demographics, including ethnicity, smoking status, mutational profiles, treatment regimens, progression-free survival (PFS), and overall survival (OS), were collected from electronic medical records.

Results: All the patients in this series were women, never-smokers, ages 64-71 at diagnosis. Two patients had mixed adenocarcinoma-squamous histology (one ALK/one EGFR), while another patient had squamous histology only. One patient was diagnosed with Stage IIIB disease and treated with induction chemotherapy and surgery followed by adjuvant osimertinib with a PFS of 23 months. One of three patients progressed in the brain after initial treatment with targeted therapy. Pathology from the brain specimen revealed squamous histology with the same EGFR mutation at the site of metastases. Tolerance to treatment was similar to patients with adenocarcinoma with commonly reported adverse events related to skin and GI toxicity to osimertinib. Responses to platinum-based chemotherapy were varied. No common pattern of resistance mutations were identified.

Conclusions: In conclusion, advanced/metastatic squamous cell lung cancer with EGFR/ALK mutations are rare but can respond to treatment. In our case series, we found increased response to treatments that target the driver EGFR/ALK mutations, in patients with no smoking history with both mixed histology adenosquamous cell carcinoma or SCC. Despite the heterogeneity observed, osimertinib remains a promising treatment modality. Further research is warranted to elucidate specific patterns of resistance to EGFR-ALK targeted therapies in lung SCC.

Keywords: Squamous cell cancer of lung, EGFR, ALK

Table 1: Clinical Characteristics and Treatment Outcomes of SCC

Age	Gender	Ethnicity	Smoking	Stage	Mutations/ Co-mutations	Targeted Therapy	Lines of Therapy	Efficacy	PFS (months)	OS (months)
64	F	NHW	Never	IV	EGFR L858R MPL R592Q PIK3CA D352Y ESR1 Y246Y	Osimertinib	7	PR	10	49, deceased
59	F	NHW	Never	IIIB/ IV	EGFR del 19 PIK3CA PD2FRA	Osimertinib in adjuvant setting	4	PR	23	36, alive
71	F	Hispanic	Never	IV	EML4-ALK STT3A-ALK	Alectinib	2	PR	NR	4, alive

NHW= Non Hispanic Whites NR=not reached

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EP.12F.01 Genome-wide CRISPR-Cas9 Screening Identifies ITGA8 Responsible for Abivertinib Sensitivity in Lung Adenocarcinoma

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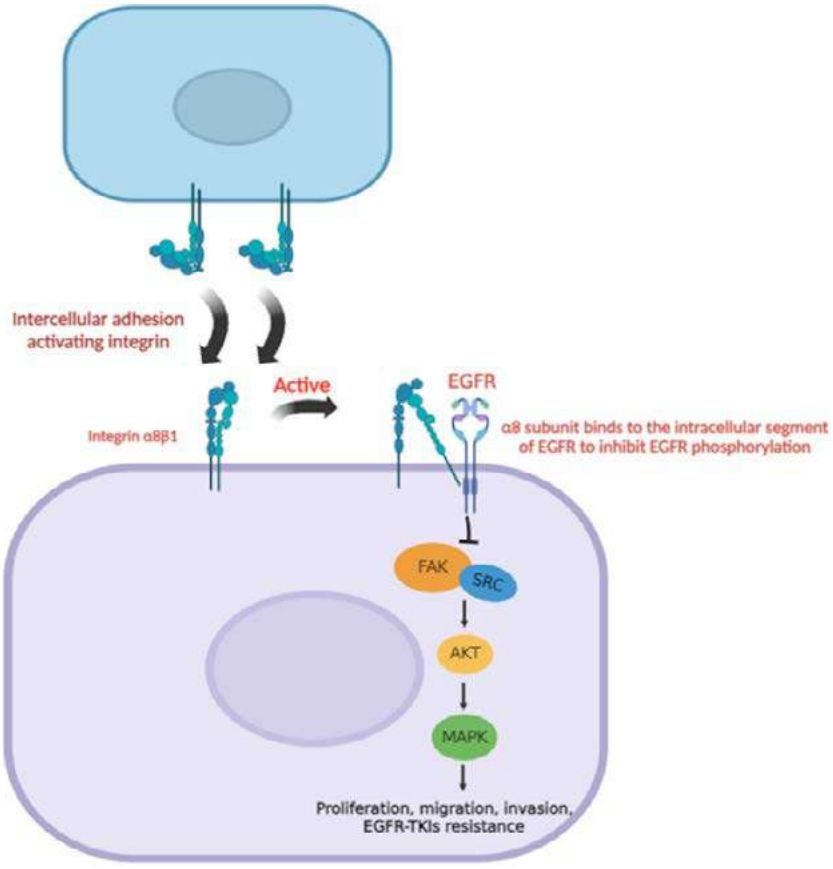
Introduction: The recent emergence of epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) has improved the prognosis of lung cancer patients with EGFR-driven gene mutations; however, the subsequent acquired resistance to EGFR-TKIs presents a major challenge to treatment. Studies on acquired resistance to EGFR-TKIs have primarily focused on developing next-generation targeted drugs based on the molecular mechanisms of resistance or inhibiting the activation of bypass pathways to suppress or reverse drug resistance. This study used a novel approach by applying CRISPR-Cas9 whole-genome library screening to identify genes that enhance sensitivity to EGFR-TKIs in lung adenocarcinoma.

Methods: Using the CRISPR-Cas9 whole-genome screening library, genes that increased the sensitivity of lung adenocarcinoma to abivertinib were identified. Bioinformatics, RT-qPCR, western blot analysis, and immunohistochemical staining were employed to validate gene expression differences between adjacent normal tissues and lung adenocarcinoma tissues. CCK8, clonogenic, EDU cell proliferation, and Transwell assays were done to assess the sensitivity of lung adenocarcinoma to abivertinib and the impact of ITGA8 on the proliferative, migration and invasion capacities of lung adenocarcinoma. Western blot analysis was used to detect changes in downstream signaling pathways at various ITGA8 expression levels. Rescue experiments were done to validate the interaction between ITGA8 and downstream FAK. In vivo experiments in nude mice were conducted to validate the effect of various ITGA8 expression levels on tumor proliferation and abivertinib sensitivity.

Results: Through CRISPR-Cas9 whole-genome library screening, ITGA8 was identified as a key gene that enhances the sensitivity of lung adenocarcinoma to abivertinib. In lung adenocarcinoma tissues, the expression of ITGA8 was markedly lower compared with that in adjacent normal tissues. ITGA8 was positively correlated with the sensitivity of lung adenocarcinoma to abivertinib and negatively correlated with the proliferation, migration, and invasion of lung adenocarcinoma. It sensitizes lung adenocarcinoma cells to EGFR-TKIs by attenuating the downstream FAK/SRC/AKT/MAPK signaling pathway.

Conclusions: ITGA8 reduces the proliferation, invasion, and migration capabilities of tumor cells, enhances the sensitivity of lung adenocarcinoma to EGFR-TKIs, improves treatment efficacy, and prolongs the duration of acquired resistance. ITGA8 is a potential therapeutic target that may address acquired resistance to EGFR-TKIs from a novel perspective.

Keywords: EGFR-TKIs, CRISPR-Cas9, ITGA8



EP.12F METASTATIC NON-SMALL CELL LUNG CANCER - TARGETED THERAPY - NOVEL TARGETS
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EP.12F.02 Brigatinib, a Newly Discovered AXL Inhibitor, and Suppresses AXL Mediated Acquired Resistance to Osimertinib in NSCLC

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Introduction: In addition to the classical resistance mechanism, receptor tyrosine-protein kinase AXL is a main mechanism of resistance to third-generation epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs) osimertinib in EGFR-mutated non-small cell lung cancer (NSCLC). Therefore, developing an effective AXL inhibitor is particularly important to sensitize osimertinib in clinical application. Here, the present study aimed to investigate a small molecule inhibitor, currently available in clinical settings, for its potential to enhance the sensitivity of EGFR-TKI in osimertinib resistance cells.

Methods: Small molecule screening and human phospho-RTK array to discover potent inhibitory activity toward AXL. Molecular modeling studies and thermal shift assay used to determine brigatinib bind with AXL kinase. Cell viability, colonial survival and cell-derived xenograft (CDX) models were used to determine antitumor activities.

Results: We established an AXL-overexpression NSCLC cell line and conducted high-throughput screening of a small molecule chemical library containing 510 anti-tumor drugs. We found that brigatinib potently inhibited AXL expression. We demonstrated that brigatinib had a potential ability to bind AXL kinase protein and further inhibit its downstream pathways in NSCLC cell lines. and that brigatinib (0.5 μM) significantly enhanced the anti-tumor efficacy osimertinib (1 μM) in AXL-mediated osimertinib-resistant NSCLC cell lines in vitro. In AXL-high expression osimertinib-resistant PC-9OR and HCC827OR cell derived xenograft mouse models, administration of osimertinib (10 mg·kg-1·d-1) alone for 3 weeks had no effect, and administration of brigatinib (25 mg·kg-1·d-1) alone caused a minor inhibition on the tumor growth; whereas combination of osimertinib and brigatinib caused marked tumor shrinkages.

Conclusions: In conclusion, our study indicated that brigatinib may be a promising clinical strategy for enhancing osimertinib efficacy in AXL-mediated osimertinib-resistant NSCLC patients.

Keywords: brigatinib, osimertinib resistance, non-small cell lung cancer

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EP.12F.03 Trametinib in the Treatment of Patients with Metastatic Lung Adenocarcinoma Harboring NF1 Mutation

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Introduction: The neurofibromin 1 (NF1) protein regulates the downstream RAS/RAF/MEK/ERK pathway and functions as a tumor suppressor. Germline mutations in NF1 are linked to Neurofibromatosis type 1. Somatic pathogenic mutations in NF1 are found in various tumor types, including Non-Small-Cell Lung Cancer (NSCLC). Trametinib, a MEK inhibitor, has demonstrated activity in tumors with NF1 alteration in preclinical models, and clinical activity in low-grade glioma and plexiform neurofibromas in Neurofibromatosis type 1. However, trametinib had limited clinical efficacy in other tumor types with NF1 mutations in the NCI-Match trial. However, only one NSCLC patient included in the former trial was evaluable for response, with a good partial response. Thus, data for MEK inhibitors in NF1 mutant NSCLC remains limited and more data is needed.

Methods: We report here 4 cases of NSCLC patients with NF1 pathogenic mutations treated with trametinib. All patients underwent extensive molecular analysis through Next Generation Sequencing (400 genes panel), copy number variations analysis (Oncoscan Assay), and were deemed to have potential NF1-loss driven tumors after case discussion in multidisciplinary molecular tumorboard. All patients were treated with oral trametinib 2mg once daily, after failure of standard therapies.

Results: Patients characteristics are shown in Figure-1. Patients were between 62 and 80 years old, had relatively altered performance status (ECOG 1-2), and were all current or former smokers. Genomic alterations are shown in Figure-2. No patients exhibited co-mutations on the MAP-kinase pathways. Trametinib was administered for a maximum duration of nine weeks. The best response observed was a stable disease in one patient. All patients died within three months of treatment initiation. No side effects warranted treatment cessation.

Conclusions: In this small case series, NSCLC patients with NF1 alterations did not benefit from trametinib. These data do not support the use of trametinib for NF1 mutated NSCLC.

Keywords: Trametinib, NF1 mutation, Non-small-cell lung cancer

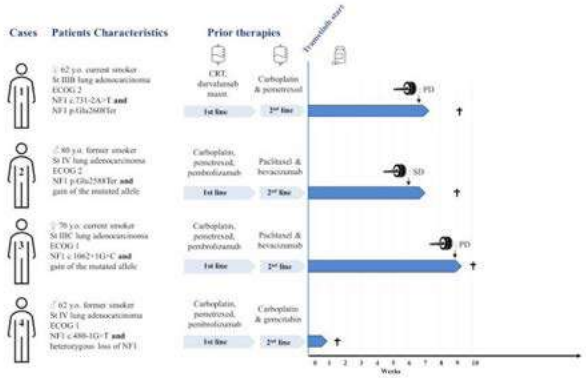

Figure 1. Patients characteristics, and treatment outcomes. St: stage ; y.o. = years old CRT: concurrent chemoradiotherapy ; PD: progressive disease per RECIST criteria ; SD: stable disease per RECIST criteria. † = death.

Figure 2. Genomic alterations.

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EP.12G.01 PFS as a Surrogate Endpoint for OS in Real-World Patients with ROS1+ advNSCLC in the United States

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Introduction: Emerging targeted therapies have broadened treatment options for patients with advanced non-small cell lung cancer (advNSCLC), including those with rearrangements of ROS1 (ROS1+). Overall survival (OS) is a gold standard in efficacy studies but requires an extended follow-up period and may be immature when progression-free survival (PFS) or objective response rate (ORR) data are available. Thus, intermediate endpoints can be attractive surrogates for OS and provide direct evidence of drug activity. This study aims to estimate the relationship between real-world PFS (rwPFS) and rwOS in patients with ROS1+ advNSCLC in a real-world setting.

Methods: The primary analyses included patients with ROS1+ advNSCLC (stage IIIB-IVB at initial diagnosis or early stage with subsequent recurrence or progression) who received at least 1 line of therapy for advNSCLC from the nationwide Flatiron Health electronic health record-derived deidentified database with a data cutoff of June 30, 2023. Kaplan-Meier (KM) estimators were used to characterize rwPFS and rwOS from first-line (1L) treatment start. Relationships between rwPFS and rwOS were evaluated using Spearman's rank correlation coefficient (ρ). In addition, Copula models were employed to estimate Kendall's tau as a supportive measure. Cox proportional hazard models were used in landmark analyses to evaluate rwOS between patients with or without progression at 12 months, adjusting for prognostic factors. Alternative landmark time points of 6 and 18 months were considered. Sensitivity analyses were performed in a similar population using Flatiron Health-Foundation Medicine NSCLC clinicogenomic database (CGDB), including patients who underwent comprehensive genomic profiling with detailed data on biomarker testing and treatment response.

Results: There were 383 patients with ROS1+ advNSCLC eligible for the primary analyses. From 2011 to 2023, 52% of the cohort received ROS1 tyrosine-kinase inhibitors (TKIs), while 14% received immunotherapy (monotherapy or in combination with chemotherapy) and 12% received chemotherapy as 1L. Median rwOS for the overall cohort was 30.6 months (95% CI: 24.0, 36.6). Median rwPFS was 7.5 months (95% CI: 6.5, 8.8). For patients receiving TKI, which is the current standard of care, median rwOS and rwPFS were 29.1 months (95% CI: 19.9, 44.5) and 8.6 months (95% CI: 6.7, 11.2), respectively. The Spearman rank correlation coefficient for the overall cohort was 0.68 (0.59, 0.76), and supplementary Kendall's tau was 0.56 (95% CI: 0.49, 0.63). In landmark analyses, disease progression at 12 months was significantly associated with higher risk of death (HR=2.1 [1.4, 3.2]); similar association was observed at 6 and 18 months. Results in the sensitivity analyses using CGDB were largely consistent with the primary results.

Conclusions: The median rwOS of the overall cohort and TKI subgroup falls within the mid-range of previous studies of similar populations, while the median rwPFS is on the lower end. Both landmark analyses and Spearman's correlation coefficient suggest that rwPFS can potentially be a good candidate surrogate endpoint for rwOS in a ROS1+ advNSCLC population, although future research is warranted to confirm the correlation on a trial/cohort level.

Keywords: ROS1 NSCLC, Surrogate endpoints, Real World Data

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EP.12G.02 Real-World Biomarker Testing and Treatment Patterns for Locally Advanced and Metastatic Non-Small Cell Lung Cancer in Canada

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Introduction: There is limited evidence outlining somatic genomic profiling uptake and treatment patterns for patients with locally advanced/metastatic non-small cell lung cancer (NSCLC) in routine clinical care. This study assessed real-world biomarker testing and treatment patterns for locally advanced/metastatic NSCLC in Canada.

Methods: This observational retrospective cohort review leveraged IQVIA's Oncology Patient Outcomes platform to obtain data regarding patients diagnosed with de novo locally advanced/metastatic NSCLC between Jan 2018 - Apr 2023. Eligible patients were not amenable to curative intent therapy and had exposure to at least 2 lines of therapy (2LOT). Patient demographics/characteristics, biomarker testing patterns, and treatment patterns were analysed descriptively.

Results: 205 patients with locally advanced (23%) or metastatic (77%) NSCLC were included. 51% were ≥65 years, 55% were male, 72% had active/prior tobacco exposure, 87% had ECOG of 0/1 at first line (1L) therapy, and 81% had adenocarcinoma. 31% (63/205) of all patients were tested for all known actionable genomic alterations (AGAs: EGFR, ALK, KRAS, BRAF, HER2, ROS-1, MET, RET, or NTRK), including 40% (53/134) and 14% (10/71) in academic vs. community settings, respectively. Among all patients tested, 57% (98/171) had an AGA present. 50% (49/98) of patients with AGAs received a targeted therapy in 1L; cumulatively, 69% (68/98) received a targeted therapy by 2LOT. 59% (63/107) of patients without AGAs received either pembrolizumab/atezolizumab monotherapy (35%, 37/107) or immune checkpoint inhibitor (ICI) + chemotherapy (24%, 26/107) in 1L. Additional treatment patterns are shown in Table 1.

Conclusions: In Canada, most patients do not receive complete testing for AGAs, highlighting the need for improved access to biomarker testing. Only 69% of patients with an AGA received a targeted therapy by their 2LOT and 59% of patients without AGAs received ICI +/- chemotherapy in 1L, indicating an unmet need for increased use of guideline recommended systemic therapies.

Keywords: Locally Advanced and Metastatic NSCLC, Biomarker, Treatment Patterns

Table 1. Treatments received in 1L and 2L by AGA status

	1L AGA (n=98)	1L No AGA (n=107)	2L AGA (n=98)*	2L No AGA (n=107)*
ICI	19% (n=19)	35% (n=37)	8% (n=8)	27% (n=29)
ICI + chemotherapy	17% (n=17)	24% (n=26)	5% (n=5)	13% (n=14)
Targeted therapy	50% (n=49)	0% (n=0)	45% (n=44)**	0% (n=0)
Chemotherapy only	13% (n=13)	41% (n=44)	40% (n=39)	56% (n=60)

Notes:
*In 2L, 2 patients with AGA and 4 patients without AGA received "Other"
**Includes 25 patients who received targeted therapy in 1L and 2 patients who received chemotherapy in addition to targeted therapy
*** Platinum doublets were the most common chemotherapy in 1L AGA/No AGA and 2L AGA, while docetaxel was the most common for 2L No AGA

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EP.12H.01 A Phase 2 Study to Assess BDTX-1535, An Oral EGFR Inhibitor, in Patients with Non-Small Cell Lung Cancer

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Introduction: The epidermal growth factor receptor (EGFR) is one of the most commonly mutated oncogenes in non-small cell lung cancer (NSCLC). In addition to the classical EGFR mutations Ex19del and L858R, there are over 100 non-classical oncogenic EGFR driver mutations which comprise 20-30% of all EGFR mutated NSCLC. Current generation EGFR small molecule inhibitors including osimertinib are poorly active against this broad spectrum of mutations and are limited by the emergence of on-target EGFR resistance mutations including C797S and low brain penetration. There is a major unmet medical need for a well-tolerated next generation EGFR inhibitor to address the full spectrum of classical and non-classical EGFR oncogenic driver mutations. BDTX-1535 is a fourth-generation oral, brain-penetrant small molecule inhibitor of oncogenic EGFR classical driver mutations, non-classical driver mutations, and the acquired resistance C797S mutation. BDTX-1535 has a MasterKey profile to target the full spectrum of mutations, and in preclinical studies potently inhibits more than 50 oncogenic EGFR mutations. The Phase 1 portion of the BDTX-1535-101 study established 100 mg QD and 200 mg QD doses as preliminary recommended Phase 2 doses based on a favorable safety and tolerability profile and EGFR target PK coverage. Durable radiographic responses by RECIST were demonstrated across all groups of mutations accompanied by mutant EGFR variant allele frequency and plasma ctDNA clearance. These results led to the expansion into the ongoing Phase 2 portion of the study.

Methods: The objective of the Phase 2 portion of the BDTX-1535-101 (NCT05256290) open-label, multicenter, multicohort study is to assess antitumor activity, safety, tolerability, PK, and optimal dose of BDTX-1535 in locally advanced or metastatic NSCLC with or without CNS disease. Patients with NSCLC are being enrolled into one of 3 cohorts based on next generation sequencing confirmed EGFR alterations at the time of enrollment; Cohort 1: patients with a non-classical driver EGFR mutation following up to 2 lines of therapy with only one prior EGFR TKI; Cohort 2: patients with the acquired resistance C797S mutation following up to 2 lines of therapy, including only one third-generation EGFR TKI; and Cohort 3: treatment-naïve (first-line) patients with a non-classical driver EGFR mutation. NSCLC patients may enroll with or without CNS metastases and must not be known to express excluded resistance mutations such as EGFR T790M or MET alterations. Cohorts 1 and 2 were initiated in September 2023, and Cohort 3 was initiated in March 2024; enrollment is ongoing. For additional information, please contact blackdiamondtx@careboxhealth.com.

Keywords: BDTX-1535, EGFR inhibitor, Non-small cell lung cancer

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EP.12H.02 Amivantamab, An EGFR-MET Bispecific Antibody, with Cetrelimab, An Anti-PD-1 Antibody, In Advanced NSCLC: Phase 1/2 Polydamas

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Introduction: Amivantamab, an EGFR-MET bispecific antibody with immune cell-directing activity, is effective against EGFR-mutated advanced non-small cell lung cancer (NSCLC) as monotherapy or in a combination. Cetrelimab is an anti-PD-1 monoclonal antibody with clinical activity in previously treated NSCLC (Felip et al. Cancer Chemother Pharmacol 2022;89(4):499-514). Simultaneous targeting of the innate and adaptive immune systems with amivantamab and cetrelimab may improve antitumor activity versus either agent alone. The PolyDamas study (NCT05908734) aims to identify the recommended phase 2 combination dose (RP2CD) and evaluate the antitumor effect of amivantamab-cetrelimab in patients with advanced NSCLC.

Methods: This open-label, multicenter, interventional study will have a combination dose selection phase, followed by an expansion phase. The primary endpoints include safety (phase 1 dose selection) and objective response rate by investigator using RECIST 1.1 criteria (phase 2 dose expansion). For dose selection, 20 patients with advanced NSCLC, with or without known driver mutations, who have progressed on or after standard of care anti-cancer therapy, will be enrolled. Dosing will be in 28-day cycles, starting with a reduced amivantamab dose (700 mg IV; 1050 mg if ≥80 kg) given once weekly (the initial dose is given as a split infusion over the first 2 days) for the first 4 weeks (Cycle 1), then every 2 weeks (Q2W) thereafter (Cycle 2 onwards). Cetrelimab will be dosed intravenously at 240 mg Q2W, with the first dose given on Day 2 of Cycle 1. Dose escalation/de-escalation will be based on the observation of dose-limiting toxicities. The RP2CD will be selected through a Bayesian optimal interval design with a 3+3 design run in.

The phase 2 expansion cohorts will enroll 30 patients each after identification of the RP2CD. Cohort A will enroll patients with advanced NSCLC harboring an EGFR exon 19 deletion or L858R mutation, who have progressed on a 3rd-generation tyrosine kinase inhibitor and platinum-based chemotherapy. Cohort B will enroll patients with treatment-naïve, wild-type advanced NSCLC (no known driver mutations) and a PD-L1 tumor proportion score ≥50%. The phase 2 secondary endpoints include duration of response, disease control rate, progression-free survival, and overall survival.

This study is exploratory in nature and hypothesis-generating; no formal statistical hypotheses exist for either phase. In both phases, patients will continue study treatment until disease progression, unacceptable toxicity, or until another criterion for treatment discontinuation is met. This study is currently enrolling, with an enrollment goal of 80 patients total.

Keywords: Amivantamab, cetrelimab, NSCLC

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EP.12H.03 Study Protocol of the Korean EGFR Registry: A Multicenter Prospective and Retrospective Cohort Study in NSCLC Patients with EGFR Mutation

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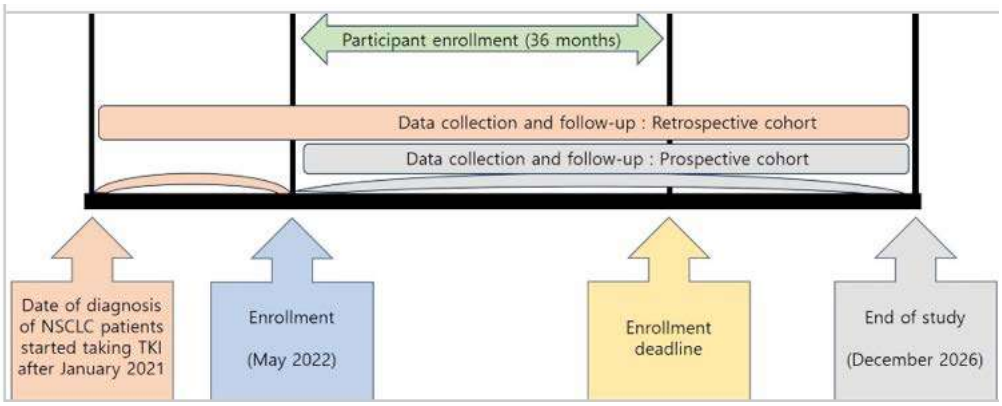
Introduction: The provision of treatment for epidermal growth factor receptor (EGFR)-mutated non-small cell lung cancer (NSCLC) patients has increased in Korea. However, multicenter studies on the clinicopathologic dataset and treatment outcomes, using large-scaled dataset, have not been conducted. The current study is a prospective and retrospective multicenter observational cohort study that registers all stages of EGFR-mutated NSCLC patients.

Methods: The Korean EGFR Registry, a prospective multicenter observational cohort study, was designed to enroll 2,000 patients with all stages of EGFR-mutated NSCLC from forty university hospitals across Korea. This study, encompassing both retrospective and prospective cohorts, aims to analyze clinical characteristics, treatment modalities, and outcomes in these patients. Data collection includes patient demographics, smoking history, quality of life assessments, pathologic data, and treatment outcomes, with follow-up until December 2026. The primary endpoint is disease-free-survival in patients who have undergone definitive therapy or progression-free-survival patients who have undergone palliative therapy according to stages of EGFR-mutated NSCLC. The study will explore the diagnostic methods for EGFR mutations, clinical outcomes based on treatment modalities, and metastatic patterns in NSCLC patients with EGFR mutations. Moreover, it will investigate various aspects, including the safety and efficacy of a new third-generation EGFR tyrosine kinase inhibitors (TKI), lazertinib, approved for both first- and second-line treatments.



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EP.12H.04 Phase II Study of Brigatinib for ALK-Positive Advanced Non-Small Cell Lung Cancer with Brain Metastases: BRAVES Trial (LOGIK2201)

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Introduction: Patients with advanced ALK positive non-small cell lung cancer (NSCLC) are highly responsive to ALK-tyrosine kinase inhibitors. However, it has been reported that approximately 30-35% of ALK positive NSCLC patients have brain metastases at diagnosis, which are associated with a poor prognosis. The efficacy of brigatinib for CNS metastases has been reported in a subgroup analysis of a phase III trial (ALTA-1L), but sample size was small and the patients with symptomatic metastases were excluded. Thus, we planned this phase II trial to analyze the genuine efficacy of brigatinib for CNS metastases of ALK positive NSCLC.

Methods: This is a multicenter single-arm phase II trial. Eligible patients have ALK-positive NSCLC with at least one brain metastasis ≥5 mm in size that has not been previously treated. Symptomatic brain metastases are also eligible, however brain metastases that require urgent radiation or emergency surgery are excluded. Patients receive brigatinib (180 mg once daily with a 7-day lead-in period at 90 mg). The primary endpoint is intracranial response rate as determined by modified Response Evaluation Criteria in Solid Tumors (RECIST) for brain metastases of ≥5 mm as target lesions. Secondary endpoints are intracranial progression free survival, extracranial response rate, extracranial progression free survival, systemic response rate, systemic progression free survival, overall survival, and safety. The expected intracranial response rate was assumed to be 70%, and we set a threshold value for the intracranial response rate of 45%. Given this assumption, the study was designed to have a power of 80% with 2-year accrual and 1-year follow-up periods, resulting in a requirement for 19 patients. Allowing for ineligibility of patients for analysis, we planed on enrolling 22 patients. Study enrollment began in June 2023 and will continue for two years among 25 sites in Japan. Four patients were enrolled at the time of submission. Clinical trial information: jRCTs071230025

Keywords: ALK, Brigatinib, brain metastases

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EP.12H.05 Phase II Study on Platinum-Pemetrexed and Lorlatinib Combination in ALK-Positive NSCLC Extracranially Progressing on Lorlatinib

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Introduction: Lorlatinib, a potent, brain-penetrant third-generation Anaplastic Lymphoma Kinase (ALK) inhibitor may be used as first or further--line treatment in advanced ALK-positive Non Small Cell Lung Cancer (NSCLC) patients. Currently, subsequent treatment to overcome lorlatinib resistance remains an unmet clinical need. Platinum/pemetrexed-combined chemotherapy (PT/pem-based-CT) is still a valid option, although with modest efficacy and poor activity in the brain, with a median Progression Free Survival (PFS) of 3.2 months reported in the literature (Lin JJ, et al.. J Thorac Oncol. 2020;15(2):258-265). Association between chemotherapy and ALK inhibitors is feasible and with interesting activity, as reported from others' and from our experience on 6 patients, in progression extra-cranially on lorlatinib and treated off-label with lorlatinib and PT/pem-based-CT (Lin JJ, et al.. J Thorac Oncol. 2020;15(2):258-265, De Carlo E et al. J Thorac Oncol., 2021 May;16(5): e31-e32).

Methods: : We conceived a multicenter, Italian, single-arm, no profit, phase II interventional study to evaluate the activity and safety of PT/pem-based-CT plus Lorlatinib in ALK-positive NSCLC with exclusively extra-cranial disease progression on Lorlatinib. Approximately 45 patients will be enrolled. Patients must be exclusively extracranially in progression on Lorlatinib; Lorlatinib may be in first- or further-line, without limitations regarding previously received therapies. Brain metastases are allowed, but they have to be stable or in response on Lorlatinib.PT/pem-based-CT plus Lorlatinib will be administered for an induction phase of four cycles. Subsequently, patients with response or stability of disease at radiological assessment will start the maintenance phase with pemetrexed-Lorlatinib in 21-day cycles until progression, unacceptable toxicity, death, or withdrawal of consent. Tumor imaging with computed tomography (chest, abdomen, and pelvis) (CT) and brain magnetic resonance (MR) will be performed at baseline, after the induction phase and then every 9 weeks (+/- 1 week) for the first 12 months and then every 12 weeks (+/- 1 week) thereafter during the maintenance phase. A liquid biopsy for DNA isolation will be performed at baseline, at disease progression, and during the treatment at every radiologic assessment. Adverse events monitoring, according to the guidelines outlined in the NCI CTCAE, version 5.0, will be recorded throughout the study. Patients reported outcomes (PROs) measures, including global quality of life (QoL), functioning domains and symptoms, will be assessed by the EORTC Quality of Life Questionnaire Core 30 (QLQ-C30) and the 13-item Lung Cancer (QLQ-LC13) module. Primary endpoint is PFS. Secondary endpoints are: intracranial PFS, Overall Survival (OS), safety, PROs and QoL. Exploratory endpoint is to explore genetic alterations of resistance detected in circulating tumor DNA at baseline, during treatment and at disease progression.

Results: The protocol has been approved through the Clinical Trials Information System/EMA platform (CTIS) - CTIS ID: 9647 - by Italian Agency AIFA and Ethical Commettee on 23 February 2024 and has started enrollment in March 2024. EUDRACT 2023-506714-43-00.

Conclusions: Updates of the trial will be provided at the Congress.

Keywords: ALK+ NSCLC, lorlatinib, chemotherapy and lorlatinib combination

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EP.12H.06 A Patient-Centric, Phase II Trial of First-Line Lorlatinib&alk TKIs in China Advanced ALK+ Non-Small Cell Lung Cancer

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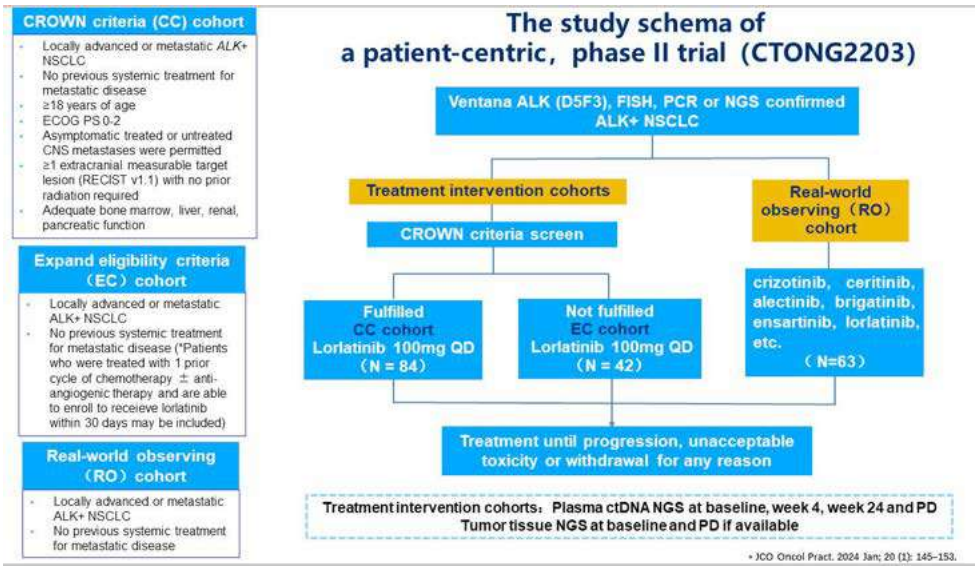
Introduction: Lorlatinib is a potent third-generation ALK tyrosine kinase inhibitor (TKI). CROWN study demonstrated remarkable efficacy data and manageable AEs of first-line lorlatinib treatment for advanced NSCLC with ALK fusion. However, only 10 ALK+ NSCLC patients were randomized to the lorlatinib group in China mainland. There is a vast vacancy of efficacy and safety regarding first-line lorlatinib treatment in China advanced ALK+ NSCLC. Additionally, understanding of the benefit-risk profile of lorlatinib in a broader population and real-world data of diversity of ALK-TKIs are limited. Here, we adopted a patient-centric trial (PCT) design to generate more generalizable data to better inform clinical decision-making. We investigate the efficacy, safety profile of first-line lorlatinib in Chinese patients with restrictive eligibility criteria and broadening eligibility criteria. And we concomitantly set up a prospective real-world observing (RO) cohort to observe the clinical outcomes of these patients treated with different ALK-TKI who received physician's therapy of choice.

Methods: This is a three cohorts, open-label, multi-center, phase II study in China, designed to prospectively enroll 189 advanced ALK+ NSCLC patients, which was divided into treatment intervention cohorts and RO cohort. The treatment intervention cohorts include 84 subjects fulfilled CROWN criteria as "CROWN criteria (CC) cohort", another 42 subjects ineligible for CROWN criteria as "Expand Eligibility Criteria (EC) cohort". The CC cohort and the EC Subjects will receive continuous daily PO dosing of lorlatinib 100mg QD, from the date of first dosing until disease progression, unacceptable toxicity, or withdrawal for any reason, or death, whichever occurs first. The primary endpoints are progression-free survival (PFS) of CC cohort per investigator, and resistance mechanism of first-line lorlatinib. Secondary endpoints are 1/2/3-year PFS, cumulative rate of central nervous system (CNS) progression, intracranial-time to progression (IC-TTP), objective response rate (ORR) and intracranial ORR (IC-ORR), overall survival (OS), safety and PRO. Exploratory endpoints include evaluation of candidate biomarkers of sensitivity or resistance to lorlatinib, dynamic ctDNA change during treatment, and effective treatment after lorlatinib resistance. The RO cohort is designed to serve as comparison cohort, which will enroll 63 treatment-naive subjects who may receive crizotinib, ceritinib, alectinib, brigatinib, ensartinib, lorlatinib, etc. Real-world efficacy and safety data of ALK TKIs were collected in the same cross-section. The primary endpoint is real-world progression-free survival (rwPFS) of ALK TKIs in the first-line treatment of advanced NSCLC patients with ALK fusion.

Keywords: Patient-centric, Lorlatinib, ALK+ NSCLC



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EP.12H.07 A Phase I Clinical Trial of Carfilzomib in Combination with Sotorasib in Patients with KRASG12C Mutated NSCLC

J. Malhotra, X. Li, J. Palmer, T.W. Synold, A. Mohanty, S. Singhal, P. Kulkarni, R. Salgia, City of Hope National Medical Center, Duarte/CA/USA

Introduction: The clinical development of covalent inhibitors of KRASG12C such as sotorasib and adagrasib is an important milestone for the treatment of advanced or metastatic non-small cell lung cancer (NSCLC). While these agents have promising clinical activity, many patients experience disease progression by the 1-year mark. It is therefore imperative to identify and overcome mechanisms of resistance to these agents. Integrin Subunit Beta 4 (ITGB4) and paxillin (PXN) in the focal adhesion complex are highly expressed in KRAS-mutated lung adenocarcinoma and their interaction plays an important role in mediating therapeutic resistance (Mohanty, iScience, 2020). By virtually screening a library of FDA-approved compounds that bind to the N-terminal region of paxillin, carfilzomib was identified to be the most effective (IC50 = 193.4 nM) (Nam, Cancer Res, 2020). We hypothesize that resistance KRAS G12C inhibitors can be through a non-genetic mechanism via ITGB4/PXN pathway that can be targeted by disrupting this pathway using carfilzomib. In preclinical experiments using mouse models, carfilzomib and sotorasib exert synergistic activity through down-regulating ITGB4 (Mohanty, Sci Adv, 2023), supporting further the development of this combination in KRASG12C mutated NSCLC. We have initiated a Phase I trial in which the combination of sotorasib and carfilzomib will be investigated for the treatment of KRASG12C inhibitor-resistant NSCLC.

Methods: This is a Phase I dose-finding study with a traditional 3+3 dose escalation. Patients with KRAS G12C mutated NSCLC who have progression on a prior KRAS inhibitor will be treated with the combination of sotorasib and carfilzomib to determine whether the combination is safe and tolerable. Participants will receive protocol therapy until disease progression or intolerable toxicity. Dose-limiting toxicities (DLT) and treatment-related toxicities will be defined by the NCI Common Terminology Criteria for Adverse Events (NCI CTCAE) v5. The primary endpoint is to determine the maximum tolerated dose (MTD) and the recommended Phase II dose (RP2D) of the combination and up to 18 patients are estimated to be enrolled. The secondary objective is to measure efficacy endpoints such as objective response rate (ORR) and progression-free survival (PFS) using RECIST1.1. The dose of sotorasib will be fixed at 240 mg oral daily at all dose levels. Carfilzomib will be administered intravenously on two consecutive days, each week for three weeks (Days 1, 2, 8, 9, 15, and 16), followed by a 12-day rest period (Days 17 to 28). Carfilzomib dose will be determined as per the dose escalation schema, with each dose level specifying a separate loading dose (Cycle 1, Days 1-2) and a dose for subsequent infusions (different than the loading dose). Each 28 days is considered one treatment cycle. Correlative studies include carfilzomib and sotorasib pharmacokinetics, along with serial tumor biopsies, serum proteomic analyses, and circulating tumor DNA (ctDNA) assessments to explore biomarkers of response and resistance. Clinical trial information: NCT06249282.

Keywords: NSCLC, KRASG12C, Carfilzomib

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EP.12H.08 SOHO-02: Phase III Trial of BAY 2927088 In Patients with Locally Advanced or Metastatic NSCLC with HER2-Activating Mutations

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Introduction: Activating human epidermal growth factor receptor 2 (HER2) mutations account for approximately 2-4% of non-small cell lung cancer (NSCLC) but represent a major area of unmet medical need as no first-line HER2-targeted therapies are currently approved for patients with locally advanced or metastatic NSCLC harboring HER2-activating mutations. BAY 2927088 is an oral, reversible tyrosine kinase inhibitor that targets HER2 and mutant epidermal growth factor receptor and has demonstrated anti-tumor activity and a manageable safety profile in previously treated patients with NSCLC and HER2-activating mutations in the Phase I/II SOHO-01 trial (LBA8598 accepted at 2024 ASCO Annual Meeting). Here we introduce the SOHO-02 trial evaluating the efficacy and safety of BAY 2927088 as first-line therapy in patients with locally advanced or metastatic NSCLC with HER2-activating mutations.

Methods: SOHO-2 is an ongoing Phase III, open-label, randomized multicenter trial of BAY 2927088 in patients with locally advanced or metastatic NSCLC with HER2-activating mutations (Figure). Eligibility criteria include patients aged ≥18 years with documented histologically or cytologically confirmed locally advanced or metastatic non-squamous NSCLC; documented activating mutation in the tyrosine kinase domain of HER2 in tumor tissue; measurable disease per RECIST v1.1; ECOG PS of 0 or 1; and adequate bone marrow, kidney, liver, coagulation, and cardiac function. Overall, 278 eligible patients will be randomized to oral BAY 2927088 (20 mg twice daily) or standard of care (SoC; pembrolizumab in combination with platinum-based chemotherapy [cisplatin or carboplatin] and pemetrexed) administered in 21-day cycles. The primary objective is to evaluate the effect of BAY 2927088 vs. SoC on progression-free survival per RECIST v1.1 by blinded independent central review (BICR). Key secondary objectives are to evaluate the efficacy of BAY 2927088 vs. SoC on overall survival, overall response rate, and duration of response per RECIST v1.1 by BICR and to assess the safety and tolerability of BAY 2927088 compared with SoC. Patients' health-related quality of life and symptomatic side effects will be measured using the EORTC QLQ-C30, NSCLC-SAQ, and EQ-5D-5L, including VAS. Enrollment is ongoing.

Keywords: NSCLC, Phase III, HER2

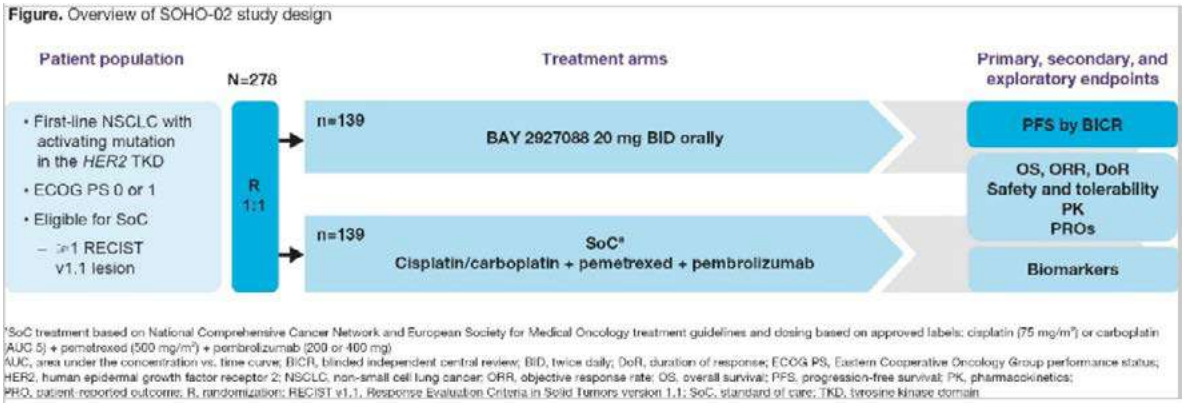

Figure. Overview of SOHO-02 study design

*SoC treatment based on National Comprehensive Cancer Network and European Society for Medical Oncology treatment guidelines and dosing based on approved labels: cisplatin (75 mg/m²) or carboplatin (AUC 5) + pemetrexed (500 mg/m²) + pembrolizumab (200 or 400 mg)
AUC, area under the concentration vs. time curve; BICR, blinded independent central review; BID, twice daily; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; HER2, human epidermal growth factor receptor 2; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics; PRO, patient-reported outcome; R, randomization; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SoC, standard of care; TKD, tyrosine kinase domain

EP.12H METASTATIC NON-SMALL CELL LUNG CANCER - TARGETED THERAPY - CLINICAL TRIALS IN PROGRESS
SATURDAY, SEPTEMBER 7, 2024 - 11:58 - 11:59

EP.12H.09 Phase 1b/2a Study of ATR Inhibitor Tuvusertib + Anti-PD-1 Cemiplimab in Patients with Advanced Non-Squamous NSCLC

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Introduction: Immune checkpoint inhibitors (ICI) have improved outcomes in non-small cell lung cancer (NSCLC), but primary or acquired resistance limits treatment options for patients with disease progression on anti-PD-(L)1 and platinum-based therapies. Growing evidence indicates that ataxia telangiectasia and Rad3-related protein kinase inhibition (ATRi) modulates antitumor immunity, and the ATRi + ICI combination is active in patients with ICI-resistant tumours. ATRi + ICI may have the potential to overcome ICI resistance and induce antitumor immune responses in patients with advanced NSCLC, particularly in tumours harbouring ATRi-sensitizing mutations.

This abstract was previously presented at the European Lung Cancer Congress (ELCC) 2024 held in Prague, Czech Republic (20-23 March 2024)

Methods: This open-label, multicentre, Phase 1b/2a study (NCT05882734) evaluates the efficacy, safety, tolerability, and pharmacokinetics of tuvusertib + cemiplimab. Eligible patients have non-squamous NSCLC that has progressed on prior anti-PD-(L)1 and platinum-based therapies, with a response of stable disease or better to prior anti PD-(L)1-therapy. Patients with tumours harbouring actionable EGFR or ALK genomic alterations are excluded. In the randomised Phase 1b, two dosing regimens, tuvusertib 100 mg once-daily (QD) + cemiplimab 350 mg every three weeks (Q3W) (n=30) or tuvusertib 180 mg QD 2 weeks on/1 week off + cemiplimab 350 mg Q3W (n=30), are being evaluated. Based on a totality of evidence approach, the most favourable regimen will be selected for investigation in Phase 2a, in which patients will be treated in 3 separate strata based on genetic alterations detected in circulating tumor DNA: stratum A (n=40), STK11 or KEAP1; stratum B (n=40), ATM or ARID1A or SMARCA4 or PBRM1; stratum C (n=40), any other/no alterations. Tumour genetic characteristics will be assessed by a central liquid biopsy assay. Primary endpoints are investigator-assessed objective response (OR; RECIST v1.1), occurrence of adverse events (AE), and treatment-related AEs in Phase 1b, and OR in Phase 2a. Secondary endpoints in both phases include duration of response, progression-free survival, and overall survival. The study is open for enrollment in centres across the USA, Belgium, Italy, Spain, France, Japan and Korea.

Keywords: non-squamous non-small cell lung cancer, DDR inhibitor, immune checkpoint inhibitor resistance

EP.13A SMALL CELL LUNG CANCER AND NEUROENDOCRINE TUMORS - CLINICAL TRIALS
SATURDAY, SEPTEMBER 7, 2024 - 11:58 - 11:59

EP.13A.01 Preliminary Efficacy and Safety of Adebrelimab Plus Famitinib as Later-line Treatment for Extensive-Stage Small Cell Lung Cancer: A Phase 2 Trial

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Introduction: The advent of immune checkpoint inhibitors (ICIs) has completely changed the treatment landscape of extensive-stage small cell lung cancer (ES-SCLC). However, the majority of patients (pts) eventually progress during immunotherapy. It has been reported that the addition of antiangiogenic agents potentially enhanced the antitumor activity of ICIs and expanded the spectrum of pts who responded to them. Famitinib is a novel and promising multitarget receptor tyrosine kinase inhibitor (TKI) against stem-cell factor receptor, vascular endothelial growth factor (VEGF) receptor 2/3 and platelet-derived growth factor receptor β (PDGFR β). This phase II trial aimed to evaluate the efficacy and safety of adebrelimab (anti-PD-L1 antibody) plus famitinib for pretreated ES-SCLC.

Methods: Eligibility criteria included aged 18-80 years, histologically or cytologically confirmed ES-SCLC, ECOG performance status 0-1, failed or intolerant to second-line systemic chemotherapy. Pts received adebrelimab (20 mg/kg, administered intravenously every 3 weeks) and famitinib (20 mg, administered orally once daily) until disease progression or intolerable toxicity. The primary endpoint was objective response rate (ORR). Key secondary endpoints included progression-free survival (PFS), overall survival (OS), disease control rate (DCR), duration of response (DoR) and safety. A Simon two-stage design was applied. If there were more than 1 patient achieved response within the first 13 pts, the cohort would expand to 34 pts.

Results: As of December 2023, a total of 13 pts were enrolled and received at least one dose of adebrelimab and famitinib. Of these pts, the median age was 64 (range 48-70), 84.6% were male and 84.6% were current or former smokers. The number of prior lines of cancer therapy ranged from 1 to 2 (median 1). 3 pts achieved confirmed partial response (PR), 6 pts achieved stable disease (SD) and 4 pts had progressive disease (PD) as best response. The ORR was 23.1% (3/13) and DCR was 69.2% (9/13). The median PFS was 4.0 months (95% CI, 2.0 to 6.0). Treatment-related adverse events (TRAEs) occurred in 11 (84.6%) pts. The most common TRAEs were white blood cell count decreased and neutrophil count decreased.

Conclusions: Adebrelimab plus famitinib demonstrated promising antitumor activity and acceptable toxicity in relapsed ES-SCLC. The results warranted further validation.

Keywords: ES-SCLC, Immunotherapy, Antiangiogenic Therapy

EP.13A SMALL CELL LUNG CANCER AND NEUROENDOCRINE TUMORS - CLINICAL TRIALS
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EP.13A.02 Adebrelimab Combined with Famitinib and Chemotherapy as First-Line Therapy for ES-SCLC: A Phase II, Single-Arm Exploratory Research

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Introduction: Small cell lung cancer is known as a type of highly aggressive neuroendocrine malignancy, in consequence the majority of small cell lung cancer patients are diagnosed in extensive-stage accordingly due to high growth fraction and early metastasis. It can be concluded in recent research that the adebrelimab plus carboplatin and etoposide have demonstrated promising anti-tumour activity in first-line treatment for extensive-stage small-cell lung cancer (ES-SCLC) in CAPSTONE-1 trial, while famitinib is a selective multiple-target tyrosine kinase inhibitor that exhibits both anti-angiogenesis and anti-proliferative effects by targeting VEGFR-2, PDGFR, c-kit, FGFR where the anti-angiogenic agents have been reported to facilitate immune infiltration. Whereupon, this study aims to explore the efficacy and safety of adebrelimab combined with famitinib and chemotherapy as the first-line treatment of ES-SCLC.

Methods: In this multicenter, open-label, phase II trial, 40 patients with ES-SCLC diagnosed pathologically or cytologically according to the Veterans Administration Lung Study Group pathology and without receiving prior systemetic therapy are anticipated to be enrolled. Patients must be 18-80 years old, have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, an expected life expectancy of at least 3 months, and adequate organ function. Patients will be excluded if they have risk of bleeding, uncontrolled hypertension, active serious infections, or uncontrolled symptomatic brain metastases. Due to a lack of data concerning the combination of famitinib, a safety run-in phase with 6 patients is performed before the phase II. If ⩽1 of the first 6 patients experience dose-limiting toxicity, the phase II trial will be performed. Patients will be dosed adebrelimab (1200 mg, iv, q3w) in combination with etoposide/platinum drugs (cisplatin 75 mg/m2 or carboplatin AUC 5, iv, q3w, 4 cycles). The primary endpoint is 6-month progress-free survival (6-month PFS) rate, and the secondary endpoints are objective response rate, disease control rate, 12-month PFS, PFS, overall survival, safety and quality of life. The study is actively recruiting.

Keywords: ES-SCLC, Adebrelimab, Famitinib

EP.13A SMALL CELL LUNG CANCER AND NEUROENDOCRINE TUMORS - CLINICAL TRIALS
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EP.13A.03 A Phase II Study of Vobramitamab Duocarmazine in Patients with Relapsed or Refractory Extensive-Stage Small Cell Lung Cancer

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Introduction: Extensive-stage small cell lung cancer (ES-SCLC) is a highly aggressive form of lung cancer, known for its frequent recurrence, even after initial response to therapy. In patients (pts) with relapsed or refractory (R/R) ES-SCLC, outcomes are poor with limited treatment options. There remains a significant need for novel therapeutic approaches for ES-SCLC. B7-H3, an immune checkpoint molecule, plays an important role in the immune evasion of cancer cells, as well as in tumor growth and metastasis. It is overexpressed in a wide range of cancer types, including SCLC, where its overexpression correlates with a poor prognosis. Its expression is limited in normal tissues, making it an ideal target for novel antibody-drug conjugates (ADCs). Vobramitamab duocarmazine (vobra duo) is an ADC comprised of an antibody targeting B7-H3 linked to duocarmazine, a duocarmycin-based payload which causes DNA alkylation. This phase II trial seeks to evaluate the efficacy of vobra duo in pts with R/R ES-SCLC.

Methods: This is an open-label, phase II, multi-center, single-arm study evaluating the efficacy and safety of vobra duo in pts with R/R ES-SCLC. Pts with ES-SCLC will be considered eligible who have experienced progression during or following treatment with platinum-based chemotherapy. Other eligibility criteria include an ECOG performance status of 0-2, measurable disease, and adequate hematologic and end-organ function. Pts with EGFR-mutant NSCLC that has transformed to SCLC will be eligible. Pts will receive vobra duo 2.7 mg/kg every 28 days continuously until disease progression or unacceptable toxicity. The primary endpoint is overall response rate (ORR) according to RECIST v1.1, with secondary endpoints including safety (adverse events per CTCAE v5.0), duration of response (DOR), progression-free survival (PFS), and overall survival (OS). A total of 17 pts will be enrolled. The null hypothesis that the true response rate is 5% will be tested against a one-sided alternative. A Simon's optimal two-stage design will be used such that 9 pts will be enrolled initially, and if at least one response is identified, the trial will proceed to the second stage with enrollment of an additional 8 pts. This design yields a type I error rate of 4.7% and power of 81.2%, when the true response rate is 25%. Exploratory analyses will be conducted to investigate the correlation between B7-H3 expression in blood (specifically within extracellular vesicles) and tumor tissue and their impact on treatment outcomes. Clinical trial information: NCT06227546.

Keywords: ES-SCLC, B7-H3, Antibody-drug conjugates

EP.13A SMALL CELL LUNG CANCER AND NEUROENDOCRINE TUMORS - CLINICAL TRIALS
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EP.13A.04 A Study of Surufatinib Combined with Low Dose Topotecan in Second or Third-Line Multiple Distant Organ Metastatic ES-SCLC

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Introduction: The addition of immune checkpoint inhibitors has expanded the therapeutic options for the first-line treatment of extensive-stage small cell lung cancer (ES-SCLC). However, there remains a significant lack of effective second- or third-line treatment options following disease progression. Surufatinib, a potent small-molecule tyrosine kinase inhibitor (TKI) with selective targeting of VEGF receptors (VEGFR)1,2, and 3, FGFR 1, and CSF-1R, has shown promise in addressing this unmet need. Additionally, topotecan hydrochloride capsules are approved for use in the second-line treatment of SCLC. This study aims to evaluate the efficacy and safety of surufatinib combined with topotecan capsules in the second- or third-line treatment of ES-SCLC.

Methods: This study is a single-arm, prospective, exploratory trial (ChiCTR2200061709) in which patients with ES-SCLC who had previously failed one or two lines of treatment were enrolled following screening and meeting the inclusion and exclusion criteria. Patients were treated with surufatinib (250mg, orally, once daily, every 3 weeks) combined with topotecan (1.4mg/m2, orally, on days1-5, every 3 weeks) until disease progression, unacceptable toxicity, or death. The primary endpoint was progression-free survival (PFS), while secondary endpoints included objective response rate (ORR), disease control rate (DCR), overall survival (OS), and safety.

Results: From May 2022 to March 2024, a total of 23 subjects were enrolled, with 21 patients being evaluable. All of them had extensive-stage small-cell lung cancer. There were 20 males and 14 patients with a history of smoking. The mean age was 65 years. ECOG scores were as follows: 22 (95.7%) patients had an ECOG score of 1 and 1(4.3%) patient had an ECOG score of 0. In terms of previous first-line regimens,15(65.2%) patients received EP/EC and 8(34.8%) received PD-1/L1 + EP/EC,9(39.1%) of the patients had received radiotherapy.21(91.3%) patients were treated as second-line treatment and 2(8.7%) as third-line treatment. All patients had distant metastasis at the time of enrollment, indicating a poor prognosis among these individuals. Among them, 12 cases (56.5%) had 3 or more distant organs metastasis;brain metastases were present in 5(21.7%) patients while liver metastases were observed in 11(47.8%) patients. As of March 25, 2024, the median follow-up was 10.6 months. Among patients with at least one post-baseline tumor assessment (evaluable pts, n=21), the median PFS was 4.2 months (95%CI 2.7-5.7). The ORR was 14.2%, and the DCR was 76.2%, including 3 cases of PR and 13 cases of SD. The median OS was 7.4 months (95%CI 5.2, 9.6). The overall safety of the study was manageable, with no unexpected adverse events reported. Most adverse events were grade 1-2, and there were 4 cases (18.1%) that were grade ≥3, including neutropenia, leukopenia,hrombocytopenia and hypertension; none of these treatment-related adverse events led to death.

Conclusions: Conclusions: The combination of surufatinib and low dose topotecan capsules has demonstrated significant clinical efficacy and a manageable safety profile when used as a second- or third-line treatment for patients with multiple distant organ metastases ES-SCLC.

Keywords: Surufatinib, Topotecan, SCLC

EP.13A SMALL CELL LUNG CANCER AND NEUROENDOCRINE TUMORS - CLINICAL TRIALS
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EP.13A.05 Prognostic Laboratory Parameters in Imfirst: Atezolizumab Plus Chemotherapy in Extensive-Stage Small-Cell Lung Cancer

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Introduction: Small cell lung cancer (SCLC) is characterized by rapid progression and recurrence. Prognostic assessment is challenging due to the lack of standardized prognostic markers beyond disease stage. IMfirst (EudraCT: 2019-002784-10) is a phase IIIb study evaluating the safety of 1L atezolizumab + carboplatin or cisplatin + etoposide in patients with extensive-stage SCLC (ES-SCLC) in Spain. Previous analysis from IMfirst showed an association between low baseline neutrophil, leukocyte and neutrophil-to-lymphocyte ratio (NLR) values and long-term benefit (LTB). In this exploratory analysis from IMfirst, we aimed to further examine the potential association of laboratory parameters with prognosis in patients with ES-SCLC treated with chemoimmunotherapy.

Methods: Laboratory parameters were categorized as below or equal to (≤) or above (>) their median baseline values. To assess their potential association with overall survival (OS) and progression-free survival (PFS), univariate Cox regression analyses, as well as multivariate Cox proportional hazard models adjusted for confounding variables with p-value <0.05 were performed. LTB patients were defined as those who lived ≥24 months, while No-LTB pts were defined as those who died within 24 months post-randomization. Parametric (Student's t) or non-parametric (Wilcoxon Mann Whitney) tests were used to evaluate differences in baseline laboratory parameters between LTB and No-LTB patients. A p-value <0.05 was considered statistically significant for all analyses.

Results: In total, 155 patients were included. Median follow-up was 28.4 months (data cut off: 14 December 2022). Table 1 shows univariate analysis of selected baseline laboratory variables for OS and PFS. Variables that showed association with OS included: leukocyte and neutrophil counts, NLR, platelet-albumin-bilirubin (PALBI) score, alanine aminotransferase (ALT), alkaline phosphatase (ALP), aspartate aminotransferase (AST), phosphate, calcium, potassium, chloride, bilirubin, glucose and lactate dehydrogenase (LDH). Parameters with a significant association with PFS included: leukocyte and neutrophil counts, NLR, PALBI score, ALT, ALP, calcium, phosphate and chloride. Of all evaluated parameters, ALP, phosphate and bilirubin showed association with OS in the multivariate analysis and only phosphate showed association with PFS in the multivariate analysis. Baseline laboratory parameters that showed significant differences between LTB and No-LTB patients included leukocyte and neutrophil counts, NLR, PALBI score, ALP, AST, calcium, chloride and LDH.

Conclusions: This exploratory analysis from IMfirst, although limited due to the single-arm nature of the study, suggests biochemical and haematological parameters of potential prognostic value in ES-SCLC patients treated with atezolizumab + chemotherapy. Further validation in prospective studies is required.

Keywords: Small Cell Lung Cancer, IMFirst, Prognostic parameters

Table 1. Univariate analysis of selected laboratory variables for OS and PFS

	Univariate analysis of OS				Univariate analysis of PFS			
Parameter (units) ≤ median > median	**n**	**Median OS (95% CI), months**	**Hazard ratio (95% CI)**	***p*-value**	**n**	**Median PFS (95% CI), months**	**Hazard ratio (95% CI)**	***p*-value**
Leukocytes (10^9/L)								
≤ 8.64	78	11.3 (8.8, 15.2)	0.64 (0.45, 0.91)	**0.013**	78	6.3 (5.8, 7.2)	0.68 (0.48, 0.94)	**0.022**
> 8.64	77	9.2 (7.5, 11.0)	Reference		76	6.1 (5.2, 6.3)	Reference	
Neutrophils (10^9/L)								
≤ 6.2	78	11.4 (9.3, 14.9)	0.67 (0.47, 0.95)	**0.026**	78	6.3 (6.0, 7.7)	0.69 (0.49, 0.96)	**0.028**
> 6.2	77	9.0 (7.5, 11.0)	Reference		76	6.0 (4.9, 6.3)	Reference	
NLR								
≤ 3.88	78	12.6 (9.3, 14.9)	0.67 (0.47, 0.95)	**0.024**	77	6.5 (6.1, 7.2)	0.70 (0.50, 0.97)	**0.034**
> 3.88	77	9.0 (7.3, 10.9)	Reference		77	5.8 (4.8, 6.2)	Reference	
PALBI score								
≤ -2.49	77	12.3 (9.3, 14.9)	0.62 (0.44, 0.89)	**0.009**	77	6.3 (5.9, 7.1)	0.68 (0.49, 0.96)	**0.026**
> -2.49	77	8.8 (7.5, 10.9)	Reference		76	6.1 (4.8, 6.4)	Reference	
ALT (IU/L)								
≤ 24	80	13.0 (9.9, 15.3)	0.59 (0.42, 0.84)	**0.003**	80	6.7 (6.3, 7.7)	0.68 (0.49, 0.95)	**0.022**
> 24	75	8.5 (6.6, 9.9)	Reference		74	5.8 (4.9, 6.2)	Reference	
ALP (IU/L)								
≤ 87	79	13.1 (10.6, 15.8)	0.53 (0.37, 0.75)	**<0.001**	79	6.5 (6.1, 8.1)	0.68 (0.49, 0.95)	**0.023**
> 87	75	7.8 (6.3, 9.0)	Reference		74	5.6 (4.9, 6.3)	Reference	
AST (IU/L)								
≤ 23	78	12.9 (9.3, 15.3)	0.60 (0.42, 0.85)	**0.004**	78	6.3 (5.8, 7.2)	0.77 (0.55, 1.07)	0.118
> 23	75	9.0 (7.6, 10.6)	Reference		74	6.1 (5.2, 6.4)	Reference	
Phosphate (mmol/L)								
≤ 1.13	82	8.6 (7.3, 10.6)	1.43 (1.00, 2.04)	**0.049**	82	5.5 (4.8, 6.3)	1.62 (1.16, 2.28)	**0.005**
> 1.13	69	11.4 (9.6, 15.2)	Reference		68	6.4 (6.1, 7.7)	Reference	
Calcium (mmol/L)								
≤ 2.35	77	12.3 (8.8, 15.2)	0.65 (0.46, 0.93)	**0.018**	76	6.6 (6.0, 8.1)	0.70 (0.50, 0.98)	**0.039**
> 2.35	76	9.4 (7.5, 10.9)	Reference		76	6.0 (4.9, 6.3)	Reference	
Potassium (mmol/L)								
≤ 4.33	79	11.4 (9.2, 15.2)	0.70 (0.49, 0.99)	**0.042**	78	6.3 (5.9, 7.0)	0.90 (0.65, 1.25)	0.528
> 4.33	76	9.2 (7.5, 10.9)	Reference		76	6.1 (4.9, 6.4)	Reference	
Chloride (mmol/L)								
≤ 101	79	9.2 (7.6, 11.0)	1.48 (1.04, 2.10)	**0.029**	79	6.0 (4.9, 6.3)	1.41 (1.01, 1.96)	**0.045**
> 101	74	11.3 (8.8, 14.3)	Reference		73	6.3 (6.0, 7.0)	Reference	
Bilirubin (µmol/L)								
≤ 9.23	78	10.9 (8.8, 14.1)	0.69 (0.49, 0.98)	**0.039**	77	6.3 (6.0, 7.0)	0.76 (0.55, 1.06)	0.110
> 9.23	77	9.4 (7.5, 11.6)	Reference		77	6.1 (4.8, 6.3)	Reference	
Glucose (mmol/L)								
≤ 5.77	81	12.9 (9.4, 16.0)	0.65 (0.46, 0.93)	**0.017**	80	6.3 (5.8, 6.8)	0.79 (0.57, 1.10)	0.169
> 5.77	74	8.8 (7.5, 10.9)	Reference		74	6.1 (5.3, 6.5)	Reference	
LDH (IU/L)								
≤ 279.5	75	13.0 (10.1, 15.3)	0.62 (0.44, 0.89)	**0.010**	75	6.3 (5.8, 7.7)	0.73 (0.52, 1.02)	0.068
> 279.5	75	8.4 (6.9, 9.8)	Reference		74	6.1 (5.3, 6.3)	Reference	

Statistically significant values are shown in bold. ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; LDH, lactate dehydrogenase; NLR, neutrophil-to-lymphocyte ratio; PALBI, platelet-albumin-bilirubin score.

EP.13B SMALL CELL LUNG CANCER AND NEUROENDOCRINE TUMORS - IMMUNOTHERAPY/SYSTEMIC THERAPY
SATURDAY, SEPTEMBER 7, 2024 - 11:58 - 11:59

EP.13B.01 Selection of Optimal Therapy for Extensive-Stage Small Cell Lung Cancer: A Systematic Review and Network Meta-Analysis

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Introduction: Multiple immunotherapy-based combination regimens have been widely explored in the first-line treatment of extensive-stage small cell lung cancer (ES-SCLC). Recently reported results from the ETER701 study showed that a novel immunotherapy-based regimen, anlotinib (multi-target angiogenesis inhibitor)+benmelstobart (programmed cell death ligand 1 inhibitor)+chemotherapy (Anl/Ben/CT), provided a median overall survival (OS) of 19.3 months in ES-SCLC, which is the longest OS obtained to date. However, there is no evidence-based medicine available proving that Anl/Ben/CT is the optimal regimen due to the lack of direct or indirect comparisons among varying immunotherapy-based regimens.

Methods: The eligible randomized controlled trials (RCTs) were identified by searching PubMed, Embase, Cochrane Library databases and major international conferences. Then, the network meta-analysis (NMA) was analyzed to compare the efficacy and safety among 15 first-line regimens in ES-SCLC.

Results: A total of 12 immunotherapy-related RCTs reporting 6178 ES-SCLC individuals were enrolled. The results indicated that most of immunotherapy-based regimens could significantly prolong progression-free survival (PFS) compared with chemotherapy alone, especially Anl/Ben/CT (HR 0.32, 95% CI 0.25-0.40) (Figure A). Among immunotherapy-based regimens, significant prolongation of PFS was observed for ES-SCLC with Anl/Ben/CT compared to the others (all HR < 1 and 95% CIs did not cross 1) (Figure A). Similar results were observed in terms of OS, that is, most immunotherapy-related regimens dramatically reduced the risk of death in ES-SCLC, with Anl/Ben/CT being the most prominent (HR 0.61, 95% CI 0.47-0.80) (Figure A). The results of Bayesian ranking probabilities showed Anl/Ben/CT ranked first in both PFS, OS and objective response rate among 15 regimens (Figure B). There are almost identical results from the sensitivity analysis to the originals, demonstrating the reliability and robustness of he NMA (Figure B).

Conclusions: To the best of our knowledge, this NMA demonstrated for the first time that adding anlotinib and benmelstobart to chemotherapy significantly improved PFS and OS compared with chemotherapy alone or chemotherapy plus immunotherapy, with an acceptable safety profile in patients with ES-SCLC. In conclusion, Anl/Ben/CT could be a new and clinically preferable first-line treatment option for this population.

Keywords: small cell lung cancer, immunotherapy, network meta-analysis

B

Sensitivity analysis

	PFS	OS	ORR	≥3AEs	PFS	OS	ORR	≥3AEs
Anl/Ben/CT	1	1	1	3	1	1	2	2
Ser/CT	2	2	5	7	2	2	4	5
Tis/CT	3	5	8	15	3	5	7	13
Niv/CT	4	9	2	4	4	10	1	4
Pha-Ipi/CT	5	7	3	2	NA	NA	NA	NA
Tor/CT	6	8	NA	11	5	7	NA	9
Ade/CT	7	3	9	10	6	3	8	8
Niv/Ipi/CT	8	13	4	1	7	11	3	1
Con-Ipi/CT	9	12	13	5	NA	NA	NA	NA
Pem/CT	10	10	7	9	8	8	6	7
Ate/CT	11	6	14	12	9	6	12	10
Dur/CT	12	4	6	13	10	4	5	12
Dur/Tre/CT	13	11	10	6	11	9	9	3
Ipi/CT	14	14	11	8	12	12	10	6
CT	15	15	12	14	13	13	11	11

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EP.13B.02 Real-World Insights: Treatment Patterns and Overall Survival in Patients with Small-Cell Lung Cancer in South Korea a Single Center Experience

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Introduction: Small Cell Lung Cancer (SCLC) represents a highly aggressive subtype of lung cancer, accounting for about 15% of all lung cancer cases worldwide. Despite relatively high initial response rates to current treatment, the prognosis for SCLC patients is dismal due to its rapid progression and development of resistance to treatment. In the current therapeutic landscape, the effectiveness of different lines of therapy, including the emerging role of immunotherapy, has not been fully elucidated, particularly outside of clinical trials. We conducted a real-world data analysis to explore the clinical characteristics, treatment patterns, and overall survival of SCLC patients in Korea.

Methods: This study is a retrospective cohort study of patients with SCLC who were diagnosed and treated at Samsung Medical Center (SMC) from 1 January 2018 to 31 December 2021, with follow-up available through 13 March 2023. The data was obtained from the Clinical Data Warehouse of SMC. The first systemic therapy regimen following initial SCLC diagnosis was classified as first-line of therapy. Subsequent lines of therapy were determined based on new regimens administered after disease progression. Overall survival (OS) from the initiation of new lines of therapy was assessed using Kaplan-Meier estimates. Death information was linked with National Administrative Data of Ministry of Interior and Safety. Patients who received a clinical study drug in any line of therapy were excluded.

Results: Out of 515 patients identified, 343 patients had extensive stage (ES) and 172 had limited stage (LS) disease at diagnosis. Both ES and LS patients were predominantly male, 92.1% and 90.1%, respectively, with a median age of 70 years for ES and 67 years for LS. A high prevalence of smoking history was observed in both groups (79.3% ES, 89.0% LS). Most patients had an ECOG performance score of 0 or 1 at diagnosis (89.2% ES, 93.0% LS). The majority of ES patients received etoposide/platinum (209/343, 60.9%) or atezolizumab plus etoposide/platinum (130/343, 37.9%) as first-line therapy; while nearly all of LS patients (164/172, 95.3%) received concurrent chemoradiotherapy (CCRT) with etoposide/platinum as their initial therapy. Irinotecan/platinum was the most common second-line therapy for ES (124/202, 61.4%) and as initial therapy for LS patients who showed disease relapse after CCRT (29/72, 40.3%). As a subsequent therapy, paclitaxel was the most common for ES (64/97, 66.0%) and LS (12/32, 37.5%) patients. In ES patients, the median OS from the initiation of first-line therapy was 11.3 months (95% confidence interval (CI), 9.7-12.2). From the initiation of second and third-line therapies, the median OS was 6.9 months (95% CI, 6.3-7.9) and 5.1 months (95% CI, 3.9-5.8), respectively. In LS patients, the median OS from the initiation of CCRT was 33.4 months (95% CI, 26.0-46.9), from the initiation of first-line systemic therapy was 11.9 months (95% CI, 7.9-16.8), and from the initiation of second-line systemic therapy was 8.3 months (95% CI, 5.1-10.8).

Conclusions: Our findings confirm once again the poor survival outcomes in SCLC. Results highlight the limitations of current treatment and underscore the urgent need for effective therapeutic strategies to improve this challenge.

Keywords: Small-Cell Lung Cancer, Treatment Patterns, Clinical Outcomes

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EP.13B.03 Real-World Outcomes of Platinum-immunotherapy as First-Line (1L) Treatment of Extensive-Stage Small Cell Lung Cancer (ES-SCLC)

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Introduction: Atezolizumab and durvalumab were approved alongside platinum-based chemotherapy as 1L treatment for ES-SCLC, based on data from two phase 3 trials, IMpower133 and CASPIAN. This retrospective, descriptive study assessed clinical characteristics and outcomes in patients with ES-SCLC receiving 1L platinum-immunotherapy in the real-world setting.

Methods: Data from the US-nationwide Flatiron Health electronic health record-derived deidentified database were collected in ES-SCLC patients aged ≥18 years receiving 1L carboplatin/cisplatin plus atezolizumab/durvalumab, with/without etoposide, between 9/25/2018 and 4/4/2021 (overall group), including patients receiving ≥1 cycle of immunotherapy as maintenance treatment (maintenance subgroup). Baseline characteristics (assessed between initial diagnosis and start of 1L treatment), treatment patterns, real-world effectiveness, and laboratory-derived adverse events of special interests (AESIs), including grade ≥3 hematological events, for each group were reported descriptively.

Results: This analysis included 1144 patients with ES-SCLC who received 1L platinum-immunotherapy. Of these, 764 patients received maintenance immunotherapy. The table presents baseline demographics/characteristics and treatment patterns. All patients received 1L platinum-etoposide plus immunotherapy, and most patients in the overall group (90.6%) and maintenance subgroup (91.2%) received atezolizumab as immunotherapy. Overall, the median (interquartile range [IQR]) duration of immunotherapy, including maintenance treatment, was 4.9 (2.8-7.1) months, and the median (IQR) duration of maintenance immunotherapy was 2.8 (1.4-4.9) months. The median (95% confidence interval) real-world overall survival (OS), progression-free survival, and time to next treatment from the start of 1L platinum-immunotherapy were 10.4 (9.8, 11.1), 5.4 (5.3, 5.6), and 6.7 (6.5, 6.9) months, respectively, in the overall group, and 13.1 (12.2, 14.1), 5.8 (5.6, 6.0), and 7.2 (7.0, 7.6) months in the maintenance subgroup. Among patients continuing immunotherapy for maintenance treatment, values were 9.7 (8.6, 10.6), 3.0 (2.7, 3.1), and 4.0 (3.9, 4.3) months from start of maintenance immunotherapy. The most common AESIs were grade ≥3 neutropenia (31.8%), anemia (24.8%), and thrombocytopenia (17.9%). Frequency of AESIs during maintenance immunotherapy was ≤2.5%. Unfavorable changes in lactate dehydrogenase levels and neutrophil-to-lymphocyte ratios were less frequent in the maintenance subgroup than in the overall group.

Conclusions: To date, this is the largest real-world study of platinum-immunotherapy in 1L ES-SCLC. Although this study population had poorer prognostic factors than those from pivotal trials (e.g., ECOG performance status ≥2 vs <2, respectively), survival outcomes were similar. Consistent with previous findings, less frequent AESIs and better prognostic factors were observed in the maintenance subgroup. The modest OS in this study underscores the unmet need for effective 1L treatment to improve survival for ES-SCLC.

Keywords: maintenance immunotherapy, prognostic factors, small cell lung cancer

Table. Patient demographics, clinical characteristics, and treatment patterns

	Total (N=1144)	Maintenance immunotherapy[a] (n=764)
Baseline demographics and clinical characteristics[a]		
Median age, years (IQR)	67.0 (61.0, 74.0)	66.0 (61.0, 73.0)
Male, n (%)	568 (49.7)	404 (52.9)
White, n (%)	791 (69.1)	530 (69.4)
Mean BMI,[b] kg/m^2 (STD)	26.8 (6.4)	27.2 (6.2)
Mean BSA,[c] m^2 (STD)	1.9 (0.3)	1.9 (0.3)
Practice type, n (%)		
Academic	99 (8.7)	63 (8.2)
Community	1029 (89.9)	689 (90.2)
ECOG performance status,[d] n (%)		
0	237 (20.7)	179 (23.4)
1	384 (33.6)	267 (34.9)
2+	220 (19.2)	128 (16.8)
Missing	303 (26.5)	190 (24.9)
Median time since initial diagnosis, months (IQR)	0.6 (0.4, 1.0)	0.6 (0.4, 0.9)
Brain metastasis, n (%)	32 (2.8)	24 (3.1)
Liver metastasis, n (%)	37 (3.2)	26 (3.4)
Baseline serum LDH level[e]		
Mean (STD), U/L	443.0 (460.7)	417 (445.0)
Missing, n (%)	789 (69.0)	519 (67.9)
NLR in $10^9/L$		
Mean (STD)	6.9 (11.5)	5.8 (7.0)
Missing, n (%)	289 (25.3)	181 (23.7)
Median crude observation time, months (IQR)	9.4 (5.6, 15.4)	8.5 (4.2, 15.4)
Treatment patterns		
Type of immunotherapy,[f] n (%)		
Atezolizumab	1036 (90.6)	697 (91.2)
Durvalumab	105 (9.2)	65 (8.5)
Both	3 (0.3)	2 (0.3)
Median duration of immunotherapy, months (IQR)	4.9 (2.8, 7.1)	5.8 (4.3, 7.9)
Median (range) cycles of platinum-based chemotherapy during 1L	4.0 (1.0, 27.0)	4.0 (2.0, 27.0)
Median duration of maintenance immunotherapy,[g] months (IQR)	n/a	2.8 (1.4, 4.9)
Initiation timing of 1L immunotherapy, n (%)		
At first cycle of platinum-based chemotherapy	962 (84.1)	638 (83.5)
At subsequent cycle of platinum-based chemotherapy	168 (14.7)	121 (15.8)
Prior to first cycle of platinum-based chemotherapy	14 (1.2)	5 (0.7)
G-CSF use during 1L, n (%)	901 (78.8)	647 (84.7)
Maximum change in serum LDH from baseline to end of follow-up,[h] n (%)		
Increased	134 (57.0)	57 (43.2)
Decreased	99 (42.1)	73 (55.3)
Missing	908 (79.4)	628 (82.6)
Maximum change in serum NLR from baseline to end of follow-up,[h] n (%)		
Increased	681 (84.4)	363 (66.9)
Decreased	126 (15.6)	180 (33.1)
Missing	336 (29.4)	217 (28.6)

[a]Baseline characteristics were assessed from the initial diagnosis to the start of 1L platinum-immunotherapy, and demographic characteristics were assessed at the start of 1L platinum-immunotherapy. As such, reported baseline data for the maintenance subgroup were at start of 1L platinum-immunotherapy, and not at start of maintenance immunotherapy.
[b]BMI calculated as weight (kilograms) / height (meters)^2.
[c]BSA calculated using the Du Bois formula as 0.007184 x height (centimeters)$^{0.725}$ x weight (kilograms)$^{0.425}$.
[d]ECOG performance status assessed as the most recently recorded value from SCLC diagnosis date to start of 1L.
[e]For serum LDH levels and NLR, the most recent value between 45 days prior to the start of 1L and the start of 1L was selected.
[f]Type of immunotherapy was assessed at the start of induction treatment for the overall group and at the start of maintenance treatment for the maintenance subgroup.
[g]Excluded duration of induction treatment with the combination of platinum-based chemotherapy and immunotherapy.
[h]Maximum changes in the overall group were assessed from start of induction treatment to end of follow-up, and these were assessed from start of maintenance treatment to end of follow-up in the maintenance group.
1L, first line; BMI, body mass index; BSA, body surface area; ECOG, Eastern Cooperative Oncology Group; G-CSF, granulocyte-colony stimulating factor; LDH, lactate dehydrogenase; IQR, interquartile; n/a, not applicable; NLR, neutrophil-to-lymphocyte ratio; SCLC, small cell lung cancer; STD, standard deviation; U/L, unit per liter.

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EP.13B.04 The Value of Radiotherapy Based on the Failure of Extensive-Stage Small Cell Lung Cancerin the Era of Immunotherapy

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Introduction: Immune checkpoint inhibitors (ICIs) have significantly prolonged overall survival (OS) in patients with extensive-stage small cell lung cancer (ES-SCLC). The role of radiotherapy (RT) in the era of immunotherapy is unclear. We assessed the value of RT based on the first failure pattern of ES-SCLC.

Methods: We conducted a retrospective analysis of patients with ES-SCLC receiving first-line chemotherapy and immunotherapy at Shanghai Chest Hospital. Our study recorded the first failure pattern in ES-SCLC, analyzed the main sites of disease progression, explored factors that may affect prognosis, estimated the value of RT, and showed the potential for patient survival extension in the immunotherapy era.

Results: Disease progression occurred in 86 patients (68%). For dismissing the impact of RT on first failure pattern, 72 patients were divided into the non-pre-progression RT group and 14 patients were divided into the pre-progression RT group. Concerning the first failure pattern in non-pre-progression RT group: 25 patients with local failure, 28 patients with distant failure, and 19 patients failed both. As for the first failure pattern in pre-progression RT group: 5 patients with local failure, 8 patients with distant failure, and only one patient failed both.The mOS of the RT group was 21.4 months (95% CI:17.0-25.8 months), while that of the non-RT group was 11.9 months (95% CI:7.5-16.3 months). he results showed that the mPFS was 8.6 months (95% CI: 7.1-10.1 months) for the pre-progression radiotherapy group and 6.7 months (95% CI: 5.7-7.7 months) for the post-progression radiotherapy group. Pre-progression RT significantly improved PFS (hazard ratio for death, 0.513; 95% CI: 0.298-0.883; P = 0.013).

Conclusions: Distant failure is still the main failure pattern for ES-SCLC patients received first-line chemotherapy and ICIs. RT improved OS in these patients, and pre-progression RT improved PFS further. Therefore, it is likely that the appropriate timing for RT is before the tumor progression, and we plan to conduct further clinical trials to verify it.

Keywords: extensive-stage small cell lung cancer, Chemoimmunotherapy, Radiotherapy

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EP.13B.05 Comparison of the Effectiveness of Cisplatin and Carboplatin with Etoposide in Treatment of Small Cell Lung Cancer: Single-center Experience

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Introduction: Small cell lung cancer (SCLC) is an aggressive type of lung cancer with poor survival. SCLC responds well to chemo(radio) therapy. Etoposide and cisplatin is most common first line treatment option, but carboplatin can be used instead of cisplatin in these group of patients. The aim of our study is to compare the effectiveness of cisplatin and carboplatin with etoposide as first-line treatment option in SCLC and demonstrate if present carboplatin is not non-inferiorty over to cisplatin.

Methods: In this single-center, retrospective study 135 patients diagnosed with SCLC were evaluated and compared according to progression-free survival (PFS) and overall survival (OS) Patients analysed according to receiving cisplatin plus etoposide (EP) and those receiving carboplatin plus etoposide(EC) in the first line restropectively. Both limited and extensive stage patients included this analysis.

Results: 53(%39,2) patients received EP, 82(%60,7) patients received EC. The median age was 60 years in the EP arm and 67.5 years in the EC arm. There was no significant difference between PFS values in limited stage patients and those receiving cisplatin and carboplatin (16 vs 10 mos p = 0,133). However, a significant OS difference in favor of cisplatin was detected in this patient group (31,2 vs 20,2 mos p = 0,021). In extensive stage patients, carboplatin was statistically more advantageous than cisplatin regarding PFS (8 vs 7 mos p = 0,025). However, no significant difference was detected in OS in the EP and EC groups (10,8 vs 11,30 mos p = 0,545). Objective response rates (ORR) were 72% in the EP arm and 83% in the EC arm in limited stage patients. In extended stage patients, the ORR were 96.4% in the EP arm and 96.2% in the EC arm.

Conclusions: Cisplatin and carboplatin with etoposide is cornerstone of SCLC treatment. While cisplatin treatment appears to be more effective in limited stage patients, its effect profile is similar to carboplatin in extensive stage patients. In our retrospecitve study no significant OS difference was shown with cisplatin vs carboplatin based combination. Due to its tolerable toxicity, carboplatin treatment may be preferred in the extensive stage patients.

Keywords: Small cell lung cancer, cisplatin, carboplatin

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EP.13B.06 Efficacy and Safety Analysis of Atezolizumab Continuation Beyond Progression in Extensive Small Cell Lung Cancer(ES-SCLC)

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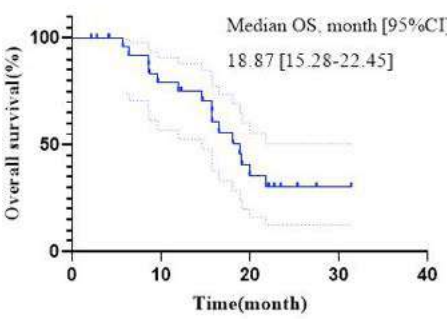
Introduction: Immunotherapy has opened up a new chapter for tumor treatment and significantly improved the survival of patients with extensive-stage small cell lung cancer (ES-SCLC), with anti-programmed death-ligand 1 (PD-L1) antibody represented by atezolizumab attaining overall survival (OS) beyond one year in the IMpower133 trial. However, a considerable number of patients acquired immunotherapy resistance or recurrence. Despite immune checkpoint inhibitors (ICIs) have brought significant benefits to patients, there has been little research on the efficacy analysis of immunotherapy continuation beyond progression, as well as the possible population of benefit. The aim of our study was to evaluate the efficacy and safety of immunotherapy continuation therapy to further optimize the immunotherapy rechallenge strategies.

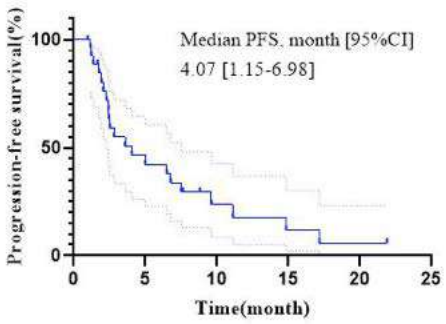
Methods: We conducted a retrospective analysis of the demographic and treatment data of patients with ES-SCLC from multiple centers between January 2020 and April 2024. All enrolled patients progressed after receiving first-line (1L) atezolizumab combination therapy upon initial diagnosis of ES-SCLC and continued to receive immunotherapy combination therapy as second-line (2L) treatment. We aimed to evaluate the efficacy of immunotherapy rechallenge, measured by median OS (mOS) and median progression free survival (mPFS). The incidence of adverse events (AEs) was used to evaluate safety.

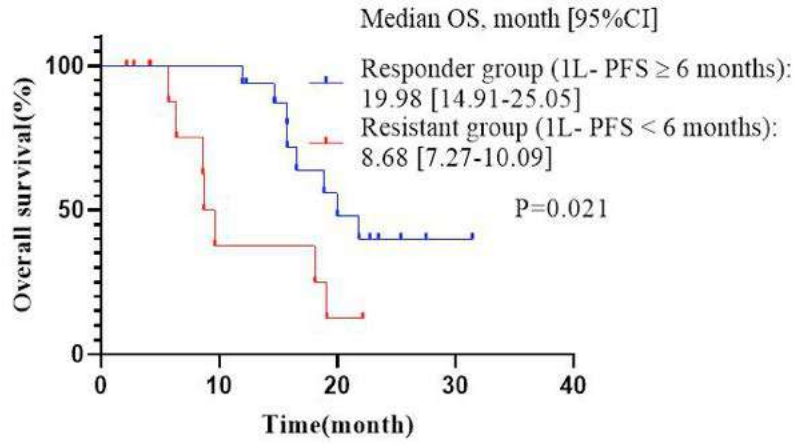
Results: Twenty-eight patients were eligible for this study, and the whole cohort received continuing atezolizumab combination therapy. After a median follow-up time of 15.7 months, 2L-mPFS was 4.07 months [95% CI: 1.15 to 6.98], the mOS was 18.87 months [95% CI: 15.28 to 22.45]. Further subgroup analysis demonstrated that the response to the 1L therapy was proposed as prognostic factor for OS. Responder group (1L-PFS ≥ 6 months) achieved longer mOS: 19.98 [95 %CI: 14.91-25.05] compared with resistant group (1L-PFS < 6 months) (p=0.021). Besides, receiving radiotherapy in 2L treatment after progression of atezolizumab was favorable prognostic factors accounting for PFS. Surprisingly, patients were with primary brain metastasis experienced more benefit in PFS and OS than those were not. In safety analysis, there were no treatment-related deaths. The most common AEs included dyspnea (53.5%), cough (39.2%) and nausea (28.5%), 1 patient developed grade 3 dyspnea.

Conclusions: The continuing immunotherapy combination therapy demonstrated favorable response in patients who experienced progression following 1L immunotherapy, especially for those who achieved PFS more than six months in 1L treatment. Additionally, combined radiotherapy during the immunotherapy continuation treatment can bring PFS benefit.

Keywords: Extensive-stage small cell lung cancer (ES-SCLC), Immunotherapy rechallenge, Atezolizumab







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EP.13B.07 Evaluation of Trilaciclib Use and Chemotherapy Induced Myelosuppression in Extensive-Stage Small Cell Lung Cancer

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Introduction: The 5-year survival rate for extensive-stage small cell lung cancer (ES-SCLC) patients is about 3% from the time of diagnosis. Chemotherapy-induced myelosuppression (CIM) is a common dose-limiting and potentially fatal toxicity of chemotherapy. This substantial burden leads to suboptimal health outcomes and increased healthcare utilization. A previous real-world study has shown that up to 98% of ES-SCLC patients had at least 1 myelosuppressive episode during follow-up and across all-chemotherapy lines of therapies. Trilaciclib is a transient cyclin-dependent kinase 4/6 inhibitor and is the first and only myeloprotection therapy approved to decrease CIM among adults with ES-SCLC when administered prior to a platinum/etoposide-containing regimen or topotecan-containing regimen. Studies elucidating the real-world outcomes of trilaciclib have been limited since its approval in 2021. The objective of this study is to evaluate CIM outcomes of patients with ES-SCLC who received platinum/etoposide-containing or topotecan-containing chemotherapy with or without trilaciclib.

Methods: This was a single-center retrospective study of patients with ES-SCLC who received chemotherapy with or without trilaciclib from January 3, 2018 to October 31, 2023, at Zuckerberg Cancer Center. The inclusion criteria for analysis included: adults 18 years and older, histologically confirmed ES-SCLC, and administration of platinum/etoposide-containing or topotecan-containing chemotherapy with or without trilaciclib. Outcomes included myelosuppression events and grade (anemia, neutropenia, thrombocytopenia) and supportive care utilization (granulocyte-colony stimulating factor (G-CSF) and RBC and/or platelet transfusion). Information on progression of disease and death was also collected. Data was analyzed using the T test and Chi-square test. For all analyses, a p-value < 0.05 was considered statistically significant.

Results: Patients in the trilaciclib cohort (N=36) and control cohort (N=58) were administered, on average, 4 cycles of chemotherapy, with the majority receiving carboplatin, etoposide, and atezolizumab. Fewer patients in the trilaciclib group experienced anemia (61.1% vs 77.6%, p = 0.207) and thrombocytopenia, (61.1% vs 19.4%, p=0.557) compared to those in control group across all grades. However, a higher percentage of patients in the trilaciclib group experienced neutropenia (25% vs 10.3%, p = 0.062). 86.2% of patients in the control group received G-CSF compared to 25% in the trilaciclib group (p <0.001).

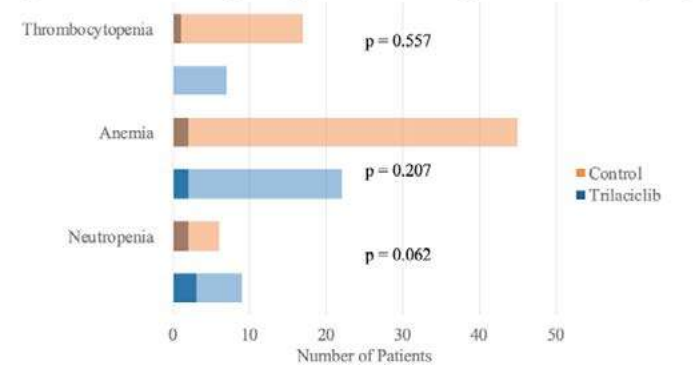
Conclusions: Early real-world outcomes following treatment with trilaciclib suggest a potential reduction in myelosuppressive HAE among patients with ES-SCLC who receive platinum/etoposide-containing regimen or topotecan-containing regimen. However, limitations to this study include its retrospective study design, small sample size, and that analysis for the two cohorts involved two different time frames.

Keywords: Trilaciclib, Extensive Stage Small Cell Lung Cancer

Table 2: Results

	Trilaciclib (n=36)	Control (n=58)	p-value
Chemotherapy regimen			0.014
Cisplatin and etoposide	2 (5.6)	1 (1.7)	
Carboplatin and etoposide	4 (11.1)	22 (37.9)	
Carboplatin, etoposide, and atezolizumab	30 (83.3)	35 (60.3)	
Cycle (median [IQR])	4.00 (3.00, 4.00)	4.00 (3.00, 4.00)	0.737
Received G-CSF, n (%)	9 (25)	50 (86.2)	<0.001
Received ESA	2 (5.6)	0	0.28
Received concurrent radiation	3 (8.3)	0	0.103
Delay in chemotherapy	8 (22.2)	11 (19.0)	0.906
Reduction in chemotherapy	6 (16.7)	7 (12.1)	0.749
Chemotherapy discontinued due to adverse events	5 (13.9)	5 (8.6)	0.645
Patient hospitalized	5 (13.9)	29 (50)	0.001
PFS (median [IQR])	4.38 (2.73, 6.77)	4.65 (3.00, 7.04)	0.66
OS (median [IQR])	5.93 (3.08, 9.66)	6.92 (3.68, 14.78)	0.278

Figure 1: Prevalence of Myelosuppressive Hematologic Adverse Effects (HAE)



EP.13B SMALL CELL LUNG CANCER AND NEUROENDOCRINE TUMORS - IMMUNOTHERAPY/SYSTEMIC THERAPY
SATURDAY, SEPTEMBER 7, 2024 - 11:58 - 11:59

EP.13B.08 Enhanced Efficacy of Anlotinib in Small Cell Lung Cancer after Immune Checkpoint Inhibitor Exposure

J. Shan, The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou/CN

Introduction: Small cell lung cancer (SCLC) is a malignancy associated with poor prognosis. Anlotinib, an anti-angiogenesis medication, has been approved in China as a third-line treatment option for SCLC. Nowadays, the current standard first-line treatment for SCLC includes PD-L1/PD-1 immune checkpoint inhibitors (ICI) in combination with chemotherapy. Several recent retrospective studies have suggested that patients with non-small cell lung cancer (NSCLC) and gastric cancer previously treated with ICI may have increased progression-free survival (PFS) with subsequent anti-angiogenic therapy compared with patients not treated with ICI.

Methods: We conducted a retrospective analysis of the data of patients with extensive-stage SCLC who received anlotinib as third-line therapy at our hospital between January 2021 and April 2023. The primary endpoints were PFS and overall survival (OS).

Results: Twenty patients who had not received prior ICI therapy (control group) and 39 patients who had received ICI therapy (treatment group) received anlotinib as third-line therapy. the treatment group significantly prolonged PFS compared with the control group (median, 11 months vs. 4 months; HR=0.34, 95%CI, 0.12-0.92, log-rank P=0.0345). Median OS was 21 months vs. 10 months (HR=0.48, 95%CI, 0.23-1.00, log-rank P=0.0228). The incidence of grade ≥ 3 adverse events (AEs) was similar between groups, 35.9% in the treatment arm and 30% in the control arm, with proteinuria being the most common AE.

Conclusions: Anlotinib shows improved efficacy in patients with SCLC who have been previously exposed to immune checkpoint inhibitors. Further prospective studies are warranted to validate these findings and elucidate the underlying mechanisms of this synergism.

Keywords: SCLC, anlotinib, Immune Checkpoint Inhibitor

EP.13B SMALL CELL LUNG CANCER AND NEUROENDOCRINE TUMORS - IMMUNOTHERAPY/SYSTEMIC THERAPY
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EP.13B.09 Outcomes of Inpatient Chemotherapy for Patients with Newly Diagnosed Extensive Stage Small Cell Lung Cancer

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Introduction: Small-cell lung cancer (SCLC) accounts for 15% of all lung cancers, of which 70% are diagnosed at extensive-stage (ES). SCLC has high sensitivity to chemotherapy due to its rapid proliferation, and treatment is considered even in patients who are very unwell. Despite this, little is known about outcomes of patients with ES-SCLC treated in the inpatient setting.

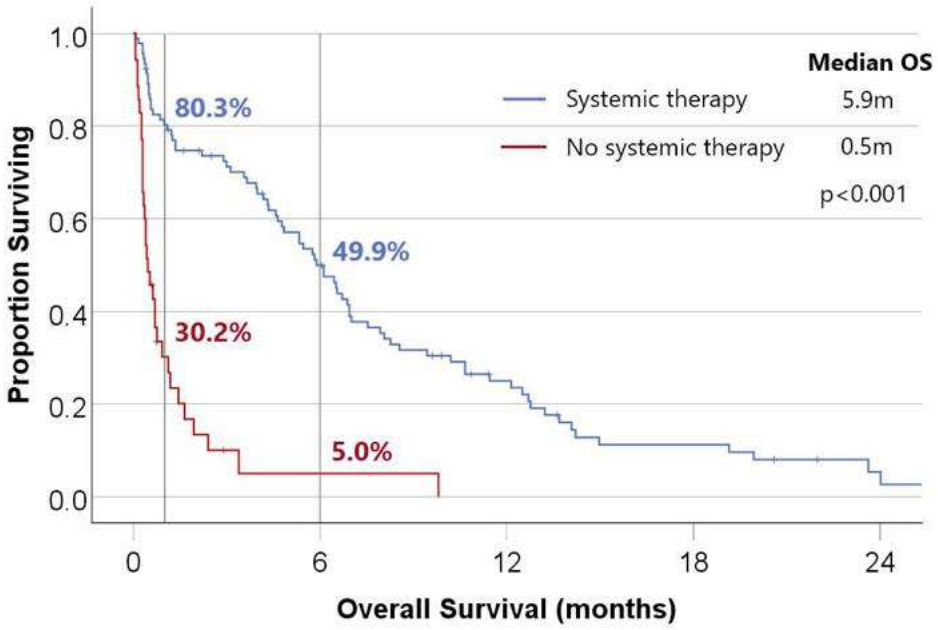
Methods: With ethics approval, we conducted a retrospective review of all patients with a de novo diagnosis of ES-SCLC at The Ottawa Hospital between January 2013 and December 2021 who had an inpatient medical oncology consultation. The primary endpoint was overall survival (OS) among patients who received systemic therapy versus those who did not. Secondary endpoints included hospital length of stay (LOS) and incidence of tumour lysis syndrome (TLS).

Results: Of the 127 patients identified, 92 (72%) received systemic therapy. Baseline characteristics at initial diagnosis: median age 68 years (range 50-87); 74 (58%) female; 121 (99%) with former or current smoking history; 27 (22%) brain metastases; 80 (64%) liver metastases. Patients in the non-treatment cohort had significantly poorer Eastern Cooperative Oncology Group performance status (ECOG-PS) versus the treatment cohort (p<0.001), with 88% and 53% patients with an ECOG-PS of 3-4, respectively. Of the 92 patients who received systemic therapy, 87 (95%) received platinum-etoposide as first-line treatment, most receiving either 1 (85%) or 2 (12%) cycles in the inpatient setting. Median OS from initial diagnosis was 4.0 months (m) (95% CI, 2.5-5.5m). The systemic therapy cohort had a median OS of 5.9m (95% CI, 4.5-7.3m), 30-day survival of 80%, 6 m survival of 50%, and median LOS of 14 days. The no treatment cohort had an abysmal median OS of 0.5 m (95% CI, 0.2-0.7 m), 30-day survival of 30%, 54% death rate in-hospital, and median LOS of 11 days. Of the 76 patients with blood work evaluable for TLS, 6 (8%) developed TLS, all of whom died within 7 days of chemotherapy. All patients with TLS had liver metastases, ECOG-PS of 2-3 and lactate dehydrogenase (LDH) >1500 (unknown for 1).

Conclusions: Despite admission to hospital, 72% of patients received systemic therapy for treatment of ES-SCLC. Patients receiving systemic therapy lived longer than those who did not. The risk of developing TLS was associated with liver metastases, poor ECOG-PS, and LDH>1500. Aggressive TLS prophylaxis should be considered among patients with these factors.

Keywords: Small cell lung cancer, Tumour lysis syndrome, Inpatient

Figure 1: Kaplan-Meier curve depicting overall survival among inpatients who underwent systemic therapy versus those that did not



EP.13B SMALL CELL LUNG CANCER AND NEUROENDOCRINE TUMORS - IMMUNOTHERAPY/SYSTEMIC THERAPY
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EP.13B.10 Impact of Pneumonitis from Radiotherapy Combined with Immune Checkpoint Inhibitor Therapy on Tumor Progression and Survival in Patients with Small Cell Lung Cancer

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Introduction: Chemoradiotherapy is the main treatment for small cell lung cancer (SCLC). With the development of immunotherapy, chemotherapy combined with immune checkpoint inhibitors (ICI) has become the first-line standard care for extensive-stage (ES) SCLC and its application in patients with limited-stage (LS) SCLC is under investigation. How the promotion of pneumonitis produced by the synergy of immunotherapy and radiotherapy affects the prognosis of SCLC is an unanswered question.

Methods: Clinical and prognostic data were retrospectively collected from ES-SCLC patients who received consolidation thoracic radiotherapy and LS-SCLC patients who received concurrent or sequential thoracic radiotherapy after ICI from January 2019 to August 2023 at our center. Treatment-related pneumonitis occurring within 6 months of completion of radiotherapy was assessed and graded by two radiation oncologists using the Common Terminology Criteria for Adverse Events version (CTCAE 5.0). The Kaplan-Meier method and log-rank test were used to evaluate the correlation of pneumonitis with progression-free survival (PFS) and overall survival (OS).

Results: A total of 35 patients treated with radiotherapy combined with ICI were included. There were 22 (62.9%) ES-SCLC and 13 (37.1%) LS-SCLC patients. The median radiotherapy dose was 45 Gy, and 17 patients (48.6%) received concurrent radiotherapy and immunotherapy. The median PFS and OS were 9(95% CI,0.4-46) months and 22(95% CI,8-46) months, respectively. ES-SCLC patients underwent consolidation radiotherapy after chemoimmunotherapy achieved a similar PFS (vs. p=0.83) and OS (vs. p=0.50) to LS-SCLC counterparts. However, PFS of LS-SCLC here was shorter than the historical data limited to the small sample size. Twenty-one patients (60%) developed treatment-related pneumonitis, of which six patients (27.3%) were grade 2 and two patients (9.1%) were grade 3, with no grade 4 or 5 pneumonitis. Of these, seven patients (31.8%) experienced radiation pneumonitis, one patient (4.5%) experienced checkpoint inhibitor pneumonitis, and five patients (22.9%) experienced mixed pneumonitis. Patients who developed grade 2 and above pneumonia had worse PFS [7(95% CI-22) months vs. 12(95% CI-46) months, log-rank, p = 0.155] but no significant difference in OS compared to those who developed grade 1 or no pneumonitis. Mixed pneumonitis appeared to contribute the most, but there was no statistical difference in the impact of the three types of pneumonitis on PFS and OS. The prognostic impact of pneumonitis was similar in the two subgroups of LS-SCLC and ES-SCLC.

Conclusions: In this study, ≥grade 2 treatment-associated pneumonitis induced byradiotherapy combined with immunotherapy shortened the PFS but not OS of SCLC patients. Mixed pneumonitis appeared to have more adverse effects, but more sample sizes are needed to confirm. Based on this, the risk of pneumonitis should be assessed more carefully when administering combination therapy with immunoradiotherapy for SCLC. Moreover, the suboptimal outcomes of LS-SCLC patients suggests that the role of immunotherapy combined with chemoradiotherapy warrants further investigation.

Keywords: radiation pneumonitis, Small-cell lung cancer, checkpoint inhibitor pneumonitis

EP.13B SMALL CELL LUNG CANCER AND NEUROENDOCRINE TUMORS - IMMUNOTHERAPY/SYSTEMIC THERAPY
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EP.13B.11 Clinical Outcomes of Continuous Immunotherapy Beyond Progression in Patients with Extensive-Stage Small Cell Lung Cancer

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Introduction: Immunochemotherapy has been approved as first-line treatment for extensive-stage small-cell lung cancer (ES-SCLC) with a 2-4 months OS benefits compared with chemotherapy only. However, the efficacy of continuous immune-checkpoint inhibitors (ICIs) beyond immunochemotherapy progression is still unknown. This multi-center retrospective study aimed to investigate the efficacy of regimens containing continuous immunotherapy as second-line treatment for ES-SCLC after first-line immunochemotherapy.

Methods: We retrospectively reviewed the medical records of ES-SCLC patients treated with first-line immunochemotherapy at Qilu hospital of Shangdong University and Shandong Cancer Hospital. All the patients enrolled achieved disease control during first-line immunochemotherapy and then suffered disease progression. Patients with primary resistance to immunochemotherapy with a progression-free survival (PFS)<3 months was excluded.

Results: From January 2020 to September 2023, a total of 97 ES-SCLC patients treated with first- line immunochemotherapy were enrolled, with a median age of 62 (range, 39-79) and ECOG score of 0-1. There were 77 males and 55 with a history of smoking, 24 with brain metastases, 28 with liver metastases, and 34 with bone metastases. Seventy-eight patients received PD-L1 antibody including atezolizumab, durvalumab, adebrelimab and envafolimab, while 19 patients received PD-1 antibody including pembrolizumab, serplulimab and tislelizumab. Overall response rate of first-line immunochemotherapy was 54.6% (95% confidence interval [CI]:44.6%-64.7%), including 51 cases of PR and 2 cases of CR. The median PFS was 6.8 (95%CI: 6.2-7.4) months. Median cycle of immunotherapy was 7.0 (range, 4-14). As for second-line therapy, 68 (70.1%) patients received continuous immunotherapy beyond progression, including 39 with immunochemotherapy±local radiotherapy, 15 with immunotherapy±local radiotherapy and other 14 patients with anti-angiogenic therapy plus immunotherapy or immunochemotherapy. A total of 29 (29.9%) patients received chemotherapy±local radiotherapy without immunotherapy as second-line therapy, and 9 of above patients received anti-angiogenic agents at the same time. The continuous immunotherapy group showed longer second-line PFS (mPFS of second-line therapy) of 4.2 months (95%CI: 3.4-5.0) compared with 3.2 months (95%CI: 2.2-4.1, p=0.126) for chemotherapy group, excluding patients treated with anti-angiogenic agents. The second-line PFS of 23 patients receiving anti-angiogenic therapy such as anlotinib and sorafenib (14 in combination with immunotherapy or immunochemotherapy and 9 in combination with chemotherapy) was 5.3 months (95%CI: 3.5-7.1), indicating combined anti-angiogenic therapy may yield better survival benefit for ES-SCLC patients treated with first-line immunochemotherapy. Overall survival data is currently immature.

Conclusions: Continuous ICIs beyond progression in ES-SCLC provide a favorable prognosis tendency. Anti-angiogenic agent containing strategy may further improved survival after first-line immunochemotherapy. The long-term efficacy is still under follow-up.

Keywords: small cell lung cancer, immunotherapy beyond progression, chemotherapy

EP.13B SMALL CELL LUNG CANCER AND NEUROENDOCRINE TUMORS - IMMUNOTHERAPY/SYSTEMIC THERAPY
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EP.13B.12 Chemotherapy Sensitivity for Recurrent Small-Cell Lung Cancer Based on Chemotherapy-Free Interval and Treatment Regimens

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Introduction: Small-cell lung cancer (SCLC) is an aggressive subtype of lung cancer. Most cases are diagnosed at advanced stages. Despite the high response rate to initial treatment, most cases experience disease recurrence. In cases whose disease recurs at least 3 or 6 months after the last initiation of cytotoxic chemotherapy, re-challenge of the first-line regimen is considered the standard of care due to the lack of effective treatment options for recurrent SCLC. The definition of sensitive relapse differs between treatment guidelines. ESMO and Japan's Lung Cancer Association guidelines define sensitive relapse as cases that experienced chemotherapy-free interval (CTFI) of 90 days after the initial response, whereas the threshold of CTFI of sensitive relapse for NCCN guidelines is 180 days. The concept of sensitive relapse was established before the advent of amrubicin (available in Japan) and lurbinectedin (recommended in ESMO and NCCN guidelines), which are effective for recurrent SCLC.

Methods: We retrospectively analyzed sequential 206 cases with SCLC who started first-line treatment from January 2014 to December 2023 at Osaka Toneyama Medical Center. Twenty-nine patients received ICI+platinum doublet, and 36 were treated with chemoradiotherapy. We analyzed the treatment sequence and response for SCLC.

Results: At the time of the abstract submission, 183 cases experienced disease recurrence (CTFI<90 109 cases, 90<CTFI<180 41 cases, CTFI>180 33 cases). Among 74 sensitive relapse cases, 63 received second-line chemotherapy. Some reasons for not receiving second-line therapy in 11 patients included rapid deterioration of the patient's condition due to disease progression, development of other malignancies, and patients' refusal of treatment. Thirty-four were treated by platinum-doublet re-challenge, and 29 received monotherapy of amrubicin, topotecan, or irinotecan. One patient received an ICI combination regimen for second-line therapy. In 90<CTFI<180 group, response rates to platinum-doublet rechallenge and monotherapy were 19% and 35%, respectively. In CTFI>180 groups, response rates to re-challenge and monotherapy were 56% and 33%, respectively. Phase 3 trials, CASPIAN and Impower133, proved that the addition of ICI to platinum+VP-16 helped improve overall survival and duration of response in patients with advanced SCLC, even with a similar response rate to conventional platinum-doublet chemotherapy. However, more than half of patients experience progression of disease within 90 days from the last dose of first-line cytotoxic chemotherapy. Treatment choice for chemotherapy resistance is crucial, but treatment options are limited.No major amendment to the definition of refractory/sensitive relapse has not been performed for about 20 years. In our limited analysis, response rates by monotherapy for recurrent SCLC were consistent regardless of CTFI. In contrast, platinum doublet rechallenges presented promising responses only in patients with CTFI>180. However, there is not enough data on the safety and efficacy of second-line chemotherapy following ICI combination regimens for SCLC.

Conclusions: PSF in first-line chemotherapy has been proven to be a surrogate marker of survival for SCLC. Treatment option with high response is warranted to improve the outcome of SCLC. It is still unclear whether the response of second-line chemotherapy following ICI is elevated compared to conventional chemotherapy. Further investigation is needed.

Keywords: Small-cell lung cancer, chemotherapy-free interval, refractory relapse

EP.13B SMALL CELL LUNG CANCER AND NEUROENDOCRINE TUMORS - IMMUNOTHERAPY/SYSTEMIC THERAPY
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EP.13B.13 Radioactive Seed Implantation Combined with PD-L1 Antibody and Chemotherapy Gt in the First-Line Treatment of ES-SCLC: A Retrospective Study.

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Introduction: Radioactive seed implantation (RSI) combined with immune checkpoint inhibitor PD-L1 antibody and chemotherapy can not only reduce the occurrence of radiation damage, but also potentially induce more abscopal effects and improve the efficacy of anti-tumor treatment. Small cell lung cancer (SCLC) is one of the deadliest cancers in humans, with a 5-year survival rate of less than 7%. This study analyzes the clinical efficacy of patients receiving RSI combined with PD-L1 antibody and chemotherapy, aiming to explore the first-line combined treatment model for ES-SCLC.

Methods: Retrospective collection of 21 ES-SCLC patients who received PD-L1 antibody and chemotherapy combined with RSI treatment from July 2020 to March 2024. Received PD-L1 antibody, etoposide, Cisplatin or carboplatin treatment every 3 weeks for a total of 4 cycles; Percutaneous RSI is performed 3-10 days before the first cycle. The treatment plan is developed based on the patient's CT image. The prescribed should be 110~160 Gy. Until the disease progresses significantly, intolerable toxicity or death.

Results: This study included a total of 21 samples, 15 males and 7 females, with a median age of 64 years, 62% of patients were smokers, 7 patients had mediastinal metastasis, 4 patients had bone metastasis. The Median PFS was 10.0 month; Median OS was 14.0 month, 3 patients experienced Grade 3/4 drug-related adverse reactions, and 1 patient discontinued medication. Because the number of patients is less, the OS data is not mature.

Conclusions: RSI combined with PD-L1 antibody and chemotherapy is safe and feasible in the first-line treatment ES-SCLC, and could effectively control the recurrence and metastasis of the disease.

Keywords: Radioactive seed implantation, Immunotherapy, ES-SCLC

EP.13B SMALL CELL LUNG CANCER AND NEUROENDOCRINE TUMORS - IMMUNOTHERAPY/SYSTEMIC THERAPY
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EP.13B.14 Extensive Small Cell Lung Cancer (SCLC): Maintenance Oral Etoposide Daily for 6 Days Every 3-4 Weeks Until Tumor Progression

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Introduction: For extensive SCLC, progression-free survival (PFS) curve log-linear plots are moderately or highly convex due to rapid tumor regrowth following induction chemotherapy[1]. Three cycles of maintenance oral etoposide (50 mg/m2/day x 21 days q28 days) improved PFS[2].

Methods: From early 2020, patients who were progression-free 3 weeks following 4-6 cycles of induction carboplatin plus etoposide were considered for maintenance oral etoposide using a convenient schedule (100 mg/m2/day for 6 days). Treatment was continued until progression. Cycles were repeated every 3 weeks. From mid 2022, durvalumab 1500 mg q28days was publicly funded in Canada and was given with oral etoposide. With durvalumab, etoposide schedule was adjusted to 100 mg/m2/day x 6 days q28days. Patients from 2018 onwards who received no maintenance therapy but were progression-free 3 weeks post induction chemotherapy served as a comparison group.

Results: Fifteen patients received no maintenance, 14 received etoposide alone and 19 received etoposide plus durvalumab. From 3 weeks post day 1 of last cycle of induction treatment, median PFS was 51 days for no treatment, 176 days for etoposide alone, 166 days for etoposide + durvalumab, and 166 days for the 33 patients with any etoposide (alone or with durvalumab) (p=0.02 across the 3 groups, p=0.006 and hazard ratio 0.43 for any etoposide vs none, p=0.98 and hazard ratio 1.01 for etoposide +durvalumab vs etoposide alone). Median post induction overall survival (OS) was 207 days with no maintenance, 293 days with etoposide alone, 313 days with etoposide +durvalumab and 315 days for etoposide +/- durvalumab (p=0.04 across all groups, p=0.03 and hazard ratio 0.49 for any etoposide vs none and p=0.68, hazard ratio 0.84 for durvalumab +etoposide vs etoposide alone). From initiation of induction chemotherapy, PFS was 188 days with no maintenance, 330 days with etoposide alone, 265 days with etoposide +durvalumab and 284 days for etoposide +/- durvalumab (p=0.24 across all groups, p=0.04 and hazard ratio 0.52 for any etoposide vs none and p=0.34, hazard ratio 1.41 for durvalumab +etoposide vs etoposide alone). From initiation of therapy, OS was 338 days with no maintenance, 429 days with etoposide alone, 456 days with etoposide +durvalumab, and 456 days for etoposide +/- durvalumab (p=0.14 across all groups, p=0.047 and hazard ratio 0.52 for any etoposide vs none and p=0.99, hazard ratio 1.001 for durvalumab +etoposide vs etoposide alone). Maintenance oral etoposide was well tolerated and demonstrated no cumulative toxicity.

Conclusions: This preliminary assessment suggests maintenance oral etoposide until progression prolongs PFS and OS. Since patient numbers are small and treatment assignment was by selection, results require confirmation. The apparent lack of added benefit from durvalumab could be due to small patient numbers. Alternatively, it might have arisen from change of etoposide to a potentially less effective 4-week schedule from a 3-week schedule when durvalumab is used. We have initiated assessment of maintenance oral etoposide with atezolizumab (3-week schedule), which has comparable efficacy to durvalumab. References: 1. Stewart DJ et al. Crit Rev Oncol Hematol 2020;153:103039. 2. Hanna N et al. Ann Oncol 2002;13;95-102

Keywords: small cell lung cancer, maintenance, oral etoposide

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EP.13B.15 Radiotherapy Combined with Immunotherapy in the Treatment of Brain Metastases from Small Cell Lung Cancer

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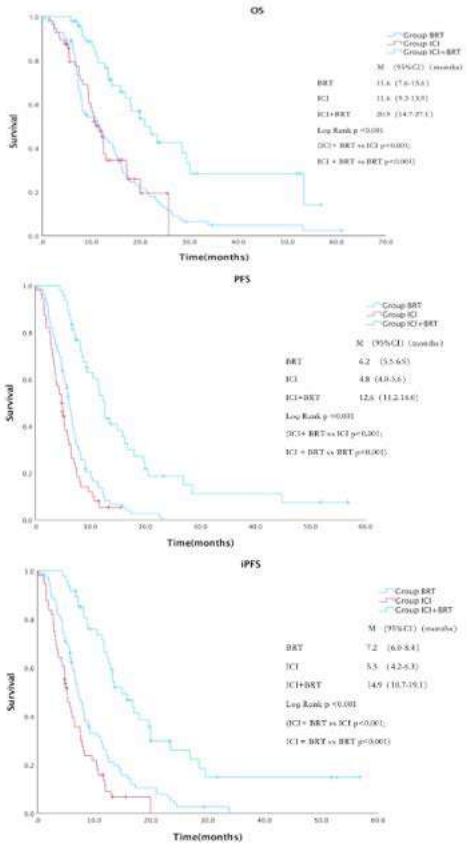
Introduction: To explore the efficacy and safety of the combination of brain radiationtherapy (BRT), chemotherapy and immune checkpoint inhibitors (ICI) in the treatment of brain metastases in patients with Extensive stage small cell lung cancer(ES-SCLC).

Methods: A retrospective analysis of 187 patients with ES-SCLC brain metastases treated from January 2017 to October 2023 in Zhejiang Cancer Hospital was performed. They were divided into BRT group, ICI group and brain radiotherapy-immunotherapy combination treatment (ICI+BRT) group based on the different first-line treatment regimens.The first-line treatment regimens of the three groups of patients included chemotherapy. The differences in age, number of brain metastases, symptoms of brain metastases, underlying diseases, KPS score, smoking history, GPA score and survival time among the three groups were evaluated separately. Cox's proportional risk regression model was used to conduct univariate and multivariate analyses of prognostic factors. Finally, the differences in efficacy were assessed between the synchronized group (ICI and BRT interval ≤4w) and the asynchronized group (ICI and BRT interval >4W).

Results: The median overall survival (OS) was 11.6 months, 11.6 months and 20.9 months in the BRT, ICI and ICI+BRT groups respectively ($p < 0.001$). Median progression-free survival (PFS) was 6.2 months, 4.8 months and 12.6 months ($p < 0.001$) respectively. The median intracranial progression-free survival (iPFS) was 7.2 months, 5.3 months and 14.9 months respectively ($p < 0.001$). Systemic and intracranial ORR and DCR were also significantly superior in the ICI+BRT group. No statistically significant difference was seen between the BRT group and ICI+BRT group at Classification criteria for acute radiation injury (Central nervous system) ($p = 0.314$). Multivariate Cox regression showed that the first-line regimen, chemotherapy cycles ≥4, bone metastases, number of brain metastases ≥3, ICI cycles ≥6, second to multiple lines antiangiogenesis targeted therapy and first-line extracranial radiotherapy had an impact on patients' OS. Immunotherapy regimen (atezolizumab, serplulimab) and radiotherapy regimen (WBRT, WBRT+boost) had a certain degree of efficacy for patients. In the synchronized group compared with the asynchronized group, PFS (P=0.013) and iPFS (P=0.029) had a significant advantage.The rest of the main therapeutic indexes and the incidence rate of adverse reactions did not show any statistically significant differences.

Conclusions: Under the premise of universal use of chemotherapy, ICI+BRT as the first-line therapy for patients with baseline ES-SCLC brain metastases has better efficacy than ICI or BRT alone.There is a trend that ICI asynchronous BRT therapy is superior to ICI synchronous BRT therapy.

Keywords: small cell lung cancer, brain radiotherapy, immunotherapy



EP.13C SMALL CELL LUNG CANCER AND NEUROENDOCRINE TUMORS - LOCAL THERAPY/LIMITED-STAGE
SATURDAY, SEPTEMBER 7, 2024 - 11:58 - 11:59

EP.13C.01 Prognosis of Surgically Resected Pure and Combined Small Cell Lung Cancer Undergoing Adjuvant Chemotherapy

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Introduction: Small cell lung cancer (SCLC) accounts for approximately 10-15% of all lung cancers. It is characterized by rapid proliferation and high malignancy, often resulting in early lymph nodes and distant metastases. Adjuvant chemotherapy following surgical resection is recommended for cases of SCLC to improve outcomes. Within the spectrum of SCLC, approximately 5-28% of cases exhibit components of non-small cell lung cancer (NSCLC) histological subtypes, termed combined SCLC. However, there is limited research comparing the prognosis of patients undergoing adjuvant therapy after surgical resection for histopathologically diagnosed pure SCLC versus combined SCLC.

Methods: We retrospectively reviewed the medical record system, and conducted analysis on 65 patients diagnosed with limited disease SCLC (LD-SCLC) who underwent surgical resection and adjuvant chemotherapy between January 1, 2008, and August 14, 2023 in National Cancer Center Hospital, Japan. Patients were categorized into two groups based on histopathological diagnosis; pure SCLC (43 patients) and combined SCLC (22 patients). Disease free survival (DFS) and overall survival (OS) curves were analyzed for both groups using EZR software.

Results: Among the 65 participants, the median follow-up period was 2.7 years. The median age at surgical resection was 71 y (range 47-84 y), with 52 patients (80%) aged 65 years or older. There were 54 male (83%) patients. The adjuvant chemotherapy regimens administered were as follows: carboplatin+etoposide (ETP) was given to 17 patients in the pure SCLC group and 8 in the combined SCLC group, cisplatine (CDDP)+ETP to 8 patients in the pure SCLC group and 9 in the combined SCLC group, and CDDP+irinotecan (IRI) to 8 patients in the pure SCLC group and 3 in the combined SCLC group.The median DFS for pure SCLC was 115.4 months (95% CI 54.2-NA), which was longer than that of combined SCLC (24.2 months (95% CI 17.5-NA)). Similarly, the median OS for pure SCLC was 115.4 months (95% CI 90.4-NA), while the arm of combined SCLC has not reached. While there was no statistically significant difference in DFS and OS between the two groups, a trend towards poorer prognosis in the combined SCLC group was observed.

Conclusions: No statistical significance was observed in DFS and OS between pure and combined SCLC groups, however the divergence in the survival curves suggests a potential poorer prognosis in combined SCLC. Further investigation should include histopathological patterns of relapse on account of the heterogeneity of combined SCLC.

Keywords: LD-SCLC, combined SCLC, adjuvant chemotherapy

EP.13C SMALL CELL LUNG CANCER AND NEUROENDOCRINE TUMORS - LOCAL THERAPY/LIMITED-STAGE
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EP.13C.02 High-Dose Radiation Therapy for Limited-Stage Small-Cell Lung Cancer: Real-World Experience from Two Tertiary Centers

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Introduction: A recent phase 2 clinical trial by Gronberg et al. have demonstrated improved survival outcomes with high-dose, twice-daily radiation therapy (RT) for limited-stage small-cell lung cancer (LS-SCLC). However, this regimen has not been widely adopted in routine practice. This study evaluates the real-world experience of dose-escalated RT in LS-SCLC patients treated at two tertiary centers.

Methods: We retrospectively reviewed consecutive LS-SCLC patients treated with concurrent chemoradiation using a high-dose, twice-daily RT regimen (60 Gy in 40 fractions over 4 weeks) between 2020-2023. Baseline characteristics, oncologic outcomes (progression-free survival [PFS], overall survival [OS], patterns of failure, response rates), and RT-related toxicity were evaluated. Dosimetric parameters, including gross tumor volume (GTV) and lung dose, were collected.

Results: Thirteen patients were included, with a median age of 59 years and 61.5% female. The median follow-up time was 27 months. The majority (92.3%) completed the planned RT course. The median OS was 30.9 months (95% CI:14.3-NR), and the median PFS was 9.1 months (95% CI: 6.1-NR). Best response rates were: complete response (CR) 46.2%, partial response (PR) 15.3%, progressive disease (PD) 23.1%, and non-evaluable 15.4%. Among patients with progression, only 1 (7.7%) had local failure, while the rest experienced distant metastases. Common adverse events included esophagitis (69.2%; Grade 1-2: 61.5%, Grade 3: 7.6%), neutropenia (61.5%; Grade 1-2: 23%, Grade 3-4: 38.4%), and pneumonitis (38.4%, all Grade 1). No Grade 5 events occurred. The median GTV was 156 cc (range: 36-444), and the mean lung dose was 15.03 Gy (range: 7.9-24).

Conclusions: In this real-world experience, high-dose RT (60 Gy in 40 fractions over 4 weeks given twice daily), for LS-SCLC resulted in promising response rates, excellent local control, and favorable early survival outcomes. These findings, consistent with the previous phase 2 trial, support the broader implementation of this intensive regimen in clinical practice.

Keywords: Small cell lung cancer, Radiation, Dose escalation

Table 1: Characteristics of patients at baseline

Variable (at diagnosis)		**All**, n (%)
All patients, n (% of all)		13 (100)
Age, median (range)		59 (46-70)
Sex	Male	5 (38.4)
	Female	8 (61.5)
ECOG performance status	0	8 (61.5)
	1	5 (38.4)
Disease stage	IIIA	3 (23)
	IIIB	6 (46)
	IIIC	1 (7)
	IV	3 (23)
Smoking status	Former	4 (30.7)
	Current	9 (69.2)

Table 2: Treatment outcomes and adverse events

Variable		n (%)
Any Chemotherapy dose reduction		2 (15.3)
Concurrent platinum agent	Cisplatin	7 (53.8)
	Carboplatin	5 (38.4)
	n/a	1 (7.7)
Completed radiation therapy		12 (92.3)
Response to chemoradiotherapy	Overall Response	8 (61.5)
	Complete response	6 (46.1)
	Partial response	2 (15.4)
	Stable disease	0
	Progressive disease	3 (23)
	n/a	2 (15.4)
Adverse evens		
Esophagitis	Grade 1-2	8 (61.5)
	Grade 3-4	1 (7.6)
Neutropenia	Grade 1-2	3 (23)
	Grade 3-4	5 (38.4)
Pneumonitis	Grade 1-2	5 (38.4)
	Grade 3-4	0

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EP.13C.03 Investigating Surgery's Role in Stage IIB-IIIB Small Cell Lung Cancer Following Chemo-immunotherapy

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Introduction: The role of surgery in treating advanced stages of small cell lung cancer (SCLC), specifically stages IIB-IIIB is contentious, despite its acceptance for early-stage disease.This study assesses the efficacy of surgical intervention following chemotherapy and immunotherapy in these patients.

Methods: We retrospectively analyzed data from 11 patients with SCLC at stages IIB-IIIB treated at Guangdong Provincial People's Hospital between 2021 and 2024. All patients underwent four cycles of etoposide and platinum-based chemotherapy combined with immunotherapy, preceding surgical resection. The primary endpoint was pathological complete response (pCR), while progression-free survival (PFS) and safety were considered secondary endpoints.

Results: The study included 3 patients with stage IIB, 5 with stage IIIA, and 3 with stage IIIB. pCR was achieved in 7 (63.6%) patients, and major pathological response in 8 (72.7%). The median follow-up was 12 months (95% CI, 6.8-17.2 months), with median progression-free survival (PFS) not reached. One patient experienced disease progression characterized as distant metastasis, which occurred 9 months post-surgery. The 12-month and 18-month PFS rates were 100.0% and 75.0%, respectively, according to Kaplan-Meier estimates. During neoadjuvant therapy, 6 (54.5%) patients experienced grade 3 or higher adverse events (AEs), and 4 (36.3%) had grades 1-2 immune-related adverse events.

Conclusions: Surgery after neoadjuvant chemo-immunotherapy improves pCR and PFS in stage IIb-IIIb SCLC, with manageable AEs, supporting its consideration as a treatment strategy.

Keywords: surgery, Small Cell Lung Cancer, pathological complete response

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EP.13C.04 Is Neoadjuvant Chemoimmunotherapy Better Than Chemotherapy in Patients with Limited-Stage Small Cell Lung Cancer

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Introduction: The addition of immune checkpoint inhibitors to chemotherapy significantly improves survival in extensive-stage small cell lung cancer (ES-SCLC). However, up to now, no study has been conducted in order to compare the effect of chemoimmunotherapy with chemotherapy in the neoadjuvant for LS-SCLC. Hereby, we conduct a retrospective study in this setting.

Methods: Patients with LS-SCLC who received neoadjuvant PD-L1/PD-1 inhibitor plus platinum-based chemotherapy or platinum-based chemotherapy alone followed by surgery between Jan 2018 and Oct 2023 in our institute were included. The primary endpoints were pathologic complete response rate and major pathologic response. The second endpoints were R0 resection rate, downstaging rate and disease-free survival.

Results: Of the 51 eligible patients, 26 received neoadjuvant chemoimmunotherapy and 25 received neoadjuvant chemotherapy (Table 1). There were 39 males and 12 females across both groups combined. Mean (range) age at diagnosis was 61.6 years (43.1-74.5) for the chemoimmunotherapy group and 59.5 years (45.8-73.2) for chemotherapy group. Pathologic complete response rate was 38.5% (10/26) in chemoimmunotherapy group versus 4.0%, (1/25) in chemotherapy group (OR 7.2, 95% CI 1.4-37.3) (Table 2). Major pathologic response rate was 53.8% (10/26) in chemoimmunotherapy group versus 12.0% (3/25) in chemotherapy group (OR 8.6, 95% CI 2.0-35.8). R0 resection rate was 92.3 (24/26) in chemoimmunotherapy group versus 80.0% (20/25) in chemotherapy group (OR 3.0, 95% CI 0.5-17.2). Pathologic downstaging rate (88.5% vs 36.0) and N2 downstaging rate (68.2 vs 24.0) were higher in chemoimmunotherapy group. After a median follow up of 17.2 months, median DFS was not reached in chemoimmunotherapy group versus 11.3 (95% CI, 6.1-16.5) months in chemotherapy group.

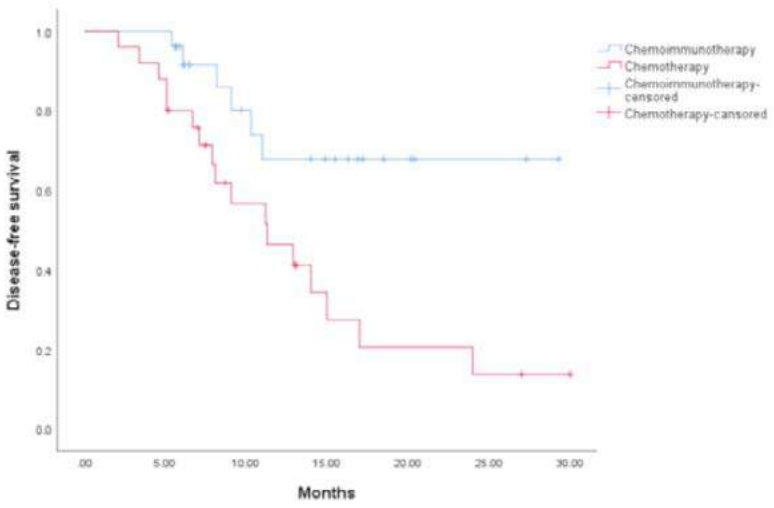
Table 1 Main results of study

Conclusions: Neoadjuvant chemoimmunotherapy demonstrated promising efficacy and feasibility, and are a potential strategy for the management of LS-SCLC. Further prospective randomized controlled trials need to explore.

Figure 1 Disease-free survival of included patients by different neoadjuvant regimens

Keywords: limited-stage small cell lung cancer, chemoimmunotherapy, neoadjuvant

Table 1 Main results of study					
Endpoints	**CI Group (N = 26)**		**CT Group (N = 25)**		
N	%		N	%	
Pathologic response rate					
pCR	10	38.5	2	8.0	
MPR	14	53.8	3	12.0	
Surgical resection rate					
R0	24	92.3	20	80.0	
R1	1	3.8	2	8.0	
R2	0	0	0	0.0	
Ru	1	3.8	3	12.0	
Downstaging rate					
Pathological	23	88.5	9	36.0	
Clinical	20	76.9	18	72.0	
N2	15	68.2	6	24.0	



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EP.13C.05 Factors Affecting Outcomes of Limited Stage (IIB-IIIC) Small Cell Lung Cancer: An Analysis of the National Cancer Database.

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Introduction: Limited stage small cell lung cancer stage IIB-IIIC (T3-T4, any N, M0) is typically treated with chemoradiation. A retrospective analysis of the National Cancer Database (NCDB) was conducted to identify factors associated with worse outcomes.

Methods: Patients with limited-stage small cell lung cancer (T3-4, N any, M0) diagnosed between 2010 and 2020, were identified from the NCDB. The following information was abstracted: age, sex, race, type of insurance, facility type, and treatment. Treatments received included: no treatment, surgery only, and chemotherapy + radiation (concurrent or sequential). Factors associated with survival were assessed using the Cox proportional hazards model.

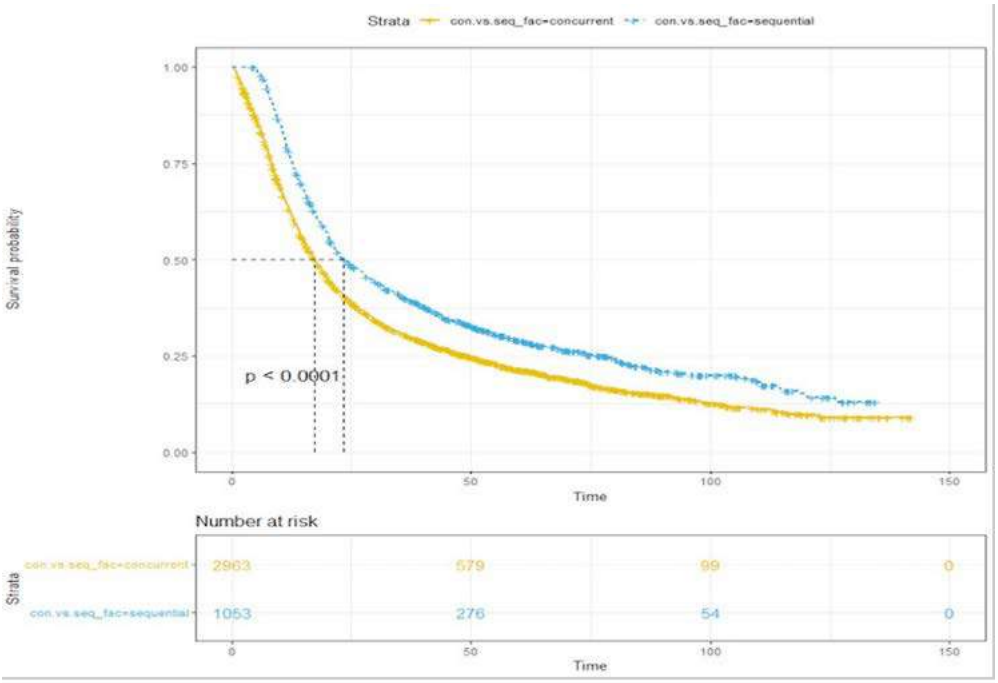
Results: This cohort included 2534 patients <65 years of age, 2915 between 65-75 years, and 1668 >75 years of age. The median overall survival (OS) for this group was 11.3 months (14.0, 12.65, and 6.01 months for the three age groups respectively). Factors associated with worse overall survival were: age > 75 (HR= 1.26 P <0.001), Age 65-75 (HR= 1.10 P=0.005), Male sex (HR= 1.15 P <0.001), year of diagnosis 2010-2015 (HR= 1.20 p= <0.001). Better OS was noted in Other races (races other than Caucasian, African American, and Native American) (HR= 0.55 p= 0.008). Better OS was also noted in patients who had private insurance (as compared to Medicare or uninsured patients) (HR= 0.91 p=0.01).

Patients who received chemoradiation were divided into two groups: concurrent and sequential chemoradiation. Patients who underwent sequential chemotherapy and radiation had a median overall survival of 23.3 months (95% CI 21.6-27.2) compared to concurrent chemoradiation who had a median overall survival of 17.4 months (95% CI 16.6-18.4) (p< 0.001) (Figure 1).

Conclusions: For patients with (T3-4, N any, M0) small cell lung cancer, overall survival was lower in patients who were >75 years of age as compared to those who were <65 years of age. Other factors associated with worse outcomes include male sex and diagnosis between 2010-2015. Better outcomes were noted in patients who had private insurance. Patients who underwent sequential chemotherapy and radiation had significantly improved overall survival as compared to patients who underwent concurrent chemotherapy and radiation, contrary to previous findings.

Figure;1- Overall survival in patients who underwent concurrent chemotherapy and radiation (yellow) vs sequential chemotherapy and radiation (blue).

Keywords: small cell lung cancer, limited stage, overall survival



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EP.13C.06 Feasibility of Hippocampal Sparing Radiotherapy in Lung Cancer Patients Requiring Cranial Irradiation (HSWBRT-LC)

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Introduction: Hippocampal Sparing Whole Brain Radiotherapy (HSWBRT) mitigates cognitive decline, thereby enhancing the quality of life for patients. This study assesses the feasibility of HSWBRT in lung cancer patients receiving cranial irradiation for prophylactic or therapeutic purposes and aimed to determine its impact on neurocognitive function and quality of life (QoL).

Methods: In this prospective study (2021-23), histopathologically proven 15 lung cancer patients requiring prophylactic cranial RT or WBRT due to brain metastasis (>5mm from hippocampus) were treated with HSWBRT. All patients underwent neurocognitive testing with Montreal Cognitive Assessment (MOCA) test, Trail A and B, Controlled Oral Word Association Test (COWAT), and QoL assessment with EORTC QLQ BN20 and C30 at baseline and then at 2, 4, 6, 9 and 12 months. The primary objective was to assess the neurocognitive function and QOL. Secondary objectives included determining intracranial relapse rates in those undergoing PCI, and overall survival (OS). These scores were compared with retrospectively collected QoL and neurocognitive scores of 15 lung cancer patients who underwent whole-brain radiotherapy without hippocampal avoidance (prophylactic or therapeutic). Differences between the baseline scores between the two groups were compared using the Chi-square test and the impact of HSWBRT was assessed using repeated measures ANOVA. Kaplan Meier curves were used for survival analysis and comparison between the two groups was done using log-rank test. All statistical analysis was done using SPSS version 23 and p-value<0.05 was considered as statistically significant. The trial has been approved by the Institute Ethics Committee (IEC/2021/SP6-865).

Results: There was no significant difference in the baseline characteristics of patients in HSWBRT and WBRT group. The median follow-up was 19 months (HSWBRT 14 vs WBRT 22, p=0.045) months. There was no significant difference in the intracranial relapse rates or overall survival between the two arms. There was no significant difference in the baseline cognitive function scores between the two arms but the risk of self-reported cognitive failure (as per QLQ C30) was lower in HSWBRT arm compared to WBRT at 12 months (scores at baseline 100 in both arms, 6 months 83.33 in both arms, 12 months: 83.33 in HSWBRT vs 66.67 in WBRT, p=0.072). Similar results were also observed in QoL analysis where the scores remained stable both at baseline and 6 months in HSWBRT arm but showed a steady decline in the WBRT arm (baseline 83.33 in both arms, 83.33 in HSWBRT vs 66.67 in WBRT, p=0.069). In the HSWBRT arm, the MOCA scores remained stable throughout even at 12 months post-treatment completion. Time required to complete Trails A and B test improved at 2 months post treatment completion in HWBRT arm (p=0.056 for Trail A and 0.06 for Trail B), then showed a slight non-significant rising trend at 4-6 months after which the scores were stable at 9 and 12 months and remained below the baseline value.

Conclusions: The utilization of HSWBRT in this study demonstrates promising outcomes in safeguarding neurocognitive function and enhancing quality of life without increase in intracranial relapse rates.

Keywords: cranial irradiation, hippocampal sparing, lung cancer

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EP.13C.07 Long-Term Oncological Outcomes of Resected Bronchopulmonary Neuroendocrine Tumors

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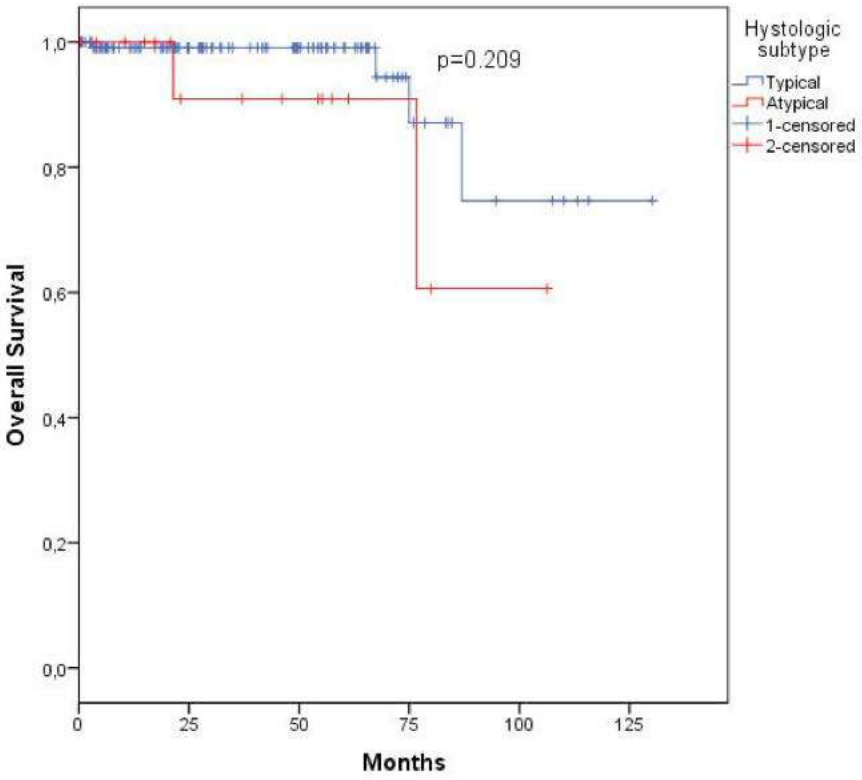
Introduction: Bronchopulmonary neuroendocrine tumors (bpNET) are well-differentiated malignancies with an overall favorable prognosis. Primary surgical resection is considered the gold standard treatment for this disease. The present study analyzes the results of lung resections for bpNET, both typical carcinoid (TC) and atypical carcinoid (AC), in a tertiary Thoracic Oncology Center.

Methods: A retrospective review of a single institution prospectively collected database was performed. Between January 2013 and December 2023, all consecutive patients (>18 years-old) who underwent curative-intent surgical resection for histopathological confirmed bronchopulmonary neuroendocrine tumors were included. Demographics, clinical, surgical and pathological data were evaluated. Patients were divided in two groups according to the histologic subtype. The primary outcome was long-term overall survival.

Results: A total of 142 patients were included, 124 with TC and 18 with AC. Baseline characteristics and comparisons for the two subgroups are described in Table 1. The median follow-up for all patients was 29 months (IQR 10-60). The median in-hospital length of stay was 4 days. Seventy-eight (54.9%) patients were approached using a video-assisted thoracic surgery (VATS) approach, requiring 10 conversions. Of the 142 patients analyzed, 4 bilobectomies, 68 lobectomies, 20 segmentectomies, 46 wedge resections, and 4 bronchial sleeve resections without lung resection were performed.Only 1 patient died because of bpNET. The 10-years overall survival was 71.6%. The mean survival time for the TC group was 116 months and for the AC group it was 89.6 months, (p=.209). Kaplan-Meier curves are shown in the

Conclusions: In this retrospective cohort study, we observed an overall favorable long-term prognosis for patients undergoing surgical resection for bpNET. There was a trend for longer median overall survival in the TC group comparative to the AC group, not achieving a statistically significant difference, possibly related to the study sample size.

Keywords: Neuroendocrine Tumor, Surgery, Thoracic, Patient Outcomes Assessment



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EP.13C.08 Leukoencephalopathy and Brain Metastasis in LS-SCLC Patients with and without PCI after Curative Thoracic RT

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Introduction: Our aim was to compare the risk of leukoencephalopathy and brain metastasis in patients with and without prophylactic cranial irradiation (PCI) of limited stage small cell lung cancer (LS).

Methods: Retrospective review of the chart from 2012 to 2022 was done for all LS patients who received curative thoracic radiotherapy (TRT) in our institution. Out of them patients who had undergone screening brain magnetic resonance imaging (MRI) before and after TRT was chosen. Overall survival (OS), progression free survival (PFS), brain metastasis free survival (BFS), and leukoencephalopathy worsening free survival was calculated and compared between the two groups. Pre-therapeutic and sequential MRIs after TRT were analyzed for leukoencephalopathy based on the modified Fazekas (MF) score by two neuroradiologists blinded to patients PCI use. MF score of one or more was regarded as worsening. Kaplan-Meier method and log rank test were used for the univariate and Cox regression analysis was used for the multivariate analysis.

Results: There were 15 female and 39 male. The median age was 67.5 (range: 50-78) years. Out of them two were patients of local recurrence after TRT. PCI was performed in 15 patients (PY) and omitted in 39 patients (PN). Median follow up was 61.5 (range: 53-293) months. MF before TRT was 1 in 45 patients, 2 in 5 patients and 3 in 4 patients. MF was worsened in 13 patients (PY 6, PN 7). OS showed a trend (5year, PY 93%, PN 66%, p=0.07) and, PFS (5year, PY 58%, PN 31%, p<0.01) and BMS (5year, PY 91%, PN 43%, p<0.01) showed statistically significant difference. These has not changed if, age, stage, recurrence/du novo were added as confounding variables in the multivariate analysis. MF scored worsening did not showed any significant difference (5year, PY 18%, PN 62%, p=0.21). This did not changed if age was added as a confounding variable in the multivariate analysis.

Conclusions: In this study the use of PCI for LS patients significantly reduced the PFS and BFS but even statistically not significant 40% of the patients in the PY showed worsening of the MF.

Keywords: PCI, Leukoencephalopathy, small cell lung cancer

EP.13D SMALL CELL LUNG CANCER AND NEUROENDOCRINE TUMORS - PROGNOSIS/BIOMARKERS
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EP.13D.01 Prognostic Factors and Outcomes of Large Cell Neuroendocrine Carcinoma of Lung: A Single Center Retrospective Cohort Study

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Introduction: Pulmonary large cell neuroendocrine carcinoma (LCNEC) is a rare entity that is historically associated with poor outcomes and underrepresented in clinical trials. The molecular landscape and optimal treatment options and sequence are not well defined. Herein, we set out to review the prognostic factors and outcomes of patients with pulmonary LCNEC.

Methods: All consecutive patients with pulmonary LCNEC in 2000 - 2022 treated in single tertiary institution were reviewed. Clinical characteristics, molecular profile, treatment modalities and outcomes were recorded. Survival time was estimated with Kaplan-Meier analyses.

Results: Forty-one patients (35 male, 6 female) were included in this study. The median age at diagnosis was 66.4 years (43.3 - 85.7). A strong association with active smoking status was identified (32 patients, 78.0%, p = 0.002), in particularly for male patients (88.6% of male vs. 16.7% of female, p = 0.002). At diagnosis, twenty-eight patients (68.3%) were diagnosed with node positive disease, of which twenty-five (61%) were with N2 or above nodal status. Twelve patients (29.3%) had distant metastases at presentation. Twenty-five patients received definitive treatment, of which nineteen received surgery and eight patients received chemoirradiation (2 overlap between two groups). Eight patients (32.0%) received adjuvant chemotherapy after surgery, with the most common regime being Etoposide-platinum based. For those ineligibles for definitive treatment, twelve patients (80%) received palliative systemic therapy, with the majority exposing to etoposide-based chemo (66.7%) with a median response of 3 months. At a median follow-up of 8.4 years, twenty-one (85.2%) patients who underwent primary treatment developed disease recurrence. The median time to recurrence was 9.2 months (range, 3.2 - 30.1 months), and the 5-year recurrence free survival at 9.3%. The median overall survival of those who received surgery and chemoirradiation was 23.9 months and 14.8 months, respectively. The median overall survival of those who were ineligible for definitive treatment was 6.9 months (3.1 - 74.4 months). Male sex is suggested to be correlated with shorter survival (HR 8.5, p = 0.096), but smoking status (HR1.18, p = 0.882) and presence of mutation status (HR 1.37, p = 0.723) were not. Twenty patients had molecular diagnostic studies performed on their pathology specimens, and 6 patients (30.0%) were identified with druggable targets, namely EGFR mutation (3 patients), ALK overexpression (2 patients) and RET translocation (1 patient). Presence of druggable targets was found to be associated with female sex (female 75.0% vs. male 18.8%, p = 0.061) and in non-smokers (non-smoker 83.3% vs. smoker 7.1%, p = 0.02). All six patients eventually received corresponding palliative treatments with tyrosine kinase inhibitors, with five patients (83.3%) achieving at least partial response. The duration of response was variable, ranging from 2 months to 65 months.

Conclusions: Our series echoed the prior literature suggestions that LCNEC remain an aggressive subtype of non-small cell lung cancer with high recurrence rate post definitive treatment. Molecular diagnostic studies were able to identify druggable mutations in a sizable portion of patients that is higher than has been traditionally reported, highlighting a potential role of personalized treatment.

Keywords: large cell neuroendocrine carcinoma of lung, Prognostic factors, Molecular Diagnostics

EP.13D SMALL CELL LUNG CANCER AND NEUROENDOCRINE TUMORS - PROGNOSIS/BIOMARKERS
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EP.13D.02 Low to Intermediate Grade Lung Neuroendocrine Tumours. A Single Centre Real World Experience

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Introduction: Lung neuroendocrine tumours (LNETs) are a rare heterogenous group of tumours with varying clinical behaviours, whose incidence has been increasing. We aimed to investigate the diagnosis, treatment, and survival patterns of patients with low to intermediate grade LNETs.

Methods: With ethics board approval, a retrospective chart review of patients with confirmed low to intermediate grade LNETs, treated at a Canadian tertiary level cancer centre from June 2010 to June 2021 was performed. Demographic, staging, treatment, and survival data were collected and analyzed.

Results: We identified 60 patients: median age 65.5; 68.3% female; average Charlson Comorbidity Index 3.5. Pathological grade was only available for 24/60 patients and differentiation available for 31/60 patients. Where reported, most were G1 (n=8) or G2 (n=10) and well (n=22) or moderately differentiated (n=8). Mitotic rate was frequently documented (n=45) and 51.7% had mitotic rates less than 2. Ki67 proliferative index was also commonly reported (n=53) with an index of less than 20% in 48/60 patients. Radiologic staging with octreotide scintigraphy was performed in 19 patients and Ga68 in only 5 patients. Forty-eight patients presented with local or locally advanced disease, of which 27 (56.2%) received curative intent surgery, with the rest receiving either radiation or palliative systemic treatment including chemotherapy or octreotide. The 5-year overall survival (OS) for those treated surgically was 84% compared to 44% in the non-surgical group. Metastatic disease was seen in 24/60 (40%) patients, with a 5-year OS in patients with stage 4 disease of 39%. Of those with advanced or unresectable disease (n=33), 26 received palliative systemic treatment with up to 3 lines of therapy. First-line treatment was most commonly chemotherapy with platinum and etoposide combination or somatostatin analogue therapy. Second-line treatment involved targeted everolimus in 5 patients and chemotherapy in 4. PRRT was also used once as a first-line and once as second-line therapy. Third-line included lanreotide or chemotherapy with capecitabine and temozolomide combination.

Conclusions: Overall, patients with surgically resectable disease had a good 5-year OS. However, inoperable or more advanced disease was associated with a poorer OS and despite a variety of different treatment options, the sequence of treatments is not well established. A number of patients received 1L chemotherapy despite low Ki67 %. This highlights the need for further research or treatment guidelines for LNET patients.

Sequence of palliative treatment options in patients with advanced or unresectable disease.

Keywords: Lung neuroendocrine tumors, Ki67, Treatment lines

Patient ID	First line option	Second line option	Third line option	Number of total lines	Ki67 range at baseline
TOH_194	Platinum, Etoposide	None	None	1	20-50
TOH_201	Doxorubicin	None	None	1	20-50
TOH_202	Platinum, Etoposide	None	None	1	10-20
TOH_203	Platinum, Etoposide	None	None	1	Unknown
TOH_209	Platinum, Etoposide	None	None	1	10-20
TOH_217	Octreotide	None	None	1	2-5
TOH_234	Platinum, Etoposide	None	None	1	2-5
TOH_235	Octreotide	None	None	1	<2
TOH_236	Lantreotide	None	None	1	2-5
TOH_237	Octreotide	None	None	1	<2
TOH_243	Capecitabine, Temozolomide	None	None	1	5-10
TOH_244	Platinum, Etoposide	None	None	1	10-20
TOH_246	Everolimus	None	None	1	10-20
TOH_247	Lantreotide	None	None	1	10-20
TOH_252	Platinum, Etoposide	None	None	1	2-5
TOH_264	Lantreotide	None	None	1	2-5
TOH_193	Doxorubicin	Cisplatin, Etoposide	None	2	5-10
TOH_222	Platinum, Etoposide	Everolimus	None	2	5-10
TOH_239	Capecitabine, Temozolomide	Everolimus	None	2	2-5
TOH_249	Platinum, Etoposide	Doxorubicin	None	2	20-50
TOH_258	Doxorubicin	Everolimus	None	2	2-5
TOH_195	Platinum, Etoposide	Topotecan	Lantreotide	3	5-10
TOH_199	PRRT	Everolimus	Capecitabine, Temozolomide	3	5-10
TOH_200	Lantreotide	Capecitabine, Temozolomide	Lantreotide	3	5-10
TOH_219	Octreotide	PRRT	Lantreotide	3	5-10
TOH_255	Octreotide	Everolimus	Capecitabine, Temozolomide	3	5-10

EP.13D SMALL CELL LUNG CANCER AND NEUROENDOCRINE TUMORS - PROGNOSIS/BIOMARKERS
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EP.13D.03 Prognostic Factors of First-Line Immune Checkpoint Inhibitors in Combination with Chemotherapy in Extensive-Stage Small Cell Lung Cancer

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Introduction: Immune checkpoint inhibitors (ICIs) have demonstrated survival benefits when combined with platinum and etoposide (EP) in first-line (1L) treatment for extensive-stage small cell lung cancer (ES-SCLC). We investigated the real-world outcomes, adverse events (AEs), and prognostic factors of Taiwanese patients with ES-SCLC receiving 1L ICI + EP.

Methods: We analyzed the clinical characteristics, objective response rates, disease control rates (DCR), progression-free survival (PFS), overall survival (OS), and treatment-related AEs of patients with ES-SCLC who received ICI + EP or EP alone as 1L treatment.

Results: A total of 33 patients received ICI + EP, and 199 received EP alone. The 1L ICI + EP group had longer OS than did the 1L EP group (median: 13.93 months vs. 8.5 months, p = 0.003). Baseline liver metastasis was associated with shorter 1L PFS, whereas undergoing consolidative thoracic radiotherapy (cTRT) was associated with longer 1L PFS. Baseline liver metastasis, severe hematological AEs (grade equal or more than 3), and a neutrophil-to-lymphocyte ratio (NLR) of equal or more than 4 were associated with shorter OS.

Conclusions: Adding ICIs to 1L chemotherapy provides survival benefits in ES-SCLC, although patients receiving such therapy require close monitoring for AEs. Liver metastasis is associated with shorter PFS and OS, and cTRT may improve tumor control. Severe hematological AEs and an elevated NLR predict poor OS in patients with ES-SCLC.

Keywords: small cell lung cancer, immune checkpoint inhibitor, chemotherapy

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EP.13D.04 The Conflicting Impacts of G-CSF on the Therapeutic Efficacy of Chemoimmunotherapy for Extensive Stage Small Cell Lung Cancer

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Introduction: Granulocyte colony-stimulating factor (G-CSF) has been reported to attenuate the immune responses of T-cells by increasing immune suppressive neutrophils and myeloid-derived suppressor cells in preclinical models. However, the clinical impacts of G-CSF on the anti-tumor immune responses induced by immune checkpoint inhibitor (ICI) are still unknown. In this multi-center retrospective analysis, we investigated the impacts of G-CSF on the therapeutic efficacy of chemo-immunotherapy for extensive-stage small cell lung cancer (ES-SCLC).

Methods: We selected 65 patients with ES-SCLC who completed four cycles of induction chemo-immunotherapy (atezolizumab or durvalumab combined with carboplatin plus etoposide) in Tokushima University Hospital and four affiliated hospitals between January 2019 and July 2022. For reference, we also analyzed 67 patients with ES-SCLC who received more than four cycles of carboplatin plus etoposide (without ICI) in Tokushima University Hospital between 2010 and 2023. We evaluated the impacts of G-CSF on progression-free survival (PFS), overall survival (OS) and durable response to ICI which was defined as PFS ≥ 12 months. G-CSF administration was defined as the following classifications in this study; Classification A: use of any G-CSF (at least one dose of either filgrastim or pegfilgrastim), Classification B: use of at least one dose of pegfilgrastim, and Classification C: use of either more than five doses of filgrastim or at least one dose of pegfilgrastim.

Results: Among 65 patients who were treated with chemo-immunotherapy, 15 patients did not receive any G-CSF. Fifty, 26, or 38 patients were defined as G-CSF users in Classification A, B, or C, respectively. No significant differences in patient characteristics at baseline were found between the groups with or without G-CSF. The patients who received at least one dose of any G-CSF (Classification A) showed significantly poorer PFS than the patients who did not receive any G-CSF (median PFS 9.5 vs. 5.3 months, p=0.005). This result was consistent in other classifications (Classification B; median PFS 6.5 vs. 5.3 months, p=0.004, Classification C; median PFS 7.9 vs. 5.3 months, p=0.02). On the other hand, the administration of G-CSF did not influence on PFS of the patients who were treated with only chemotherapy (without ICIs). The patients who received any G-CSF tended to show poorer OS, however, no statistically significant difference was observed between two groups (median OS 26.4 vs. 17.8 months, p=0.139). In the multivariate analysis, the administration of G-CSF was associated with poorer PFS (hazard ratio [HR] 3.529, 95% CI 1.600-7.782, p=0.002), regardless the other variables such as dose intensity of chemotherapy. Furthermore, in the binomial logistic regression analysis, the administration of G-CSF was identified as a determinant factor for durable response (HR 0.161, 95% CI 0.037-0.714, p=0.016). Similar results were observed in the other classifications.

Conclusions: Our study suggests that the indication of G-CSF administration during chemo-immunotherapy should be carefully considered to avoid attenuating the therapeutic efficacy of chemo-immunotherapy in the patients with ES-SCLC.

Keywords: Small Cell Lung Cancer, Chemo-immunotherapy, G-CSF

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EP.13D.05 Predictive Impact of Peripheral Blood Lymphocyte Subsets and Serum Markers in First-Line Immunotherapy for ES-SCLC——A Real-World Study

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Introduction: In recent years, the emergence of immune checkpoint inhibitors become the first-line treatment for extensive small cell lung cancer, which have brought new hope to patients with extensive small cell lung cancer.However, real-world data are still lacking, and the search for potential biomarkers is essential. Our research aimed to evaluate the effectiveness of first-line immune checkpoint inhibitors (ICIs) and explore the potential predictive markers including lymphocyte subsets and serum markers in peripheral blood.

Methods: In the "CAPTRA-LUNG" database(NCT03334864),a total of 278 ES-SCLC patients including the first-line ICIs plus platinum-containing chemotherapy patients (n=152) as the study group and the first-line simple chemotherapy patients (n=126) as the control group in the Shanxi Cancer Hospital from January 2020 to January 2023. Patients who applied first-line immunotherapy were collected clinical parameters, including tumor markers(NSE,CYFRA-211,PROGRP), inflammatory markers(NLR,PLR,LMR,SII,SIRI,ALI,LDH,ALB,A/G), lymphocyte subsets(CD3+CD45+T cells,CD3+CD4+T cells, CD3+CD8+ T cells, CD4+/CD8+, CD45+CD19+B cells, NK cells and Tregs cells). The follow-up deadline was January 20, 2024.

Results: There were significant differences in OS (mOS: 16.93m vs 14.0m,P<0.05) and PFS (mPFS: 9.17m vs 5.93m,P<0.05) among subgroups.The ORR of the study group and the control group were 79.5%and 64.3%, and the DCR was 91.7% and 85.7%, respectively.In the study group, there was significant difference in OS between the two groups (mOS:17.07m vs16.93m,P=0.0007)but no significant difference in PFS (mPFS:7.43mvs.10.20m,P=0.624).Multivariate analysis showed that NLR,ALI and A/G are risk factors for PFS. 91 of total ES-SCLC patients were evaluated peripheral blood lymphocyte subsets by flow cytometry before treatment with immune checkpoint inhibitors (ICIs),we didn't find any meaningful indicator related to PFS and OS unfortunately.

Conclusions: Our real-world data suggests that immune checkpoint inhibitors combined with platinum-containing chemotherapy as first-line treatment could be beneficial to the ORR, DCR, PFS, and OS of ES-SCLC patients with comparable safety.Baseline NLR,ALI and A/G have the potential to serve as biomarkers for immunotherapy in SCLC.

Keywords: Lung neoplasms, Immunotherapy, Biomarker

EP.13D SMALL CELL LUNG CANCER AND NEUROENDOCRINE TUMORS - PROGNOSIS/BIOMARKERS
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EP.13D.06 Factors Affecting Outcomes of Limited-Stage I, IIA (T1-T2, N0, M0) Small Cell Lung Cancer: An Analysis of the National Cancer Database.

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Introduction: Surgery is recommended for patients with early-stage small cell lung cancer (SCLC)(T1-T2, N0, M0). A retrospective analysis of the National Cancer Database (NCDB) was conducted to see factors associated with receipt of treatment and outcomes.

Methods: Patients with T1-2, N0, M0 (SCLC) diagnosed between 2010 and 2020, were identified from the NCDB. Data abstracted included: age, sex, race, type of insurance, facility type, and treatment. Factors associated with survival were assessed using the Cox proportional hazards model.

Results: For early stage I-IIA (T1-2, N0, M0) we identified 2602 patients <65 years of age, 8081 aged 65-75, and 1756 patients >75 years of age. The median overall survival (OS) for this group was 12.2 months (15.2, 13.4, and 6.6 months for the individual age groups respectively). Factors associated with a higher risk of death included age > 75 (HR= 1.28 P <0.001), age 65-75 (HR= 1.11 P = 0.001), male sex (HR= 1.17 P <0.001), year of diagnosis 2010-2015 (HR= 1.35 p < 0.001). When compared with Caucasians, Native Americans have worse OS (HR= 1.48 p=0.03) while Other races (which include Non-Caucasian, African American, or Native American races) have better OS (HR= 0.76 p=0.007). Patients who were recommended surgery but did not receive it (HR= 2.15 p- <0.001) and those who were not recommended surgery at all (HR= 2.18 p- <0.001) had worse outcomes compared to those who received surgery. A greater proportion of patients >75 were not recommended surgery compared to 65-75 and <65 years (57.92%, 45.76%, vs 47.27% respectively). A greater proportion of patients >75 years were not recommended radiation compared to those 65-75 and <65 years (16.57; 10.16; 7.38). A larger proportion of younger patients were treated in Academic/Research centers (30.33% vs 26.03% vs 23.12%). Analysis for patients who underwent surgery showed that OS was worse in patients who were > 75 years of age (HR= 1.37; P <0.001), 65-75 years (HR= 1.12; P <0.001) compared to younger patients. OS was also worse for uninsured patients (HR= 1.20; P = 0.02). On the other hand, Female patients (HR= 0.83; P < 0.001), Other races (HR= 0.49; P = 0.001), African American race (HR= 0.62 P = 0.02), treatment at Academic/Research Program (HR= 0.90 P = 0.04) and year of diagnosis 2016-2020 (HR= 0.72 P-value < 0.001) has better OS

Conclusions: For patients with T1-T2, N0, M0 small cell lung cancer, OS was lower for patients who were >75 years of age, male patients, and patients diagnosed between 2010-2015. Patients who received surgery had the best OS. Patients who were > 75 were less likely to be offered surgery or radiation. For patients who underwent surgery, OS was worse for older and uninsured patients. Female gender, age <65, diagnosis between 2016-2020, and treatment at an Academic/Research facility was associated with better OS.

Keywords: small cell lung cancer, limited stage, overall survival

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EP.13D.07 Impact of Antiemetic Steroid Use on Survival in Small Cell Lung Cancer Patients with Immune Checkpoint Inhibitors and Chemotherapy Combination

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Introduction: First-line treatment for extensive stage small cell lung cancer (SCLC) often involves combination therapy with immune checkpoint inhibitors (ICIs) and conventional chemotherapy. The chemotherapy regimens combined with ICIs are mainly platinum-based compounds. These agents, being highly emetogenic, necessitate the use of prophylactic anti-emetic medications. However, antiemetic regimens often include steroids, known for their immunosuppressive properties, which can adversely affect the efficacy of ICIs. While the impact of steroids on ICI monotherapy has been extensively studied, there is a lack of information regarding their effects in combination therapy with ICIs. Therefore, this study aims to investigate the effects of prophylactic steroid use for anti-emetic purposes on the survival and treatment efficacy in patients with SCLC undergoing combination therapy.

Methods: This retrospective cohort study utilized data from the National Health Insurance Service, focusing on patients diagnosed with lung cancer between August 2020 and June 2022 who received treatment with atezolizumab, etoposide, and carboplatin. The study estimated the use of antiemetic steroids, specifically dexamethasone, within a 4-day window following chemotherapy administration. Patients were categorized into three groups based on the steroid dosage: low (0-12mg of dexamethasone), moderate (13-24mg), and high (25-36mg). We conducted a 3:1:1 propensity score matching across these groups to assess the impact of anti-emetic steroid dosage on overall survival (OS) and time to next treatment (TTNT).

Results: A total of 3,186 patients were initially identified for the study. After a 3:1:1 propensity score matching, the analysis included 1,425 patients in the low dose group, 475 in the moderate dose group, and 475 in the high dose group. Median OS and TTNT were 8.7 months (interquartile range [IQR], 5.0-13.9) and 6.5 months (IQR, 4.0-11.4) in the low group, 8.2 months (IQR, 5.0-13.2) and 6.6 months (IQR, 4.1-10.3) in the moderate group, and 8.2 months (IQR, 4.3-12.9) and 6.8 months (IQR, 3.7-11.2) in the high group, respectively, with no statistically significant differences between the groups. The 1-year overall survival rate was 31.7% in the low group and 27.8% in the high group. When the analysis was expanded to include total steroid dose for other purposes, patients receiving doses of 36 mg or greater had significantly increased hazard ratios for OS (1.27 [95% CI, 1.13-1.44]) and TTNT (1.25 [95% CI, 1.12-1.39]).

Conclusions: The dosage of antiemetic steroids used in combination therapy with ICIs and chemotherapy does not appear to have a significant impact on survival and treatment response in SCLC. However, the total administration of larger dosages of steroids, including for purposes other than antiemetics can significantly affect outcomes. Further investigation is warranted to explore the nuances of steroid use in cancer therapy.

Keywords: immune checkpoint inhibitors, steroids, antiemetics

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EP.13D.08 Impact of Thoracic Radiotherapy on First-Line Treatment Outcomes in ES-SCLC Patients

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Introduction: The therapeutic advantage of thoracic radiotherapy (tRT) as an adjunct to first-line immunotherapy and chemotherapy in patients with extensive-stage small cell lung cancer (ES-SCLC) remains unclear. We sought to elucidate this in a retrospective cohort study comparing the effectiveness and safety of tRT in combination with first-line immunotherapy and chemotherapy.

Methods: Our retrospective study included patients with ES-SCLC, treated at the West China Hospital between January 2019 and December 2022. They received first-line immunotherapy and chemotherapy and were categorized into two cohorts based on the administration of tRT. The primary outcomes were overall survival (OS) and progression-free survival (PFS). Cox regression analysis was utilized to identify potential independent predictors of prognosis and to compare the treatment outcomes across various patient subgroups. Treatment-related toxicities across both cohorts were compared using the Chi-square test.

Results: Out of 99 patients eligible for the study, 55 received tRT. The median duration of follow-up was 23 months. Remarkably, patients who received tRT demonstrated superior OS and PFS in comparison to those who did not (P<0.001). Subgroup analysis confirmed these findings. Multivariate analysis identified staging and treatment group as independent prognostic factors (P<0.05). The incidence of grade 3-4 adverse events showed no statistically significant difference between the two cohorts.

Conclusions: Thus we confirm that the addition of tRT to the conventional regimen of first-line chemotherapy and immunotherapy yields better survival outcomes without a significant increase in toxicity.

Keywords: Thoracic Radiotherapy, first-line immunotherapy and chemotherapy, extensive-stage small cell lung cancer

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EP.13D.09 Characteristics and Survival in Never-Smoking Small Cell Lung Cancer Cases an Analysis from the Thoracic Tumor Registry

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Introduction: Small cell lung cancer (SCLC) is the most aggressive histological type of lung cancer, with a one-year survival rate of 35.6% and a five-year survival rate of 7.9%. SCLC is strongly associated with tobacco use and there is limited scientific evidence available on this type of lung cancer in never smokers. Thus, the objective of this study was to characterize subjects diagnosed with SCLC who have never smoked and to analyze their survival.

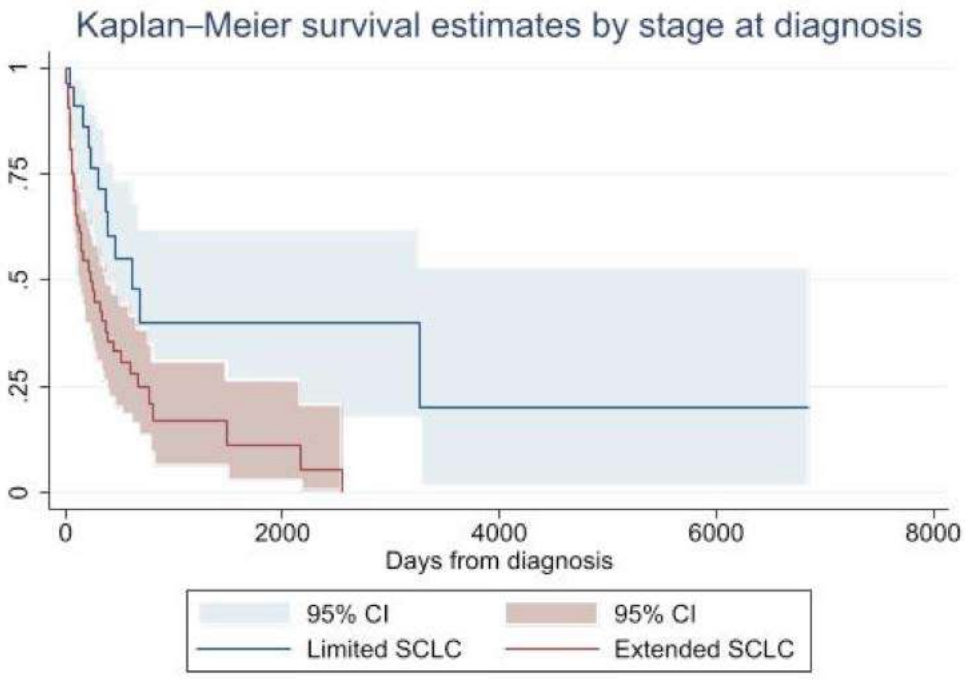
Methods: The main data source was the Thoracic Tumor Registry of the Spanish Lung Cancer Group, which is representative of lung cancer cases diagnosed in Spain by age and sex. Patients have been recruited since 2016 by oncologists in more than 80 participating hospitals. SCLC cases in never smokers were included in this analysis. Descriptive analysis was performed on their characteristics, as well as their symptoms at diagnosis, globally and according to the stage of the disease (extended or limited). To analyse survival, we performed a time-dependent analysis using the Kaplan-Meier survival analysis.

Results:

A total of 86 never-smoking SCLC cases were included, comprising 2.7% of all lung cancer cases registered among never smokers. Median age at diagnosis was 71.0 years (interquartilic range 59.0-78.0 years) and 69.8% were women. Of the 86 cases included, 61 (70.9%) had extended SCLC and 59 (68.6%) had at least one comorbidity at diagnosis. Fourteen (16.3%) cases were exposed to environmental tobacco smoke at home in the past 20 years and 3.5% indicated that their longest occupation was in agriculture/farming or professional cleaning. Cough was the most common symptom at diagnosis (34.1%). There were no significant differences between the frequency of any symptom at diagnosis according to disease stage. Overall, one-year survival rate was 47.1% (95% Confidence Interval (95%CI) 35-59%), 66.0% (CI95% 41.3-82.2%) and 37.9% (CI95% 24.1-51.6%) for limited and extended SCLC, respectively ($p<0.05$) (Figure 1).

Conclusions: SCLC in never smokers is more frequent in women compared to men and almost two out of three of these patients present extended disease at diagnosis. One-year survival rate is lower in extended compared to limited SCLC.

Keywords: small cell lung cancer, survival, characteristics



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EP.13D.10 Breast Metastases from Small Cell Lung Carcinoma

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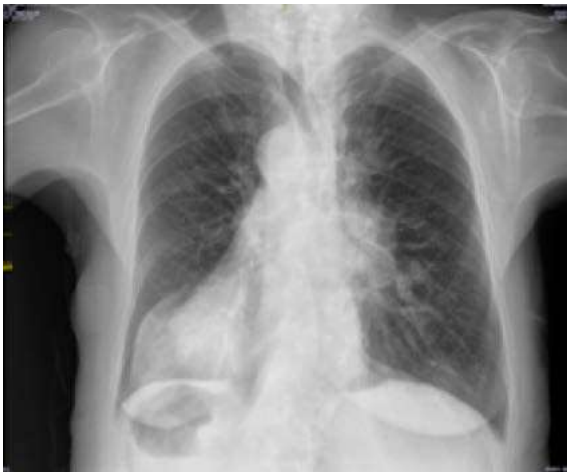
Introduction: Metastases are the leading cause of morbidity and mortality in cancer patients. Small cell lung carcinoma (SCLC) accounts for approximately 15% of all lung tumors and is considered a systemic disease, often presenting with distant metastases at the time of diagnosis.

Methods: Case report of metastasis of small cell lung carcinoma.

Results: A 73-year-old female patient was hospitalized in July 2021 for diagnostic evaluation of radiologically detected changes in the right lung lobe. A chest CT scan revealed a soft tissue mass in the right lung lobe in segment 2 measuring 47x37 mm, with enlarged lymph nodes at positions 10R and 4R with diameters up to 21 mm. Bronchoscopy was performed, revealing a tumor (possibly compressive) in the depth of the right segment 2. Histopathological examination of bronchial biopsy from the tumor and transbronchial puncture through the tumor and lymph nodes at positions 10R and 4R confirmed a diagnosis of small cell lung carcinoma, clinical stage T3N2M0. Upon decision of the Oncology Council, she received chemotherapy according to the PE protocol, four cycles, on November 5, 2021, followed by radiotherapy with a dose of 52Gy/26 fractions on April 8, 2022. A CT scan of the head was performed on November 21, 2022, for planning prophylactic cranial radiotherapy, revealing a 3cm diameter frontal right lesion with perifocal edema, most likely representing a secondary deposit. In January 2023, palliative radiotherapy to the cranium was administered. Upon admission, a change involving the entire left breast and another round lesion in the left anterior axillary line were observed. Both lesions were subjected to puncture, and cytological analysis confirmed metastases of small cell lung carcinoma.

Conclusions: Breast metastases are rare, and it is important to differentiate between primary and metastatic breast malignancy, which influences further therapeutic planning.

Keywords: small cell lung carcinoma, metastasis, breast



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EP.13D.11 Proportion and Characterization of Pulmonary Neuroendocrine Carcinoma via Synaptopysin IHC

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Introduction: Pulmonary neuroendocrine carcinoma represents a significant entity within the spectrum of lung cancers, characterized by diverse biological behaviors and prognosis. The diagnosis and subclassification of neuroendocrine tumors rely heavily on immunohistochemical markers, among which Synaptopysin stands out for its specificity. This study aims to determine the proportion of pulmonary neuroendocrine carcinoma and its subtypes through Synaptopysin immunohistochemistry at Persahabatan Hospital National Respiratory Center, thereby contributing to refined diagnostic accuracy and therapeutic strategies.

Methods: This cross-sectional descriptive study retrospectively analyzed the medical records of patients diagnosed with pulmonary neuroendocrine neoplasms through histopathological examination at the oncology clinic of Persahabatan Hospital National Respiratory Center from January 2019 to May 2023. Immunohistochemistry using Synaptopysin was conducted to confirm the diagnosis. Data on patient demographics, smoking history, and clinical outcomes were also collected to ascertain the characteristics of the neuroendocrine carcinoma population within the study setting.

Results: Out of 50 samples analyzed, a significant proportion demonstrated positive Synaptopysin expression, indicative of neuroendocrine differentiation. The study found that the majority of patients with neuroendocrine carcinoma were male, aged ≥60 years, with a heavy smoking history, emphasizing the potential etiological role of tobacco in neuroendocrine tumor development. The histopathological analysis revealed a diverse distribution of neuroendocrine tumor subtypes, with small cell lung carcinoma and large cell neuroendocrine carcinoma representing the high-grade variants in the cohort. The application of Synaptopysin IHC not only confirmed the neuroendocrine nature of the tumors but also facilitated the accurate subclassification essential for guiding therapeutic decisions.

Conclusions: The significant proportion of Synaptopysin-positive pulmonary neuroendocrine carcinomas at Persahabatan Hospital National Respiratory Center underscores the prevalence and diagnostic challenge of these tumors. Immunohistochemistry with Synaptopysin proves to be a crucial tool in the confirmation and subclassification of pulmonary neuroendocrine neoplasms, aiding in the development of targeted treatment approaches. This study highlights the importance of comprehensive diagnostic protocols that include Synaptopysin IHC in the effective management of neuroendocrine carcinoma patients, contributing to the body of knowledge on the epidemiology and pathology of these tumors within the Indonesian context.

Keywords: : Pulmonary Neuroendocrine Carcinoma, Synaptopysin, Immunohistochemistry

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EP.13D.12 International Consortium Real-World Outcomes in Extensive Disease Small Cell Lung Cancer Compared to IMPOWER133 And CASPIAN

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Introduction: The landscape of extensive disease small cell lung cancer (ED-SCLC) management has changed over the last several years with the addition of immunotherapy to platinum-doublet chemotherapy following results from the pivotal trials (CASPIAN and IMpower133). Translating these trials into clinical practice requires an understanding of how similar outcomes of the control arms of these trials are to the real-world setting. Contextualizing the potential benefit of these new immunotherapies for funders also requires an understanding of the potential prognostic factors in ED-SCLC.

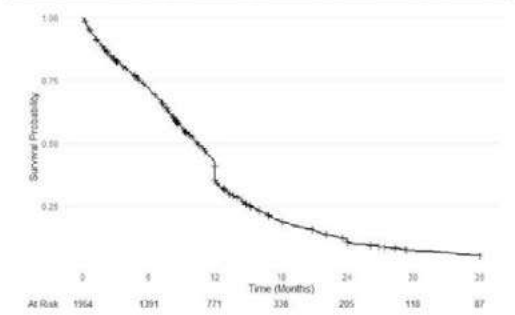
Methods: There were 1,964 patients analyzed, from 19 sites across Europe, North America, and Asia in the harmonized international lung cancer consortium (ILCCO) dataset, who were diagnosed with ED-SCLC between 1990 and 2020 and have available stage and clinicodemographic data. Cox regression models were generated to evaluate potential prognostic factors for overall survival (OS). Median follow-up time was measured in years using the reverse Kaplan-Meier method.

Results: Data was acquired from 12 North American, 6 European and 1 Asian studies. Median age was 65 years (interquartile-range: 58-72) and 90% were White, 47% had a cardiometabolic comorbidity, of which 13% had diabetes and 40% had a respiratory comorbidity, including 25% with COPD. With a mature median follow-up of 8.6 years, median OS was 10.3 months (95% CI: 10.0, 10.9). The Kaplan Meier survival curve for all patients with ED-SCLC, and survival probabilities for different ED-SCLC time cohorts defined by year of diagnosis are presented in the figure. In univariate analyses, being male, a former smoker (vs current), and being 70+ years were each associated with having poorer OS (at p<0.05). In multivariate analysis, poorer OS was associated with male sex, HR=1.39 (95% CI: 1.22, 1.57; p<0.001) and older age, HR (per 10 year increase) = 1.22 (1.14, 1.30; p<0.001). OS did not vary across the year of diagnosis or cohort time.

Conclusions: Disappointingly, overall survival in ED-SCLC has not changed in the 30 years prior to the introduction of immunotherapy. When comparing aggregate OS in our international cohort of patients from across the world to the standard of care arms in the CASPIAN and IMPOWER133 studies, we observed identical median OS of 10.3 months. Further, our demographics were similar to these trials: predominantly male, white, in their 60s and ever-smokers. Our international, multi-site real-world data supports the global generalizability of the CASPIAN and IMpower133 trial results.

Keywords: Small cell lung cancer, Real world outcomes, Overall survival

Year of Diagnosis	Overall Survival Probability (95% CI)				
	6 Month	12 Month	18 Month	24 Month	36 Month
1990-2002	0.72 (0.68,0.76)	0.32 (0.29,0.37)	0.17 (0.14,0.20)	0.09 (0.07,0.12)	0.04 (0.03,0.06)
2003-2008	0.69 (0.65,0.73)	0.34 (0.30,0.38)	0.18 (0.15,0.21)	0.10 (0.08,0.13)	0.05 (0.04,0.07)
2009-2020	0.74 (0.71,0.77)	0.39 (0.36,0.43)	0.21 (0.18,0.24)	0.12 (0.10,0.15)	0.06 (0.04,0.08)



EP.13D SMALL CELL LUNG CANCER AND NEUROENDOCRINE TUMORS - PROGNOSIS/BIOMARKERS
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EP.13D.13 Exploring COVID-19's Impact on Treatment and Survival in Small Cell Lung Cancer

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Introduction: Emerging data has indicated that the COVID-19 pandemic severely impacted patients with cancer. Descriptive analyses have found the 30-day mortality rate in patients with newly diagnosed small cell lung cancer (SCLC) significantly increased with the pandemic. However, little research has explored the effect of COVID-19 infection on mortality or adverse outcomes associated with chemoimmunotherapy treatment. This analysis aims to fill this gap.

Methods: We conducted a propensity score-matched, retrospective study focusing on patients diagnosed with small cell lung cancer (SCLC) undergoing chemotherapy or immunotherapy after January 1, 2019. We utilized datasets from the TriNetX database and the US Collaborative Network, which includes 60 healthcare organizations. We performed propensity score matching accounting for variables including age, race, gender, and existing comorbidities. The primary objective was to assess risk of mortality at 1 and 3 years, with secondary aim focusing on the incidence of adverse events related to their cancer treatments.

Results: The initial study population consisted of 98 patients with a diagnosis of SCLC and a concurrent COVID-19 positive status, and 649 SCLC patients who were COVID-19 negative. After propensity score matching, the analytic cohort consisted of 86 matched patients. For the outcome of overall mortality at the 1-year interval, the COVID-19 positive group demonstrated a significant decrease in the relative risk (RR) of mortality at 0.73 (95% CI: [0.54, 0.98], $p<0.03$). However, at the 3-year mark, the reduction in mortality risk was not statistically significant, with an RR of 0.87 (95% CI: [0.70, 1.08], $p<0.20$). For the outcome of adverse effects of chemoimmunotherapy, there was no significant difference between the COVID-19 positive and negative groups at 1-year (RR 1.3, 95% CI:[0.87, 1.85], $p<0.22$) or 3-year mark (RR 1.3, 95% CI: [0.90, 1.83], $p<0.17$).

Conclusions: This retrospective analysis showed no significance of COVID infection on mortality at three years and adverse effects of chemoimmunotherapy over both 1 and 3-year periods. The significant decrease in mortality at 1-year with COVID-19 was unexpected, but potentially suggestive of an overlapping benefit from the supportive therapies traditionally employed in the management of SCLC and COVID-19. This convergence in treatment modalities may have inadvertently contributed to improved survival rates, underscoring the importance of a multidisciplinary approach in patient care and the potential for cross-application of therapeutic strategies. This study's limitations include inherent constraints of retrospective reviews such as the limited ability to establish causality, biases from variations in staging data availability, and diverse coding practices among healthcare providers. Future studies can include analyses of COVID-19 vaccination status to better understand its role in survival and treatment outcomes.

Keywords: Small Cell Lung cancer, COVID-19, Mortality

EP.13E SMALL CELL LUNG CANCER AND NEUROENDOCRINE TUMORS - TRANSLATIONAL/BASIC
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EP.13E.01 Genetic Landscape and Prognostic Markers of Small Cell Lung Cancer: A Comprehensive Study

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Introduction: Preliminary analysis at the genetic and molecular levels has provided us with in-depth insights into small cell lung cancer. However, the correlation between genomic profiles and clinical characteristics, differences in genetic profiles between Eastern and Western populations, and genomic alterations before and after frontline treatment remain unclear.

Methods: A retrospective analysis was conducted on 88 patients with pathologically confirmed SCLC, who underwent various chemotherapy or immunotherapy treatments at different clinical stages. Genomic profiling of these patients was carried out utilizing a next-generation sequencing-based gene panel. Additionally, a cohort of Western population samples from a public database was randomly enrolled to explore genetic differences between Eastern and Western populations.

Results: In the study cohort, there were 15 female and 73 male participants, with a median age of 64.5 years (range: 58-70). Among them, 56 were current or former smokers, with a median smoke index of 800 (range: 300-1400).In the cohort receiving chemotherapy combined with PD1 or PD-L1 inhibitors, patients with PD-L1 TPS ≥1% exhibited improved progression-free survival (PFS) compared to those with TPS <1%, a trend not observed in the chemotherapy-alone group. Across all treatment modalities, patients harboring mutations in the MAPK pathway demonstrated improved overall survival (OS) (Multivariate Cox analysis: HR: 0.0905, 95% CI: 0.0125-0.656, P=0.0175), while those with mTOR/Ras pathway mutations within the chemotherapy group experienced compromised PFS. Moreover, patients with baseline mutations in the PI3K-Akt pathway in the chemotherapy arm displayed improved PFS. However, no significant disparities in PFS and OS were discerned based on tumor mutational burden (TMB) levels. Analysis of specific gene variants unveiled associations between certain mutations (KDR/KIT, CSF3R, RICTOR, MNT2D) and adverse prognostic outcomes. Patients with concurrent TP53/RB1 mutations manifested a higher incidence of LRP1B mutations compared to those with sole TP53 mutations, although the latter exhibited higher PD-L1 expression level than the former. Chromosomal instability and whole-genome duplication were correlated with advancing age. Additionally, smokers displayed a heightened prevalence of SMAD4 mutations, whereas females exhibited a greater frequency of EGFR mutations. A subset of 43 Chinese and 49 Western individuals was randomly recruited. Both Chinese and Western SCLC populations were predominately male smokers around 65 years old, with TMBs averaging 8.5 mutations/Mb. In the Western cohort, mutation frequencies in CSMD3, NAV3, CSMD1, EP300, and PCDH11X were significantly elevated compared to those in the Chinese cohort; however, KMT2D, KMT2C, and PRKDC mutations were more prevalent in the Chinese group. Notably, the NHEJ pathway exhibited markedly higher mutation rates in the Western population. Comparative analysis of genomic alterations pre- and post-first-line treatment was performed in three advance-stage SCLC patients. Patient 1, treated with etoposide and carboplatin, exhibited AKT1 CN_amp upon recurrence. Patient 2, subjected to EC with atezolizumab, displayed TMPRSS2_p.R289H post-treatment, along with deletions at the INSF_p.M531I, FGFR1_p.S109T, and JAK1_p.H421Y loci. Patient 3 demonstrated MYC amp loss following etoposide and afatinib therapy.

Conclusions: This study provides insights into the gene profile and prognosis of SCLC in Chinese patients, emphasizing the importance of understanding ethnic variations and individualizing treatment strategies.

Keywords: small cell lung cancer, genetic landscape, chemoimmunotherapy

EP.13E SMALL CELL LUNG CANCER AND NEUROENDOCRINE TUMORS - TRANSLATIONAL/BASIC
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EP.13E.02 Multi-Omics Analysis of Patients with Extended-Disease Small Cell Lung Cancer Who Received Chemoimmunotherapy: APOLLO-Bio Study.

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Introduction: Although chemoimmunotherapy (Chemo-IO) is the standard of care in patients with extended-disease small cell lung cancer (ED-SCLC), the prolongation of progression-free survival (PFS) was almost one month. To explore the potential biomarkers of efficacy, we conducted this analysis.

Methods: APOLLO-Bio (UMIN000039600) is the translational analysis of APOLLO study: a multi-centered, prospective study to explore the efficacy and safety in ED-SCLC patients with Chemo-IO in the real-world data setting (Fujimoto D, JAMA Network Open 2023). Of 207 participants, we collected 137 formalin-fixed paraffin-embedded specimen and DNA and RNA were extracted. Gene alterations and expression were analyzed using next-generation sequencing. Immunohistochemistry (IHC) was stained for ASCL1, NEUROD1, YAP1, and POU2F3. Clinical information was integrated to explored the predictive biomarker of response with Chemo-IO.

Results: Patients background was as follows: median age was 73, 83% was male, and 97% had smoking history. Overall PFS and overall survival were 5.0 months and 14.8 months, respectively. Primary lung lesion was the most common site of specimen collection (68%), followed by lymph nodes (22%) and others (10%). Of those, 94.6% had at least one gene alteration and TP53 (73%), RB1 (33%), and EPHB4 (25%) mutations were frequently observed. Median tumor mutation burden was 3 (range, 0-11). KMT2D mutation was found in 10% of patients and mostly co-occurred with TP53 mutation. Patients with TP53 and KMT2D mutation had significantly worse PFS compared with those with TP53 mutation only or TP53 wild-type (HR 2.07-2.27, $p < 0.05$). Regarding IHC, ASCL1- or NEUROD1-positive populations were dominant (48 patients, each) and others were either positive for POU2F3, or YAP1 (18 and 4 patients, respectively). Patients with ASCL1 / NEUROD1-negative by IHC tended to have shorter median PFS (3.94 months) than NEUROD1-, or ASCL1-positive groups (5.72 and 5.06 months, respectively). Through the hierarchical clustering by gene expression profile, we could categorize patients into two groups. Although their prognosis did not significantly differ, one group mainly consisted of patients with ASCL1 / NEUROD1-negative by IHC. Finally, we compared the gene expression profile between long responders (PFS ≥ 360 days) and non-responders (PFS < 60, or 90 days) and found that genes encode immunoglobulin receptor-binding, chemokines and IDO activity were significantly upregulated in long-responders. Gene set enrichment analysis demonstrated that interferon-related and JAK-STAT signaling pathway were upregulated in long-responders.

Conclusions: This multi-omics study revealed the potential of molecular subtyping in patients with ED-SCLC who receive Chemo-IO.

Keywords: hiroaki2

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EP.13E.03 ASCL1 Regulated by HDAC1/RBBP7 Inactivates Gsk3ß to Reverse Drug Resistance in Small Cell Lung Cancer

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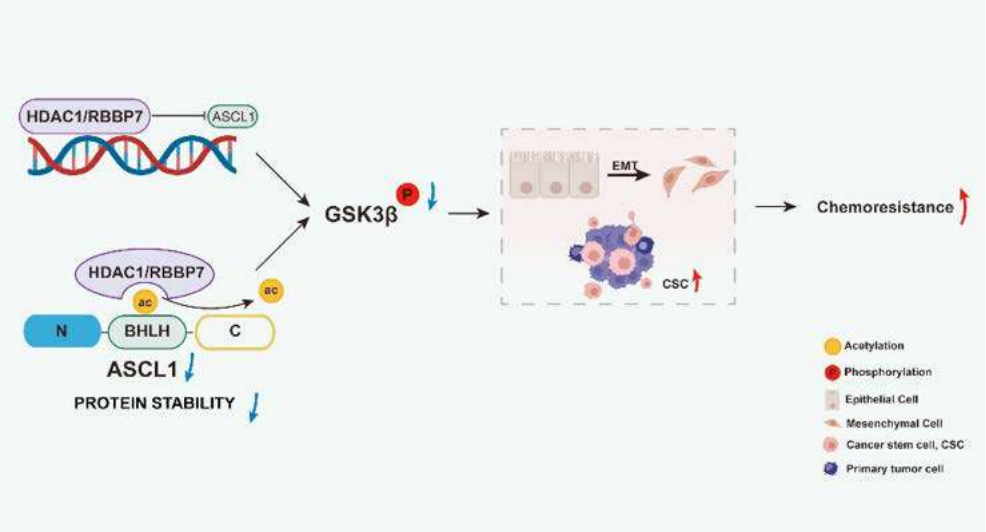
Introduction: Achaete-scute homolog 1 (ASCL1) is a transcription factor with a helix-loop-helix (bHLH) domain. Numerous studies have reported that ASCL1 is crucial for neuronal differentiation and the early development of neuroendocrine progenitor cells. regulatory mechanism of ASCL1 in chemosensitivity remains elusive. In this study, we aim to investigate the biological function, mechanism and clinical significance of ASCL1 in small cell lung cancer (SCLC).

Methods: Differentially expressed ASCL1 between chemoresistant and chemosensitive cell lines were identified using qRT-PCR and Western Blot. The functional roles of ASCL1 and its structural fragments were demonstrated through a series of in vitro and in vivo experiments. Co-immunoprecipitation (quantitative proteomic analyses), serial deletion analysis, and luciferase assays were employed to investigate the potential mechanisms of ASCL1.

Results: The results revealed that ASCL1 expression was significantly downregulated in chemoresistant cell lines compared to parental chemosensitive cell lines. In a cell-derived xenograft model, both ASCL1 and ASCL1 (B) enhanced the chemosensitivity of small cell lung cancer. Overexpression of Ascl1-mutant eliminated the original chemosensitivity function of ASCL1, further specifying the specific region of chemosensitivity function. In exploring the underlying interaction between HDAC1/RBBP7 and ASCL1, we identified that the bHLH domain was acetylated at lysine 156 on ASCL1 by the NuRD complex (HDAC1/RBBP7), thereby promoting Ser9 phosphorylation on GSK3β and inhibiting tumor stemness and EMT.

Conclusions: In summary, our findings demonstrate the essential role of ASCL1 regulated by HDAC1/RBBP7 in inactivating GSK3β and inhibiting tumor stemness and EMT, thereby reversing SCLC chemoresistance, and providing insights toward a better understanding of the mechanism of resistance to chemotherapy drugs of SCLC.

Keywords: Small cell lung cancer(SCLC), ASCL1, chemoresistance



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EP.13E.04 Racial Disparities in Genomic Subtypes of Small Cell Lung Cancer Patients

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Introduction: Recent studies have identified 4 distinct subtypes of small cell lung cancer (SCLC) defined by the expression of several transcription factors. Immunohistochemistry (IHC) based analysis can help define these genomic subtypes. Previous analyses included very few samples from Black patients with SCLC. We present the initial results of IHC expression of relevant transcription factors in tumor samples from Black and White SCLC patients.

Methods: SCLC patients diagnosed between January 2018 and January 2023 at Henry Ford Health were included. Demographics, including self-defined race, clinical characteristics and therapeutic details were retrieved from electronic medical record. A tissue microarray (TMA) was constructed using standard published protocols (1.0 mm cores in triplicate). The constructed TMA and an additional subset of whole sections were used for IHC staining for ASCL1, NEUROD1, POU2F3 and YAP1. IHC scoring was performed using H-score (score >10 was considered positive). Chi-square statistics and independent t-test was used for statistical analysis in the SPSS 28 software.

Results: Of 258 patients with SCLC, adequate tissue for IHC scoring of all transcriptional factors was obtained for 58 patients (32 on TMA; 26 on whole sections). Of these, 28 were male and 30 female, mean age was 68 years (range: 52-86). 98% of patients were current or former smokers. Nine patients were Black and 49 were White. No statistical differences were observed for demographics, stage at diagnosis and presence of brain metastases between Black and White patients. YAP1 expression was more common in tumors of Black patients compared to tumors of White patients (33% vs 12%, p=0.136), while the expression of POU2F3 (0 vs 13%, p=0.575) and NEUROD1 (22% vs 45%, p=0.282) were more common in White patients. Positivity for more than one marker was noted in 22% of Black vs 8% of White patients (p=0.231). POU2F3 negative patients had significantly better overall survival than positive patients (p=0.034). Other markers did not show a statistically significant difference in survival. Survival analysis stratified by race was not conducted due to limited sample size.

Conclusions: The initial results of our study show that the prevalence of genomic subsets of SCLC defined by IHC expression of relevant transcription factors differs between self-defined Black and White patients. We are evaluating more samples to confirm our initial results. If these differences persist with further analysis, this data could suggest differences in SCLC biology among different racial groups and may have therapeutic implications.

Comparison between White vs Black patients

Keywords: Small cell lung cancer, Genomic subtypes, IHC

Variable		White	Black	p-Value
Total N (%)		49 (85%)	9 (15%)	
Age at diagnosis	Mean (SD)	68.8 (8.4)	65.3 (10.4)	0.275
Gender	Male	24 (49%)	4 (44%)	0.999
	Female	25 (51%)	5 (56%)	
Smoking status	Current/former smoker	49 (100%)	8 (89%)	0.155
	Never smoker	0 (0%)	1 (11%)	
Stage at diagnosis	Extensive stage	38 (78%)	7 (78%)	0.999
	Limited stage	11 (22%)	2 (22%)	
Genomic subtypes (Positive)	ASCL1	37 (76%)	6 (67%)	0.682
	POU2F3	6 (13%)	0 (0%)	0.575
	YAP1	6 (12%)	3 (33%)	0.136
	NEUROD1	22 (45%)	2 (22%)	0.282
Overall survival	Median (95% CI)	6 (3.7 – 8.3)	8 (3.8 – 12.2)	0.978

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EP.13E.05 Proteomics Profiling Reveals the Metastasis Mechanism of Small Cell Lung Cancer

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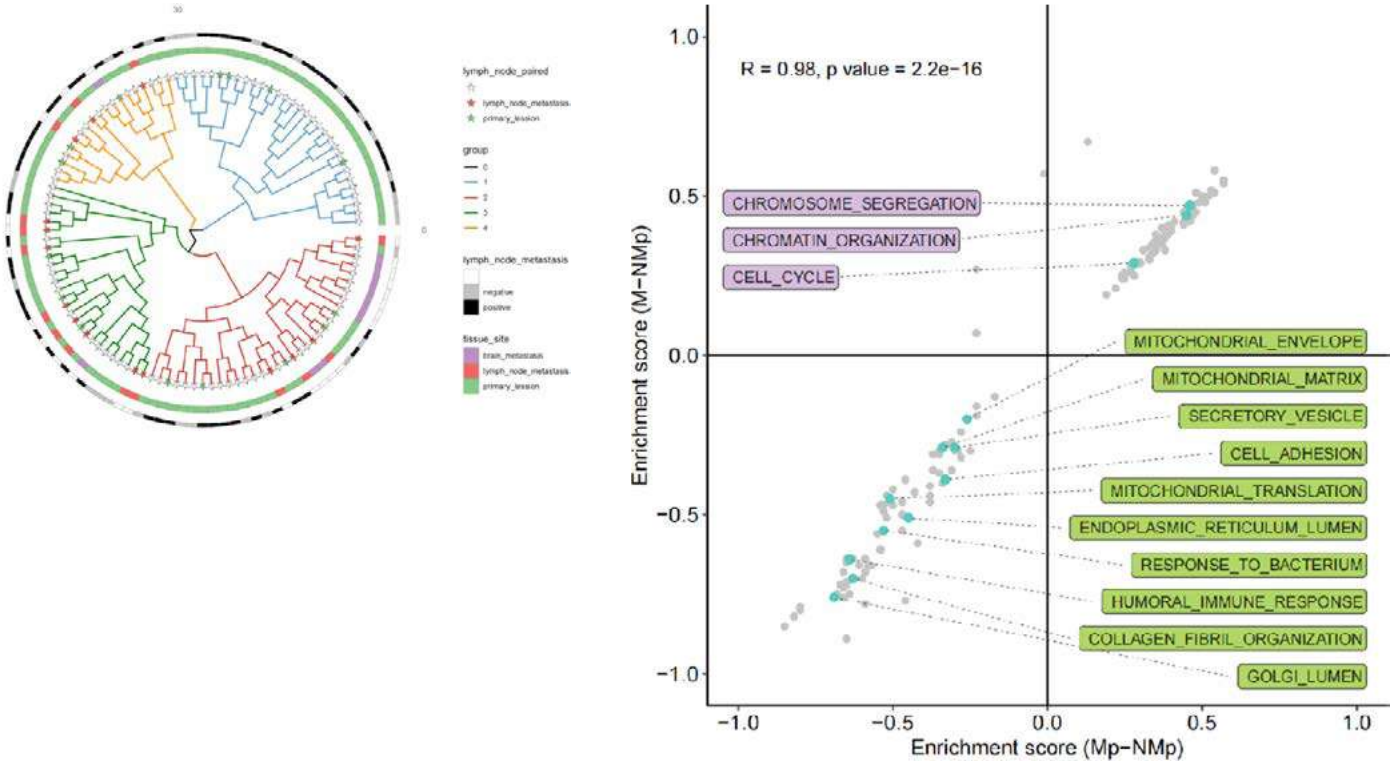
Introduction: Small cell lung cancer (SCLC) is a highly metastatic and recalcitrant malignancy with poor overall survival, while the molecular biological mechanisms underlying its aggressive characterization still remains largely unexplored.

Methods: In order to comprehensively explore molecular mechanisms of SCLC metastasis, we performed an unbiased proteomic study of 111 SCLC tumor samples, including 85 primary tumors, 15 patient-matched lymph node metastatic tumors and 11 brain metastatic tumors. All of the FFPE specimens were obtained from patients who underwent surgical resections. Liquid chromatography tandem mass spectrometry analysis was conducted based on the data-independent acquisition method. Unsupervised clustering and pathway enrichment analysis were performed to reveal the heterogeneity of protein expression profiling.

Results: 31 primary tumors, 54 primary tumors and 26 metastatic tumors were respectively assigned to non-potential metastatic (NMp) group, potential metastatic (Mp) group and metastatic (M) group, in which Mp and M group were clustered together. This was also supported by the results of the Uniform Manifold Approximation and Projection dimension reduction. Following Gene set enrichment analysis, proteomaps, protein-protein interactions network and two-dimensional annotation enrichment analysis of the significant differentially expressed proteins between different groups (NMp vs Mp, NMp vs M) revealed the strikingly biological resemblance of the protein profile between the Mp group and the M group. The NMp group was dominated by higher levels of cell adhesion, extracellular matrix, extracellular exosome, lipid metabolism and immune stimulation-related proteins, while the Mp group and the M group were enriched in pathways associated with cell cycle, cell division and chromosome.

Conclusions: There are distinct metastatic potentials between NMp and Mp groups, which could be further utilized to explore the metastasis mechanism of small cell lung cancer.

Keywords: small cell lung cancer, proteomics, metastasis mechanism



EP.14A MESOTHELIOMA, THYMOMA, AND OTHER THORACIC TUMORS - MESOTHELIOMA
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EP.14A.01 Prospective Analysis of Patterns of Care and Clinical Outcomes for People Diagnosed with Mesothelioma in Australia

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Introduction: The Victorian Mesothelioma Outcomes Registry (VMOR) was set up in 2022 to collect clinical information and report on standards of care for people diagnosed with mesothelioma across the state, linked to an established lung cancer registry (VLCR). Australia has a high incidence of mesothelioma and the aim of this state-based registry was to collect additional clinical information about quality of care, not routinely collected by the federal Australian Mesothelioma Registry.

Methods: Hospital Health Information Services thoracic cancer coding extracts received by the VLCR for 2022 were prospectively analysed to identify patients diagnosed with mesothelioma (ICD C45). Data was collected and entered into a secure database for the following variables: diagnosis, clinical staging, co-morbidities, performance status, treatment planning, surgery, radiatiotherapy, systemic anti-cancer therapy (SACT) including chemotherapy and immunotherapy, palliative and supportive care and overall survival. Baseline VMOR reporting included assessing the feasibility of reporting on ten key clinical quality indicators (CQIs) identified through a national modified Delphi process run through TOGA (Thoracic Oncology Group Australasia) for benchmarking care: time from referral to diagnosis, discussion at a multidisciplinary meeting (MDM), documentation of asbestos exposure, performance status and histologic sub-typing, receipt of systemic anti-cancer therapy (SACT), access to a cancer nurse specialist for support, evidence of supportive care screening and (for pleural mesothelioma only) definitive management of pleural effusion and use of pleural-phase contrast CT for diagnosis.

Results: 105 participants diagnosed with mesothelioma in 2022 from 19 health services were registered into VMOR. Median age at diagnosis was 76 years (IQR 67-82), 81% were male, 92% with pleural mesothelioma. 59% participants had referral to diagnosis in under 28 days, 67% were presented at an MDM, 94% had histologic subtype documented (60% epithelioid). 77% had a documented performance status and 65% documentation of prior asbestos exposure in medical records. Active treatment including SACT (59%), radical surgery (6%) and radiotherapy (13%) was received in combination by 69%, with 31% receiving supportive care alone. 30% had access to a cancer nurse specialist and 28% a record of supportive care screening. For pleural mesothelioma 18% had definitive effusion management. It was feasible for VMOR to collect 9/10 CQIs but not possible to ascertain use of pleural phase contrast CT based on granularity of current data collection methods. One year overall survival was 19% for the whole cohort, and significantly higher 31% (HR 4.29 p<0.001) for those receiving SACT compared to those who did not.

Conclusions: This real-world data supports clinical trials showing improved survival for people diagnosed with mesothelioma who receive SACT and offers an opportunity to understand reasons why people did not receive SACT and variation across health services. Increasing the proportion of mesothelioma cases discussed at an MDM may help increase active treatment and access to clinical trials. Our findings highlight an unmet need to increase support for people diagnosed with this high burden disease and their carers, in particular access to cancer nurse specialists. A customised patient survey has also been introduced for 2023 to explore this further.

Keywords: Mesothelioma, systemic anti-cancer therapy, cancer nurse specialist

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EP.14A.02 Prognostic Factors in Malignant Pleural Mesothelioma Patients Receiving First-Line Chemotherapy: A Baseline Risk Score

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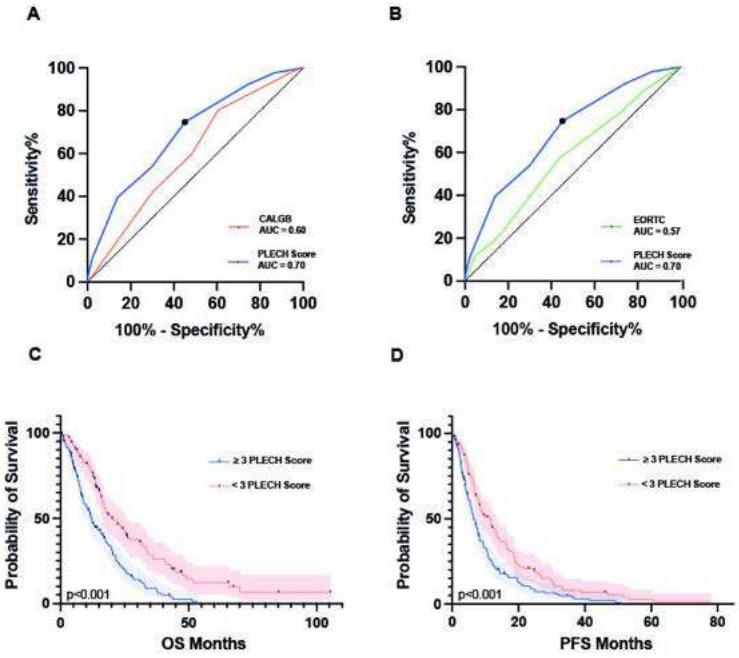
Introduction: Malignant Pleural Mesothelioma (MPM) is a highly aggressive cancer with a dismal prognosis, often detected at advanced stages where systemic modalities are the mainstay, with chemotherapy remaining the most commonly used therapy. Prognostic assessment is crucial for balancing chemotherapy's adverse effects with its survival benefits and for guiding treatment decisions, but the interplay of multiple factors complicates it. Traditional prognostic scores like EORTC and CALGB have limitations, especially in reflecting contemporary chemotherapy regimens and demographic diversity, while newer scores often depend on novel biomarkers that are not widely accessible or validated. Our study aimed to develop a simple and effective prognostic score for patients with MPM, based on readily available clinical and laboratory data.

Methods: A retrospective study was conducted at two large Mexican cancer centers. It included patients with unresectable MPM who received first-line chemotherapy from 2010 to 2023. We evaluated baseline variables from electronic medical records and their relationship with overall survival (OS) and progression-free survival (PFS). Variables with prognostic value identified through univariate analysis and subsequently confirmed as independent factors in a Cox-proportional hazard model were used to create a weighted baseline-risk score. The score's performance in predicting 1-year OS was compared with CALGB and EORTC scores using the area under the curve (AUC) of receiver operating characteristic (ROC) curves. Its prognostic capacity in creating distinct groups was assessed through Kaplan-Meier analysis.

Results: Among 262 patients (69.1% male, 80.5% with epithelioid histology), a 0-7 point PLECH score was developed based on five variables: Platelet count (P: +2), high LDH (L: +1), ECOG ≥ 2 (E: +1), Chest pain at diagnosis (C: +2), and non-epithelioid Histology (H: +1). The score had an AUC of 0.70 for predicting 1-year OS, outperforming CALGB and EORTC scores (0.60 and 0.57, respectively), with an optimal cutoff of 2.5 (sensitivity 75%, specificity 55%). Patients with a high-score (≥3) had significantly shorter OS (12.3 vs. 20.1 months; p<0.001) and PFS (6.4 vs. 11.3 months; p<0.001) compared to those with a low score. Significance was maintained when evaluating patients from both centers independently.

Conclusions: The PLECH score, developed from a substantial cohort, offers a straightforward and accessible prognostic tool for MPM patients, surpassing traditional scores in our demographic. It identifies a "high-risk" group potentially unsuited for conventional chemotherapy, suggesting that alternative treatment strategies could enhance their survival and quality of life.

Keywords: Mesothelioma, Prognosis, Chemotherapy



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EP.14A.03 Analyzing the Impact of COVID-19 Infection on Adverse Outcomes in Mesothelioma: A Multicenter Study

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Introduction: Little research has explored how COVID-19 affects the efficacy and side effects of mesothelioma treatments. This multicenter propensity matched retrospective cohort study, the largest of its kind, aims to explore the effect of COVID-19 infection on risk of mortality and adverse outcomes of chemotherapy and immunotherapy in patients being treated for mesothelioma.

Methods: Data were gathered from the TriNetX database and the US Collaborative Network, which includes 60 healthcare organizations. A propensity-matched retrospective cohort study was conducted on patients with mesothelioma undergoing treatment. Patients were divided into two cohorts based on their COVID-19 status and treatment: those treated for mesothelioma with immunochemotherapy without a positive COVID-19 test (unmatched n=819, matched= 128) and those undergoing the same treatments with a positive COVID-19 test (unmatched n=137, matched = 129). Cohorts were matched for age, race, sex, and comorbidities The study focused on post-infection outcomes at one and three years, with mortality as the primary endpoint, and adverse effects of immunotherapy/chemotherapy as the secondary endpoint.

Results: Risk of mortality did not change with COVID infection: relative risk of mortality at one year was 0.70 (95% CI: [0.46, 1.07], p<0.094), and at three years, relative risk was 1.03 (95% CI: [0.75, 1.41], p<0.86). COVID infection did not increase risk of adverse events associated with immunochemotherapy treatment: Relative risk of adverse effects of immunotherapy/chemotherapy was 0.81 at one year (95% CI: [0.48, 1.36], p<0.42) and 0.83 at three years (95% CI: [0.51, 1.34], p<0.44).

Conclusions: Mesothelioma patients experienced stable outcomes across risk for mortality and adverse events of treatment over the course of the study. The results suggest that COVID-19 infections were not substantially associated with an increased risk of mortality or adverse events associated with immunochemotherapy, contrary to early concerns regarding immunosuppression and inflammation associated with COVID-19 as potential exacerbators of cancer progression. However, this study faces limitations, including the inherent challenges of database research such as variations in ICD coding, as well as other limitations in staging data and treatment variations. Future research exploring the long-term inflammatory effects of COVID-19 and its interaction with chronic inflammation in mesothelioma is required, as well exploration into COVID-19 related complications such as hospitalization, mechanical ventilation, and venous thromboembolism.

Keywords: mesothelioma, COVID-19, mortality

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EP.14A.04 Microbial Supernatant Library Screening Suggested that Induction of Ferroptosis is an Effective Therapeutic Strategy Against Mesothelioma

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Introduction: Therapeutic drugs for mesothelioma are limited, and there is a need to identify and develop novel agents. Ferroptosis is a programmed cell death caused by iron ion-dependent lipid peroxidation. Induction of ferroptosis in mesothelioma cells is considered as a novel therapeutic strategy, but the mechanism determining susceptibility to ferroptosis remains unclear.

Methods: Fifteen human mesothelioma cell lines and four immortalized mesothelial cell lines were used. The library of 1,188 soil- and marine soil-derived microbial supernatant used to search for new candidate agents was provided by Kitasato University, Japan. Mesothelioma cells were spread in 96 wells, 1/100 volume of microbial supernatant was added, and calorimetric assay was performed after 72 hrs. Substances in the supernatant that showed growth inhibitory effects were separated by HPLC and their structures were analyzed by NMR. RSL3 was used as the ferroptosis inducer. Ferroptosis induction was determined by nonapoptotic cell death, increased lipid peroxidation levels, and inhibition by a ferroptosis inhibitor, ferrostatin-1. Gene knockdown was performed by shRNA transfection using lentivirus.

Results: The microbial supernatant library screening was performed to examine induction of cell death in three mesothelioma cell lines and one immortalized mesothelial cell line, which revealed supernatants that specifically cause cell death of mesothelioma cell lines. NMR analysis of the supernatant identified Brefeldin A. Using the purified compound of Brefeldin A, we confirmed that it is a strong cell death inducer of mesothelioma cells and that the cell killing effect of Brefeldin A is not apoptosis, but rather ferroptosis. Since Brefeldin A is highly toxic and future clinical development is difficult, we proceeded with the analysis using a known ferroptosis inducer, RSL3. We detected that easy induction of ferroptosis was detected in approximately 40% of the mesothelioma cell line panel. In contrast, immortalized mesothelial cells and the other 60% of cell lines showed resistance. Comprehensive gene expression analysis of the ferroptosis-sensitive and non-sensitive cell lines identified 13 genes that were significantly up-regulated in the sensitive lines and 9 genes that were down-regulated. Knockdown of each of these genes was examined for changes in susceptibility to ferroptosis. Currently, candidate genes involved in susceptibility have been picked up and their detailed mechanisms are under investigation.

Conclusions: Microbial supernatant library screening suggested that small molecular compounds that induce ferroptosis in mesothelioma cells are important for the development of novel drugs against mesothelioma. Furthermore, our results suggest that the expression of specific genes is involved in the susceptibility of mesothelioma cells to ferroptosis.

Keywords: mesothelioma, ferroptosis, cell line

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EP.14A.05 Targeting ADAR1 for Mesothelioma Therapy

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Introduction: Adenosine deaminase for double-stranded RNA 1 (ADAR1) is proposed to be an important protein in promoting cancer development and growth. In melanoma and colon cancer models, inhibition of ADAR1 by shRNA leads to markedly improved response to immune therapy in murine models and delayed tumor growth. In addition, tumor-derived type I interferon (IFN) primes cancer cells for susceptibility to immune checkpoint therapies following ADAR1 loss. ADAR1 is highly expressed in malignant mesothelioma, and in this context is hypothesized to play a role in the development of the cancer phenotype. While the role of ADAR1 in cancer is complex, it is possible that a targeting strategy for ADAR1 in mesothelioma cells may generate a robust response and lead to impaired tumor growth.

Methods: ADAR1 gene editing was carried out by CRISPR/Cas9 in the AB12, 40L, H2373, and H2461 cell lines. Sequencing and western blot analyses were carried out to confirm loss of ADAR1. Tumor formation was assessed in syngeneic, nude, and NSG mouse models. In addition, evaluation of interferon response was carried out by western blot analyses. A to I editing was confirmed by RNA-seq analyses.

Results: ADAR1 gene editing by CRISPR/Cas9 was confirmed with sequencing and western blot in both murine (40L and AB12) and human (H2373 and H2461) mesothelioma cells. For 40L ADAR1 knockout (40LKO), there was complete abrogation of tumorigenicity in syngeneic immune competent mice as well as athymic and NSG mice, suggesting that the mechanism of ADAR1 mediated tumorigenesis is not dependent on the presence of an intact immune response. AB12KO (in BALB/c mice) tumor formation was observed, however these were markedly smaller and slower growing compared to parental AB12 tumors. H2373KO formed small tumors when compared to parent cells when xenografted into nude mice As ADAR1 is involved in regulation of interferon (IFN) response, we further examined downstream interferon response genes after interferon beta stimulation (IFNβ) for both the parent and KO cells. ADAR1 parent and KO cells express similar levels of phospho- and total STAT1 and PKR in the presence of IFNβ stimulation. In addition, elf2alpha was not activated or induced by IFNβ. H2373 and the KO cells were IFNβ treated or left untreated in triplicate and RNA-seq analysis was performed. Genes were identified that were differentially expressed and the clustering pattern determined. Also, the level of A to I editing was evaluated indicating a difference between the parent and the knockout cells. Finally, the effect of blocking the in vivo interferon response on the tumorigenic phenotype in both the parental and KO cells was assessed.

Conclusions: ADAR1 silencing is a strong signal in mesothelioma cells reversing the tumorigenic phenotype. The loss of tumorigenicity is unlikely to be dependent on T cell related responses but possibly is mediated through interferon response pathways. In light of abrogation of tumor formation being less dependent on immune factors, specific therapies targeting the adenosine deaminase activity of ADAR1 may prove attractive in mesothelioma therapy.

Keywords: ADAR1, Mesothelioma, interferon

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EP.14A.06 Outcome of Multimodality Therapy Including Radical Surgical Treatment for Malignant Pleural Mesothelioma at a Japanese Regional Institution

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Introduction: The role of surgical therapy for malignant pleural mesothelioma (MPM), including the results of the MARS trials, is currently controversial. On the other hand, excellent results of multimodality treatment including radical surgery have been reported mainly from leading centers in Japan. It has been suggested that the size of the facility and the caseload may play an important role in the outcome of treatment for MPM. In the present study, we report the results of multimodality treatment at our institution, which is a medium-sized regional institution in Japan.

Methods: Of the 110 patients diagnosed with MPM at our institution during the 15-year period from 2009 to 2023, 25 received multimodality treatment including radical surgical treatment with extra pleural pneumonectomy (EPP) or pleurectomy/decortication (P/D). The patients who ended up with exploratory thoracotomy were excluded. These 25 cases were retrospectively reviewed in detail based on clinicopathological parameters and the survival outcome was analyzed focusing on changes of treatment strategy and the surgical procedure. Survival duration was defined as the date of death or last confirmed date of survival from the start of treatment.

Results: The mean age of all 25 patients was 65.2 ± 8.7 (48-79) years, 24 were male and 1 female, and the pathologic types of mesothelioma were 17 epithelioid, 6 biphasic, 1 sarcomatoid, and 1 other. Regarding pathologic stage (UICC ver. 8), 21 patients had stage IB disease, 1 patient with stage IIIA, and the remaining 3 had stage IIIB.As for surgical procedure, EPP was performed in 13 patients and P/D in 12 cases. In terms of the treatment era, 10 cases were treated in the first 8 years and 15 cases in the second 7 years. Regarding surgical procedure, P/D was performed in only one case in the early era, but 11 patients underwent P/D in the second era. In the second half, all patients received any chemotherapy including immunocheckpoint inhibitor prior to surgery. No surgical mortality was observed in the cohort. Major morbidity occurred in 5 patients, 4 of them were observed in the early era.13 death were observed in the series, only one of which was due to COVID-19, but all the others were due to progression of MPM. The median survival time (MST) for all patients was 30.3 months (95% CI: 20.6-169.8), with 1-year OS 79%, 2-year 68%, 3-year 47%, and 5-year 24%. Comparing survival outcomes in the first and second treatment era, MST in the first era was 19.8M (95%CI: 2.7-43.3) and MST in the second era was significantly longer (p=0.01) with 42.3 months (95%CI: 28.7-67.9), 1-year OS 93%, 2-year 93%, 3-year 58% and 5-year 29% in the second era.

Conclusions: The outcomes of multimodality therapy for MPM including radical surgical treatment at our institution were acceptable enough compared to other reported outcomes or historical results, although the cohort may have been biased. Additionally, in the latter seven years, treatment outcomes have clearly improved. However, there are still issues regarding long-term survival.

Keywords: malignant pleural mesothelioma, multimodality treatment, radical surgery

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EP.14A.07 Molecular Characterization and Validation of Live Cell Biobank for Pleural Mesothelioma

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Introduction: The use of tumor derived primary cell cultures for research approaches, especially for in vitro drug testing, can overcome the drawbacks of long-term cultures of cell lines. Here we aim to fully characterize 228 pleural mesothelioma (PM) low passage primary cell cultures generated over the past 16 years at our hospital. In addition to data presented at ESTS 2024, we have completed the cultivation of all available cell cultures and performed analyses in many more cultures.

Methods: For the identification of tumor cells, we performed a stepwise characterization. To exclude fibroblasts, we evaluated epithelial cell origin by immunohistochemical staining (IHC) of pan-Cytokeratin (pan-CK) in FFPE cellblocks. Pan-CK staining intensity was scored as weak (1), moderate (2) and strong (3). Finally, histo (H)-score (sum of intensity multiplied with % positive cells, range 0-300) was calculated. We performed cell growth characterization using colorimetric assay for cell metabolic activity (MTT assay).

Results: We have taken all the frozen stock cells to grow in culture using our established workflow. 132 primary cultures (57.9%) grew after thawing and we could generate more frozen aliquots. Median pan-CK H-score analyzed from 106 primary cultures was 79.6 and ranged from 0-300 (figure 1a). Among them, 34 primary cultures have an H-score over 150. The doubling time, analyzed from 121 cell cultures, ranged from 37-1136 hours (median 89.7 hours) (figure 1b).

Conclusions: We have successfully re-cultured a large number of primary cell stocks, and shown that the doubling time is within a good range for future experiments. Only pan-CK high expressing cell cultures (H-score >150) will be selected for further staining with additional PM tumor markers by IHC compared to the original tumor tissues. The cultures with concordant marker expression compared to the original will be further selected for assessment of copy number variation assay for the final validation. These primary cells represent an invaluable tool for the future use as translational research model for PM.

Keywords: Primary culture, mesothelioma

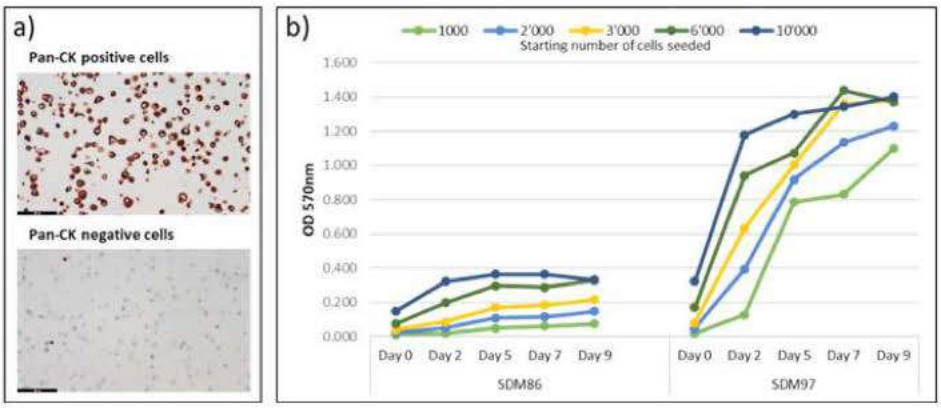

Figure 1
a) Examples of pan-CK staining in positive (H-score 300) and negative cultures (H-score 20)
b) Growth curve of 2 cultures performed over 9 days with MTT assay (optical density measurement with 570 nm light). We show here examples of slow growing (SDM86) and fast growing (SDM97) cultures.

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EP.14A.08 Pleural Mesothelioma: Changes the 9th TNM Staging Brought,a Critical Appraisal of the Clinical T-Stage

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Introduction: Debate regarding the diagnosis, treatment and staging of pleural mesothelioma (PM) is still ongoing. Based on the PM 9th TNM Staging Project of the International Association for the Study of Lung Cancer (IASLC), pleural thickness is the main component to determine the clinical T-stage. However, there is not enough information about the clinical T-stage of PM patients with pleural effusion alone without pleural thickening. This study investigates how survival would be affected in the absence of pleural thickening in PM patients.

Methods: This study included 34 patients between 2009 and 2021 who received multimodal treatment including Pleurectomy/Decortication (P/D). Age, gender, tumour localization, preoperative Computed Tomography findings [(Patients were divided into two groups as the ones with pleural thickening (PT) and pleural effusion (PE)], histological subtypes, pathological stage, and overall survival were evaluated. For statistical analysis, 23.0 software (IBM Corp., Armonk, NY, USA) was used. Median survival was calculated with Kaplan-Meier analysis. A confidence level %95 and a P-value of <0.05 were accepted as statistically significant.

Results: The demographical, clinical and pathological data are summarized in Table 1, and no significant statistical difference was to be found between the groups (p>0.05). The median follow-up time was 30.5 months. The 2-year overall survival was calculated as 63.3% for all patients, 66.7% and 62% for the PE and PT groups, respectively (p = 0.28).

Conclusions: The cardinal issue regarding PM staging is an incompatibility between clinical and pathological staging. The main goal of the 9th TNM staging is to redefine clinical T-stage descriptors to eliminate this inconsistency and to reveal clear survival differences between stages. Hence, T-stage groups were defined by using tumour thickness measurements at different levels of the thorax by utilizing computed tomography. This study reveals that the survival of PM patients with only pleural effusion without pleural thickening is similar to those with present pleural thickening. This group of patients may be included as a brand new T stage descriptor with future staging studies to come feasibly.

Table 1

Keywords: pleural mesothelioma, T-stage, multimodal treatment

Variables	**PE (n=12)**	**PT (n=24)**	**P-value**
Mean Age (years)	56,7	59,3	0,16
Gender (n)			
Male	4	11	0,23
Female	8	11	
Localization (n)			
Right	4	10	0,32
Left	8	12	
Histopathological type (n)			
Epithelioid	9	16	0,28
Mixed	3	6	
Pathological stage (n)			
Stage 1	11	16	0,13
Stage 2	1	6	

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EP.14A.09 Influence of Post-Pleurectomy/Decortication Peritoneal Dissemination Recurrence of Pleural Mesothelioma on Long-Term Survival

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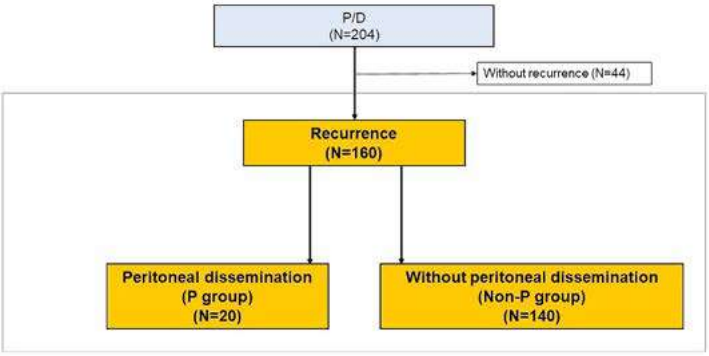
Introduction: In clinical practice, peritoneal dissemination after curative-intent surgery for pleural mesothelioma occasionally recurs. We aimed to investigate the risk factors and prognosis associated with post-pleurectomy/decortication peritoneal dissemination in pleural mesothelioma, which is rarely reported.

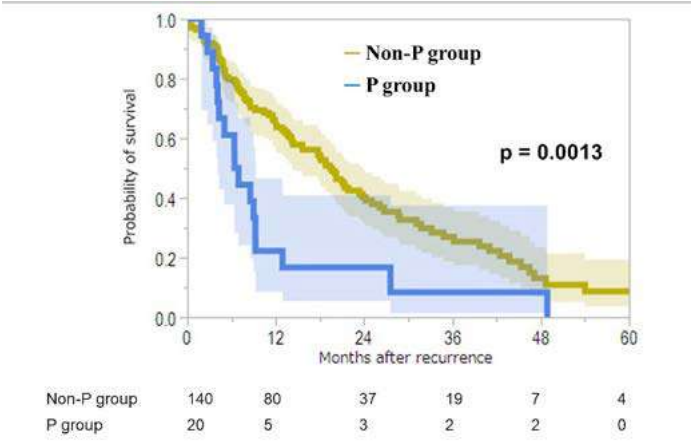
Methods: In this retrospective review, we included 160 patients who experienced recurrence after pleurectomy/decortication for pleural mesothelioma between January 2011 and December 2021. Patients with recurrence were classified according to the initial recurrence pattern: the P group developed recurrence with peritoneal dissemination, and the non-P group developed recurrence without peritoneal dissemination. We determined the risk factors of peritoneal dissemination by multivariable analysis. Survival was analysed using the Kaplan-Meier method and log-rank test.

Results: Of the 160 patients, 20 (12.5%) exhibited peritoneal dissemination and were assigned to the P group, whereas 140 (87.5%) had recurrence without peritoneal dissemination and were assigned to the non-P group. Multivariable analysis revealed that female sex (odds ratio 3.7, 95% confidence interval 1.26-10.8, p = 0.017) and diaphragm reconstruction (odds ratio 2.8, 95% confidence interval 1.0-8.0, p = 0.048) were associated with the P group. Post-recurrence survival was worse in the P group than in the non-P group (1-year post-recurrence survival: 22.2% vs 65.3%, median: 6.7 months vs 19.4 months, p = 0.0013).

Conclusions: Peritoneal dissemination occurred in approximately one in every eight patients with recurrence after pleurectomy/decortication for pleural mesothelioma, and the incidence was significantly higher in females and patients undergoing diaphragm reconstruction. Moreover, post-operative recurrence of peritoneal dissemination was associated with poor prognosis.

Keywords: pleural mesothelioma, pleuractomy/decortication, peritoneal dissemination





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EP.14A.10 The Impact of Serum-Based Inflammatory Biomarkers on Tumor Proliferation and Prognosis in Malignant Pleural Mesothelioma

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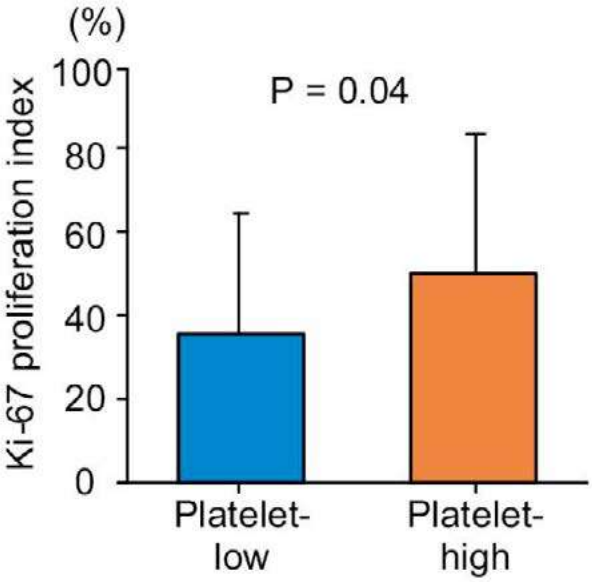
Introduction: Malignant pleural mesothelioma (MPM) is a highly aggressive disease with a poor prognosis. However, prognostic biomarkers for MPM patients are not yet fully understood. This study aims to evaluate the impact of serum-based inflammatory biomarkers on tumor proliferation and prognosis in MPM patients.

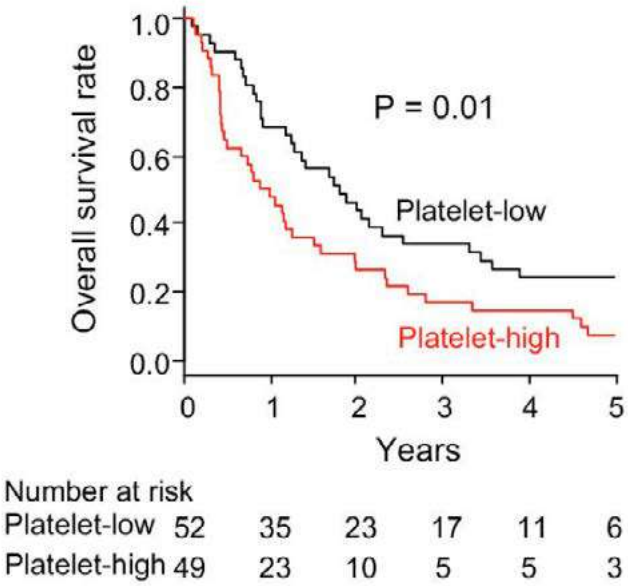
Methods: A total of 83 MPM patients diagnosed from 1998 to 2010 were studied. Tumor proliferation was evaluated using the Ki-67 proliferation index. The cut-off values for pretreatment levels of white blood cell count, neutrophil count, lymphocyte count, platelet count, C-reactive protein, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio (PLR), and systemic immune-inflammation index (SII, platelet count × neutrophil count / lymphocyte count) were determined using receiver operating characteristic curve analysis for predicting 5-year survival. Univariate and multivariate Cox regression analyses were performed to estimate the prognostic impact of parameters on 5-year overall survival (OS).

Results: There were 45 epithelioid, 22 sarcomatoid, and 16 biphasic types. Patients were distributed as follows: 10 in stage I, 14 in stage II, 26 in stage III, and 33 in stage IV. Twenty-three cases underwent surgical treatment, and all of them were treated with extrapleural pneumonectomy. The mean ± standard deviation of the Ki-67 proliferation index in MPM samples was 43.5 ± 31.5%. The median OS was 15.0 months. Platelet count was significantly associated with the Ki-67 proliferation index in MPM cells. In univariate analysis, platelet count, PLR, and SII were significant prognostic factors. Multivariate Cox regression analyses revealed platelet count and PLR as significant prognostic factors for 5-year OS, after adjusting for clinicopathological factors.

Conclusions: Among serum-based inflammatory biomarkers, platelet count may be a useful prognostic marker related to tumor proliferation in MPM patients.

Keywords: mesothelioma, biomarker





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EP.14A.11 Mortality Based on Treatment in Stage III Non-Epithelioid Pleural and Pericardial Mesothelioma - A Review from a National Cohort

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Introduction: Mesothelioma is a rare condition with an extremely high mortality rate. The epithelioid pathology pattern has previously been associated with significantly better outcomes and responses to treatment when compared to the non-epithelioid patterns. Since immunotherapy was introduced as a preferred treatment option in mesothelioma, data on patients who are not eligible for treatment has been difficult to obtain. This study aimed to evaluate mortality outcomes in these patients with stage III non-epithelioid mesothelioma using the Surveillance, Epidemiology, and End Results (SEER) database.

Methods: The SEER*Stat software was utilized to extract data on patients diagnosed with pleural and pericardial non-epithelioid mesothelioma (ICD-O-3 codes 8810, 8811, 8820, 8821) between 2004 and 2017. The patients were further categorized by stage (III) and treatment received (chemotherapy alone, surgery alone, surgery with chemotherapy, or no chemotherapy or surgery). The primary outcome was overall survival (OS), analyzed using Kaplan-Meier curves and compared with hazard ratios (HR) with a 95% confidence interval (CI). These outcomes were calculated using SPSS software.

Results: Of the patients (n=872) diagnosed with stage III non-epithelioid mesothelioma with known survival, 53.9% were under the age of 75, 80.2% were male and 13.0% received some form of radiation therapy. Of those who received surgery (n=250), 62.8% were under 75, 80.0% were male and 35.6% had a total pneumonectomy. The 3-year survival for patients who did not receive chemotherapy or surgery was 9.7%. The mortality of patients who received chemotherapy and surgical treatment as well as surgery alone was significantly better than those who did not receive these treatments (Figure 1), especially in the first year. Those who received chemotherapy alone did not receive any significant benefit from treatment.

Conclusions: The benefit of surgical treatment noted in this study with and without chemotherapy has not been noted previously in patients with stage III non-epithelioid mesothelioma. The survival of the patients receiving surgery with stage III disease was like a previous study from Flores et al. in 2008 showing a median survival of 11 months for their patients overall with worse results in non-epithelioid histology. This new data may improve our understanding of surgical treatment in these patients and may provide evidence for further exploration of surgical treatment of these patients.

Keywords: Mesothelioma, Non-Epithelioid, Survival

Treatment	Patients (%)	Hazard Ratio (95% CI)	1-Year Survival (p-value)	2-Year Survival (p-value)	3-Year Survival (p-value)
No Chemotherapy or Surgery	341 (39.1)	--	32.8%	14.1%	9.7%
Chemotherapy Alone	281 (32.2)	1.06 (0.897-1.25)	26.3% (0.078)	13.9% (0.944)	7.8% (0.419)
Surgery Alone	95 (10.9)	0.857 (0.759-0.968)	44.2% (0.040)	20.0% (0.157)	12.6% (0.403)
Chemotherapy and Surgery	155 (17.8)	0.922 (0.864-0.985)	40.9% (<0.001)	16.1% (0.550)	6.5% (0.237)

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EP.14A.12 Impact of a Multidisciplinary Team on Overall Survival in Patients with Pleural Mesothelioma: Experience from a Single Institution in Mexico

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Introduction: Pleural mesothelioma is a complex disease that often requires specialized treatment approaches. Multidisciplinary team (MDT) provide patients with access to a wide range of expertise and resources that may not be available in a single medical specialty or institution. The MDT for thoracic malignancies was established in 2014 in our center.

Methods: All cases diagnosed between January 2011-January 2023 were assigned to pre- and post- MDT intervention cohorts. Local databases were the source of the data extraction. Overall survival was recorded from date of first suspicious imaging to death. A 12-months follow-up was conducted on all cases. Kaplan-Meier survival analysis and the log-rank test were used to calculate OS. Univariate and multivariate analysis to identify variables associated with OS were assessed using Cox regression model. The data capture and statistical analysis will be carried out in the SPSS v.20 program (SPSS Inc,Chicago, IL, USA).

Results: We evaluated a total of 49 patients. The median age for the patients was 53.1 ± 13.4 years old. Patients comprised 83.8 % males and 16.1 % female; male/female ratio: 1/0.26). By WHO classification criteria for pleural tumor, 80.6% of the tumors were epithelioid cell type and 19.4 % nonepithelioid cell type. Among these patients, 29% were classified as stage III and 71% stage IV. According to pre and post MDT, 15 (30 %) were pre and 34 (70 %) post MDT group. Median OS of patients in the pre and post MDT were 9.9 and 22 months, respectively. The Kaplan Meier method and log-rank test indicated that MDT intervention was associated with superior OS (p=0.032).

Conclusions: The establishment of MDT is associated with improved overall mean survival. Our results may be explained by improved access to more specialized care, novel therapies, advanced surgical techniques and supportive care services, more research is needed. These findings supports a boader adoption of MDT.

Keywords: pleural mesothelioma, survival, MDT

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EP.14A.13 Gender and Racial Disparities in Hospitalization and Outcomes of Malignant Mesothelioma in the United States

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Introduction: Research on sex and racial disparities in-hospital outcomes for Malignant mesothelioma (MM) hospitalizations is limited. This study examined disparities in hospitalization and outcomes for MM by sex and race across the United States.

Methods: The nationwide inpatient sample was queried from 2017 to 2020 using relevant ICD-10 diagnostic codes. All adult hospitalizations for MM were included. Baseline characteristics and in-hospital outcomes in patients with a primary diagnosis of malignant mesothelioma were compared between males and females and between white and nonwhite patients using Pearson's $\chi 2$ tests and linear regression for categorical and continuous variables. Multivariable logistic regression models adjusted for potential confounding factors and statistically significant comorbidities between the two cohorts.

Results: Approximately 35,230 hospitalizations for malignant mesothelioma were identified and analyzed. Of these, 24,585 (69.8%) were male and 10,645 (30.2%) were female. Approximately 25,885 (73.5%) were white compared with 9,345 (26.5%) nonwhite individuals. Male patients were significantly older and had a higher comorbidity burden than females (Charlson score of ≥3: 71% vs. 59.4%; P<0.001; Table 1). A total of 3,900 mortalities were recorded during the study period. Male sex (aOR: 1.23; 95% CI: 1.01-1.37; P=0.043) and older age (aOR: 1.01; 95% CI: 1.01-1.02; P=0.001) were significantly correlated with greater odds of mortality. Race was not a significant modifier of mortality odds. Compared with hospitalizations for male and white individuals, females (mean LOS: 9.3 vs. 7.7; P<0.0001) and nonwhite individuals (mean LOS: 10.7 vs. 7.3; P<0.0001) were hospitalized for longer durations. White race was associated with significantly lower hospital costs compared with nonwhite individuals ($97,464 vs. $167,715; P<0.001). Females incurred greater costs than males ($135,864 vs. $107,520; P<0.001). Female sex was associated with lower odds of any arrhythmias (aOR: 0.82; 95% CI: 0.71-0.94; P = 0.004) and greater odds of depression (aOR: 2.13; 95% CI: 1.06-4.25; P = 0.004), atelectasis (aOR: 1.68; 95% CI: 1.08-1.80; P = 0.035), and generalized anxiety (aOR: 1.98; 95% CI: 1.10-3.57; P = 0.023). Race was not significantly correlated with the risk of respiratory failure, atelectasis, or heart failure.

Conclusions: Male sex was significantly correlated with a greater risk of mortality from malignant mesothelioma. Female sex was significantly correlated with poorer outcomes, except mortality, compared with men. White race was correlated with longer hospital stays and higher hospital costs than nonwhite individuals with malignant mesothelioma.

Keywords: Mesothelioma, Malignant, Gender

Table 1: Baseline Characteristics of Hospitalized Malignant Mesothelioma Patients: Gender-Stratified Comparison of Patient and Hospital-Level Covariates

	N (%) Unless otherwise specified		
Variable	**Male**	**Female**	***P*-value**
Patients	24,585 (69.8)	10,645 (30.2)	
Mean age, yr. (SD)	62.3 ± 2.4	61.5 ± 4.3	<0.001
Race			<0.001
White	18,675 (81.0)	7,200 (72.7)	
Black	1,835 (8.0)	1,170 (11.8)	
Hispanic	1,965 (8.5)	1,155 (11.7)	
Asian/Pacific Islanders	505 (2.2)	345 (3.5)	
Native Americans	84 (0.4)	40 (0.4)	
CCI			<0.001
0	713 (2.9)	522 (4.9)	
1	541 (2.2)	703 (6.6)	
2	5,900 (24)	3,098 (29.1)	
≥3	17,455 (71.0)	16,323 (59.4)	
Hospital location/teaching status			0.003
Rural	1,545 (6.3)	515 (4.8)	
Urban nonteaching hospital	4,170 (17.0)	1,570 (14.8)	
Urban teaching hospital	18,860 (76.7)	8,560 (80.4)	
Insurance type			<0.001
Medicare	16,455 (69.3)	5,615 (53.8)	
Medicaid	1,580 (6.7)	1,259 (12.1)	
Private, including HMO	5,275 (22.2)	3,345 (32.2)	
Self-pay	400 (1.9)	225 (2.2)	
Comorbidities			
Obesity	1,185 (4.8)	710 (6.7)	0.002
Hypertension	9,620 (39.2)	3,985 (37.4)	0.192
Hyperlipidemia	8,295 (33.8)	2,780 (26.1)	<0.001
Tobacco use	11,095 (45.2)	3,060 (28.8)	<0.001
Old MI	2,070 (8.4)	605 (5.7)	<0.001
CCF	4,810 (19.6)	1,510 (14.2)	<0.001
Peripheral vascular disease	1,885 (7.7)	485 (4.6)	<0.001
Cerebrovascular disease	1,044 (4.3)	510 (4.8)	0.325
COPD	6,550 (26.7)	2,335 (21.9)	<0.001
Dementia	995 (4.1)	264 (2.5)	0.002
Rheumatoid disease	685 (2.8)	1,055 (9.9)	<0.001
Chronic renal disease	4,795(19.5)	1,325 (12.5)	<0.001
Chronic liver disease	1,377 (5.6)	1,623 (6.6)	0.134
Diabetes types 1 and 2	6,097 (24.8)	2,033(19.1)	0.008
AIDS	325 (1.3)	85 (0.8)	0.076
All Patient Refined DRG: Risk of Mortality			0.023
Minor likelihood of dying	1,925 (7.8)	840 (7.9)	
Moderate likelihood of dying	6,205 (25.3)	2,565 (24.1)	
Major likelihood of dying	9,825 (40.0)	3,995 (37.5)	
Extreme likelihood of dying	6,620 (27.0)	3,245 (30.5)	

P values are significant at<.05

MI, myocardial infarction; CCF, congestive cardiac failure; COPD, chronic obstructive pulmonary disease; DRG, diagnosis-related groups; HMO, health maintenance organization

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EP.14A.14 Clinical Insights and Survival Outcomes of Malignant Pleural Mesothelioma: An Experience from a Tertiary Care Centre in India

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Introduction: Malignant pleural mesothelioma (MPM), a rare cancer comprising only 0.13% of cancer incidences in India has dismal survival. There is limited literature on clinicopathological profile and treatment outcomes of MPM in India, with scant information primarily confined to few case reports.

Methods: This is a retrospective cohort study conducted at a tertiary care cancer centre from north India. Case records of patients of MPM treated between January 2016 and July 2023 were analysed for clinicopathological profile and treatment outcomes. Response rates, progression-free survival (PFS) and overall survival (OS) were recorded. Descriptive statistics were employed for clinicopathological characteristics, and Kaplan-Meier analysis assessed survival.

Results: A total of 25 patients were identified with MPM, with a median age of 48 years and a male-to-female ratio of 1.3. Asbestos exposure was documented in only 8 (32%) cases. Common symptoms included breathlessness (72%), cough, and chest pain (64% each). Predominant histology was epithelioid, seen in 21 (84%) patients followed by biphasic and sarcomatoid, in 3 (12%) and 1 (4%) patients, respectively. Majority of the patients (64%) presented with a metastatic disease. Of 25 patients 18 (72%) received systemic chemotherapy, with pemetrexed-platinum (either cis- or carbo-platin). Among them 4 (22.2%) patients received bevacizumab as maintenance. Objective response rate (ORR) for first-line systemic therapy was 44.4% with a clinical benefit rate of 83.3%. Extrapleural pneumonectomy was performed in 4 (16%) patients. 10 patients received subsequent lines of systemic therapy which included immunotherapy (nivolumab + ipilimumab), gemcitabine (with or without bevacizumab) and oral metronomic therapy (containing cyclophosphamide, etoposide and pazopanib). Median PFS and OS for patients receiving systemic therapy were 14.6 (95% CI: 6.9 - 22.3) and 26 (95% CI: 23.3 - 28.7) months, respectively.

Conclusions: With the response rates of 44.4% and median survival of 26 months, the outcomes of systemic therapy in MPM are comparable with the global population. Given the aggressive nature and grim prognosis of the disease, it is imperative to advance our comprehension of its biology and treatment efficacy factors.

Keywords: Mesothelioma, Rare tumor, LMIC

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EP.14A.15 Racial Disparities in Risk of Bone Metastasis at Diagnosis of Malignant Pleural Mesothelioma

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Introduction: Malignant pleural mesothelioma (MPM) is a rare and aggressive cancer primarily caused by exposure to asbestos in occupational and environmental settings. Despite the ban on asbestos in the 1970's, the latency period of 20-40 years post-exposure continues to pose a significant public health challenge. Bone metastases are reported in around 11% of MPM cases. To our knowledge, disparities in the presence of bone metastases at the time of MPM diagnosis among different racial groups have not yet been explored in the literature. This retrospective study aims to uncover such disparities.

Methods: Utilizing the SEER Research Plus Database, this study focused on patients diagnosed with MPM between 2000-2020. Inclusion criteria consisted of confirmed malignant behavior, specified age, and precise histological classification of mesothelial neoplasms (morphology histology recode 9050-9059), with the primary site identified as "pleural." Individuals aged 18 or younger were excluded. Variables studied were sex, race, survival months, median income, residential area, marital status, and metastases (bone, brain, lung, and liver) at diagnosis. Disease stage was classified into localized, regional, or advanced disease. Logistic regression was employed to assess odds of bone metastases at diagnosis among different racial groups while controlling for pertinent factors.

Results: 5797 individuals were included. 79.63% were White (W), 3.88% Asian/Pacific Islander (API), 4.97% Black (B), 11.11% Hispanic (H) and 0.41% American Indian (AI). 50.15% were 65-79 years of age, followed by ≥ 80 years old (31.33%). 76.90% were male, married (66.33%), lived in an urban area (89.65%) and earned at least $50,000 per year. At time of diagnosis, 5.12% had bone metastases, 0.62% brain metastases, 2.48% liver metastases and 7.16% lung metastases. Individuals with bone metastases at the time of diagnosis were more likely to be API when compared to W and have concomitant liver metastases, lung metastases and brain metastases. Females demonstrated reduced odds of bone metastases at MPM diagnosis. Other variables studied were not significantly associated.

Conclusions: Our study found that Non-Hispanic Asians/Pacific Islanders were significantly more likely to present with bone metastases at the time of MPM diagnosis compared to White-population. This finding underscores the importance of integrating bone imaging more frequently into clinical evaluation of patients with advanced MPM, particularly within the API demographic. Future research endeavors should dive deeper into understanding the underlying mechanisms driving these disparities, considering genetic predisposition, environmental exposures and access to healthcare services.

Factors associated with bone metastases at presentation in patients with MPM

Keywords: Mesothelioma, Racial disparities, SEER

Variable	OR	p value	95% CI
Race			
Asian/Pacific Islander	1.99	**0.007**	1.20-3.31
Black	0.79	0.451	0.44-1.43
Hispanic	0.92	0.689	0.61-1.37
American Indian	0.56	0.611	0.62-5.07
Age			
50-64 years old	1.05	0.906	0.45-2.41
65-79 years old	0.76	0.519	0.33-1.72
≥80 years old	0.58	0.215	0.25-1.36
Income			
$35,000-$49,999	0.35	0.072	0.11-1.09
$50,000-$64,999	0.43	0.141	0.14-1.31
$65,000-$74,999	0.35	0.072	0.11-1.09
≥$75,000	0.43	0.138	0.14-1.31
Marital status			
Married	0.87	0.485	0.59-1.27
Divorced	1.18	0.534	0.69-2.03
Widowed	0.86	0.581	0.51-1.44
Domestic partner	0.99	0.997	0.17-5.65
Residential Area			
Metropolitan	1.12	0.642	0.68-1.83
Sex			
Female	0.67	**0.021**	0.48-0.94
Metastases at diagnosis			
Liver metastases	6.85	**<0.001**	4.57-10.27
Lung metastases	3.79	**<0.001**	2.78-5.16
Brain metastases	3.59	**0.003**	1.55-8.29

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EP.14A.16 Effect of Talc Pleurodesis on the Treatment of Diffuse Pleural Mesothelioma Patients Treated with Chemotherapy

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Introduction: Diffuse pleural mesothelioma (DPM) is a malignant tumor with a poor prognosis for which no generally accepted treatment protocols have yet been developed. As most patients are not eligible for surgery or radiotherapy due to the location and spread of the tumor, they are treated with chemotherapy. Talc pleurodesis for DPM, which is widely used in the palliative treatment of malignant pleural effusions, is controversial. Although a limited number of studies indicate that talc induces apoptosis and may prolong survival, there is uncertainty about the effect of talc on survival in DPM. The aim of this study was to investigate the effect of talc pleurodesis on the survival of DPM patients treated with chemotherapy.

Methods: The study included 328 patients who were treated with a platinum-gemcitabine or platinum-pemetrexed chemotherapy protocol between 1999 and 2023. Those who underwent talc pleurodesis in addition to chemotherapy formed one group (Chemo-talc group), and those who received chemotherapy formed the second group (Chemo group). The demographic and clinical characteristics of the patients were obtained from the mesothelioma database of the Lung and Pleural Cancers Research and Clinical Center (Eskisehir, Turkey) and analyzed.

Results: The mean age of the patients was 62.59±10.23 years, 194 (59.1 %) of the patients were male and 134 (40.9 %) were female. Pleurodesis with talc was performed in 106 (32.3 %) of the 328 patients. When we compared the demographic and clinical characteristics of the two groups, patients in the chemo-talc group were older (p=0.003), had higher asbestos exposure (p=0.034), had a higher epithelioid subtype (p=0.037) and had higher stage I-II disease (p=0.018) than the chemo group. Survival time was 15.00±1.43 months in the chemo-talc group and 11.00±0.65 months in the chemo group. The median survival rate was higher in the chemo-talc group (p=0.008). The 12-, 24- and 36-month survival rates were 58.4%, 23.8% and 11.9% in the chemo-talc group. In the chemo group they were 42.3 %, 15.9 % and 5.9 % (p: 0.027). The factors that influenced survival were histopathology [HR: 26.31 (1.64-1.3); p<0.001] and stage [HR: 12.21 (1.57-1.22); <0.001] in multivariate Cox regression analysis. Pleurodesis with talc had no effect on survival [HR: 1.83 (0.84-0.66); p=0.176] after adjustment for histopathology and stage.

Conclusions: According to the study data, the multivariate analysis showed no significant influence of talc pleurodesis in addition to chemotherapy on the survival of patients with DPM. However, the study was conducted retrospectively and could be biased. Despite this negative result, the significant relationship between median survival times and survival rates of the study groups by talc pleurodesis in univariate analyses suggests that prospective, randomized, controlled, multicenter studies should be conducted on this topic.

Keywords: Mesothelioma, Talc pleurodesis, Chemotherapy

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EP.14A.17 A Retrospective Study Looking at the Demographics and Occupations of Patients with Mesothelioma in Kent, South East England

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Introduction: Mesothelioma is highly associated with prior asbestos exposure, with a significant proportion of occurring occupationally. There is usually a significant latency period between the asbestos exposure and the development of mesothelioma. Due to the significant reduction in asbestos use towards the end of the 20thcentury and the latency, it is expected that the peak of mesothelioma should have occurred before 2030. This study aimed to find out the epidemiology, demographics, and occupational histories of patients with mesothelioma in the region of Kent. In doing so, looking to gain an understanding of the current risk factors.

Methods: The sample group included patients diagnosed with mesothelioma in Kent between April 2019 to January 2024 which were identified in the database managed within the Kent Oncology Centre. The anonymised database included the occupational or asbestos exposure histories of mesothelioma patients, where available. It additionally included demographical data such as age, gender, histological subtype, and location in Kent where diagnosed. This demographical data was then collated and analysed, enabling comparisons to be made within Kent and to prior studies in the UK. The occupations or stated likely route of asbestos exposure was assigned into defined categories which were then ranked by the highest number of cases to the lowest. Research ethics was sought for the study from the KMMS Research Ethics Advisory Group (REAG) and the study was registered as a service evaluation at the MTW NHS trust.

Results: Over this 4 year period 409 cases were identified, with April 2020 to March 2021 having the highest number of cases at 117, and April 2022 to March 2023 having the lowest number of cases with 87 being identified. 337 cases were male (82.4%) and 72 were female (17.6%). The mean age of diagnosis was 75.7 years old of those where this was identified, with males this being 75.9 years old and for females 74.9 years old. Where the histological subtype was identified, epithelioid accounted for the most cases (72.5%), followed by sarcomatoid (16.0%), biphasic (11.2%) and desmoplastic (0.3%). When comparing the age of diagnosis for each of the main histological subtypes, epithelioid was 74.1, sarcomatoid 76.3 and biphasic 74.7 years old. There was no statistical difference in age by histological subtype, gender and NHS trust. In 202 cases, the occupation(s) or stated likely route of asbestos exposure was identified. The categories ‘Construction’ (37.3%), ‘Other’ (9.8%), ‘Shipbuilding and dockyards’ (8.4%), ‘Armed forces’ (6.7%) and ‘Boiler, pipe and heating’ (6.7%) were the highest 5 categories. When looking at trades within the construction category, the 3 highest were builders (33.7%), carpenters (20.9%) and plumbers (11.6%).

Conclusions: Overall, the demographics appear to be congruent with previously identified trends within the UK and south east England. There was no significant variation in these demographics within Kent. The occurrence of mesothelioma is consistent with existing data on occupational exposure. We plan to serially assess this as the incidence drops over the next 10 years to detect any changes in trends.

Keywords: Mesothelioma, Exposure, Occupational

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EP.14A.18 Single-Center Experience of Hyperthermic Intrathoracic Chemoperfusion for Malignant Mesothelioma

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Introduction: The management of malignant mesothelioma requires a multidisciplinary approach, and heated intrathoracic chemoperfusion (HITHOC) may play an important role in better disease control. We evaluated our institutional experience with cytoreductive surgery and HITHOC for malignant mesothelioma.

Methods: We performed a single-institution, retrospective study on patients who underwent cytoreductive surgery (extrapleural pneumonectomy or pleurectomy with decortication) and intraoperative HITHOC for malignant mesothelioma from January 2009 to December 2022. After debulking the thoracic disease, chest tubes were placed, and a chemotherapy solution heated to 40 or 42 degrees Celsius was circulated for one hour. When cisplatin was used, the dose was 175-200 mg/m2, and 30 mg when mitomycin was used. Preoperative, operative, short-term post-operative, and long-term survival data were collected and analyzed.

Results: During the study period, 38 patients underwent HITHOC along with cytoreductive surgery (34 pleurectomy with decortication and 4 extrapleural pneumonectomy; Table). Twenty-one patients (55.3%) underwent concomitant diaphragmatic resection, and 10 patients (26.3%) had wedge lung resection. The median operative time was 8 hours and 40 minutes, with an estimated blood loss on the median of 850 ml. Complication ≥ Grade III was seen in 10 patients (26.3%), and the median length of stay was 8 days. There was no 30- or 90-day mortality, and one-year survival was 80%, with a median follow-up of 19 months. Adjuvant chemotherapy was delivered in 20 patients (52.6%), which was associated with significantly longer overall survival (median: 93 months vs 16 months; p=0.003; Figure).

Conclusions: HITHOC with cytoreductive surgery was a feasible treatment modality with a good short-term outcome. Reasonable long-term survival was observed in the patients, especially those who underwent adjuvant chemotherapy. However, conclusions regarding the survival benefit from these interventions are difficult to assess, owing to the rarity of the disease and lack of a comparison group.

Keywords: Malignant mesothelioma, Hyperthermic intrathoracic chemoperfusion, Adjuvant chemotherapy

Figure. Overall Survival with or without Adjuvant Chemotherapy

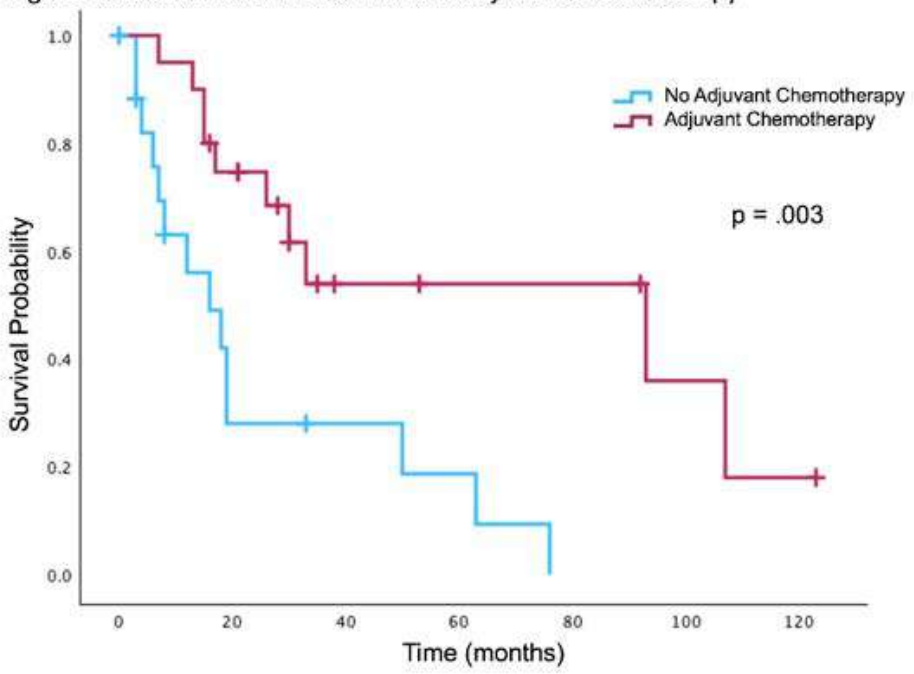

Table. Demographics

Total		38
Age (year-old, median)[IQR]		68 [63-73]
Sex	Male	29 (76.3%)
	Female	9 (23.7%)
Median Follow-up (month)[IQR]		19 [8, 36]
Histological Subtype	Epithelioid	30 (78.9%)
	Biphasic	8 (21.1%)
Laterality	Right	16 (42.0%)
	Left	22 (58.0%)
Pathological T Stage	pT1	7 (18.4%)
	pT2	14 (35.9%)
	pT3	14 (35.9%)
	pT4	3 (7.8%)
Pathological N Stage	pN0	23 (60.5%)
	pN1	13 (34.2%)
	pN2	2 (5.3%)
Paghological M Stage	pM1	2 (5.3%)
Simultaneous/Metachronous Peritoneal Mesothelioma		4 (10.5%)
Procedure	PD	34 (89.5%)
	EPP	4 (10.5%)
HITHOC Agent	Cisplatin	35 (92.2%)
	Mitomycin C	3 (7.8%)
Estimated Blood Loss (ml, median) [IQR]		850 [475-1200]
OR Time (minute, median)[IQR]		520 [281-614]
Chest Tube Days (day, median)[IQR]		5 [6-8]
Length of Hospital Stay (day, median)[IQR]		8 [7-11]
Complication ≥Grade III		10 (26.3%)
30-day Mortality		0 (0%)
90-day Mortality		0 (0%)
Neoadjuvant Chemotherapy		10 (26.3%)
Adjuvant Chemotherapy		20 (52.6%)

IQR: Interquartile Range, HITHOC: Hyperthermic Intrathoracic Chemotherapy,
PD: Pleurectomy and Decortication, EPP: Extrapleural Pneumonectomy

EP.14A MESOTHELIOMA, THYMOMA, AND OTHER THORACIC TUMORS - MESOTHELIOMA
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EP.14A.19 Pleurectomy Decortication for Malignant Pleural Mesothelioma: Safe and Faster Technique

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Introduction: Pleurectomy decortication (PD) is a relatively new surgical treatment for malignant pleural mesothelioma (MPM), and its usefulness compared to extrapleural pneumonectomy (EPP) is not fully elucidated.

Methods: We retrospectively evaluated data from 79 patients with MPM who underwent EPP or PD at our institution between 1999 and 2022. Perioperative outcomes and postoperative prognoses were compared between EPP and PD.

Results: EPP was performed in 41 cases (51.9%), and PD was performed in 38 cases (48.1%). Since 2017, PD has been performed using a standardized procedure with the collaboration of multiple surgeons. The median operation duration was significantly shorter in PD than in EPP (PD: 231 minutes [interquartile range: 203-261], EPP: 350 minutes [231-570], $P < 0.01$). The median amount of intraoperative bleeding ($P = 0.42$) and length of postoperative hospital stay ($P = 0.42$) were not different between EPP and PD. The postoperative complication of Clavien-Dindo grade 3 or more was more frequent in EPP group (incidence rate of 31.7%) than that in P/D group (5.3%) ($P < 0.01$). Patients who underwent EPP and PD had a two-year OS of 48.8±8.08% and 60.5±9.6%, respectively ($P = 0.58$).

Conclusions: PD can be completed safely and quickly using a standardized procedure. Since EPP and PD have a comparable postoperative oncologic prognosis, PD would be recommended over EPP as surgery to cure MPM because it is safer and less invasive.

Keywords: mesothelioma, Pleurectomy decortication, extrapleural pneumonectomy

EP.14A MESOTHELIOMA, THYMOMA, AND OTHER THORACIC TUMORS - MESOTHELIOMA
SATURDAY, SEPTEMBER 7, 2024 - 11:58 - 11:59

EP.14A.20 Hyperthermic Intrathoracic Chemotherapy Following Cytoreductive Surgery in Patients with Pleural Mesothelioma

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Introduction: Hyperthermic intrathoracic chemotherapy (HITOC), in combination with cytoreductive surgery, has demonstrated better control of primary tumors, lower rates of recurrence and markedly improved survival rates in patients with pleural mesothelioma as compared to cytoreductive removal alone. Along with the improvements in mortality and recurrence with this mode of chemotherapeutic delivery, the current literature describes higher concentration of chemotherapy in the thoracic cavity with reduced systemic toxicity. Because of the rarity of pleural mesothelioma, more data and cases must be described to fully elucidate how beneficial HITOC can be for patients with pleural malignancies.

Methods: This is a case series on 7 patients with pleural mesothelioma who received HITOC after cytoreductive surgery. Analysis included demographics, type of malignancy, date of diagnosis, date of surgery, 30-day survival from date of operation, length of progression-free survival, and whether patients received systemic chemotherapy or immunotherapy in addition to perioperative HITOC. Also included are post-operative complications.

Results: The cohort was composed of 5 white Hispanic patients, 1 black non-Hispanic patients, and 1 white non-Hispanic patient, with a median age of 63 (31-69). 6 of the 7 patients had pleural mesothelioma of epithelioid type, and the 7th patient had biphasic type. The mean progression-free survival in months from the date of surgery is 13.9 months (range 5-25 months). 1 patient has not progressed at all, with a progression-free survival of 25 months. The mean length of hospital stay was 20 days (4-57). 3 patients suffered post-operative DVTs, 1 patient suffered a pericardial effusion, 3 patients suffered cardiac arrythmias, 1 patient suffered an empyema, 1 a pleural effusion, and 2 a pneumothorax. 2 of the patients had no post-operative complications. 3 of the patients received adjuvant chemotherapy, 2 patients received both adjuvant chemotherapy and immunotherapy, and 1 patient received perioperative immunotherapy.

Conclusions: This series of patients who received HITOC for pleural mesothelioma demonstrates lower progression-free survival and overall survival than is noted in the medical literature. This highlights the bias of patient selection on this treatment modality. Our case series also demonstrates the safety of immunotherapy prior and following HITOC in pleural mesothelioma. It is important to study cases of pleural mesothelioma treated with HITOC prospectively to elucidate the effectiveness of this treatment and proper patient selection. The reduced systemic toxicity with HITOC compared to systemic chemotherapy, along with its increased penetrance into tissue of the pleural cavity, provides incentive to further explore this therapy for pleural mesothelioma.

Keywords: Hyperthermic Intrathoracic chemotherapy, Pleural Mesothelioma

EP.14B MESOTHELIOMA, THYMOMA, AND OTHER THORACIC TUMORS - THYMUS
SATURDAY, SEPTEMBER 7, 2024 - 11:58 - 11:59

EP.14B.01 Prognostic Impact of Tumour Size in Resected Thymic Epithelial Tumours - A Validation Analysis of the 9th TNM Staging System -

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Introduction: In the ninth edition of the TNM classification for thymic epithelial tumors, modifications were introduced to the categorization of T factors. Previously, T1 was differentiated based on the presence or absence of encapsulation, while other T factors did not incorporate tumor size into their classification, unlike the approach taken for other cancer. This revision's reclassification of T1 according to tumor size represents a significant alteration. Furthermore, the involvement of the lung and diaphragmatic nerve, which was formerly categorized as T3, has been reclassified to T2.

Methods: In this study, we retrospectively reviewed 67 cases of thymic epithelial tumors undergone operation from 2013 to 2023 at our hospital.

Results: Of the 67 patients, 30 were males, and 37 were females. The median age was 63 years (range: 23-84 years). A total of 56 cases were diagnosed as thymoma, and 11 as thymic carcinoma. Histology of thymic carcinoma cases included eight of squamous cell carcinoma, one of thymic carcinoid, and two of other types. According to the 8th edition of the TNM classification, the distribution across T categories was as follows: T1a/T1b/T2/T3/T4 in 45/11/1/8/2 cases, respectively, with stage distribution classified as Stage I/II/IIIa/IIIb/IVa in 56/1/5/2/3 cases. The World Health Organization (WHO) histological classification for thymomas identified A/AB/B1/B2/B3 types in 16/6/12/14/6 cases. The median postoperative follow-up period was 52 months (range: 6-140 months). Among cases undergoing complete resection (n=63), there were three recurrences, all of which were thymic carcinomas, Five year recurrence free survival (RFS) rate of 96.2% (100% for thymoma, 50.0% for thymic carcinoma). The maximum tumor diameter prior to treatment initiation averaged 33 mm (range: 13-83 mm). Tumor doubling time (TDT) was assessable in 39 cases, with an average TDT of 802 days for thymomas (n=34) and 312 days for thymic carcinomas (n=5), indicating a significantly slower growth rate in thymomas (p=0.04). For tumors exceeding 5 cm in diameter, a significantly shorter RFS was observed, consistent with findings for thymomas (n=56).

Conclusions: Thymic epithelial tumors exceeding 5 cm in diameter have been identified as having a high risk of recurrence, thereby affirming the revised TNM classification's validity. Currently, T1a and T1b are both categorized under stage I. It may become imperative in future iterations to further subdivide stage I, analogous to the stratification employed for primary lung cancer.

Keywords: TNM classification, Thymic epithelial tumors, Thymoma

EP.14B MESOTHELIOMA, THYMOMA, AND OTHER THORACIC TUMORS - THYMUS
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EP.14B.02 Perioperative Efficacy and Safety of Efgartigimod in Thymoma Associated Myasthenia Gravis

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Introduction: This study provides primary data about perioperative efficacy and safety of efgartigimod in patients with thymoma associated myasthenia gravis (TAMG).

Methods: We conducted a prospective analysis of TAMG patients in acetylcholine receptor antibody-positive (AChR-Ab+) generalized myasthenia gravis who underwent efgartigimod weekly (maximum 4 weeks) during the perioperative period of thymectomy. Efgartigimod was administered intravenously over approximately 1 hour at a dose of 10 mg/kg according to patient's weight.

Results: A total of 13 cases of TAMG were enrolled with a median age of 43 years. According to Myasthenia Gravis Foundation of America (MGFA), there were 2 cases of MGFA class II, 7 cases of MGFA class III, 4 cases of MGFA class IV. The mean interval time from myasthenic symptom onset to efgartigimod administration was 6.4 months. The mean interval time from efgartigimod administration to surgery was 9 days. Ten patients underwent T2b surgery with modified subxiphoid thoracoscopic surgery, and 3 patients underwent T3b surgery (trans-sternal thymectomy). According to the ninth edition of TNM staging, 6 patients were at stage I, 3 patients at stage II, 2 patients at stage IIIB, 2 patients at stage IVa. Pathologically, 7 cases were diagnosed as type B2 thymoma, 3 cases of type B3, 2 cases of type B1, and 1 cases of type AB. All patients were MG Activities of Daily Living (MG-ADL) responders and Quantitative Myasthenia Gravis Scale (QMG) responders, with improving muscle strength across ocular, bulbar, limb motor, and respiratory muscle groups. Despite the small sample size, clinically meaningful improvement was achieved, with mean reduction of 4.0 points (-4.0) on the MG-ADL, -7.1 points on the QMG scores after the first infusion; and -7.4 points on the MG-ADL, -12.2 points on the QMG scores after the fourth infusion compared to baseline. Significant reduction was observed in total serum levels of IgG and AChR-Ab after both the first (-38.7% for IgG, -59.5% for AChR-Ab) and the fourth infusion (-59.2% for IgG, -78.8% for AChR-Ab). There was no myasthenic crisis, complication nor adverse event during perioperative period. The mean postoperative hospitalization time was 3 days. After thymectomy, neurological status revealed 6 cases of pharmacological remission and 7 cases of minimal manifestation, with 9 cases of hormone decrement.

Conclusions: The satisfactory outcomes support the effectiveness and safety of efgartigimod during the perioperative period of thymectomy for TAMG. Large-scale clinical trials are needed to validate our important findings.

Keywords: thymoma, myasthenia gravis, efgartigimod

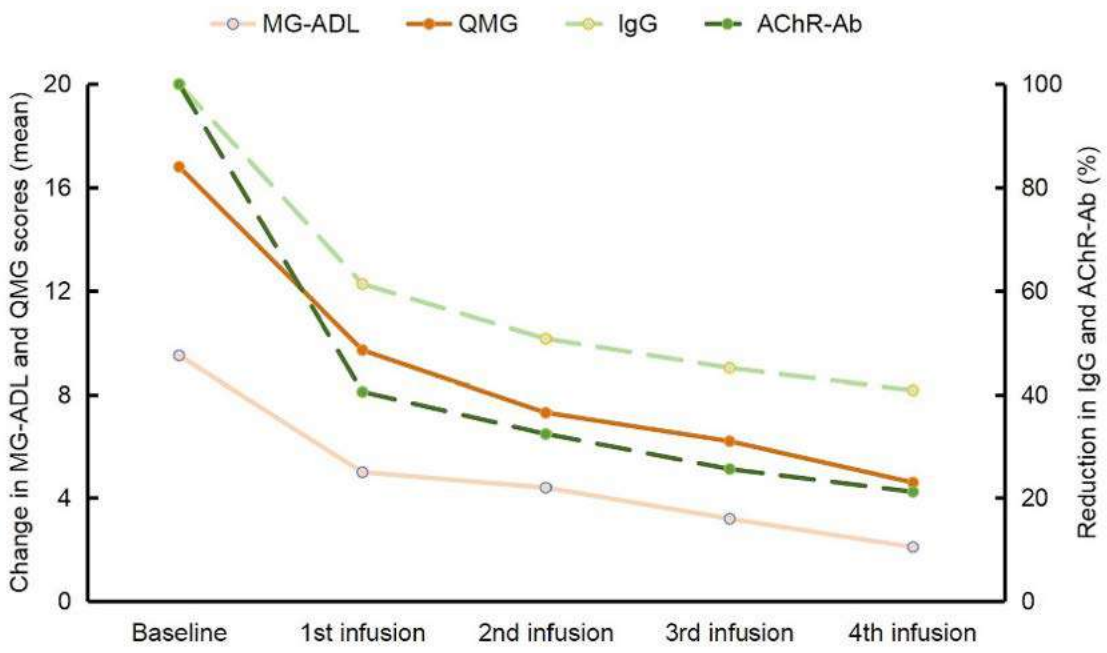

Figure 1. The mean change from baseline in MG-ADL, QMG scores, and percentage change from baseline in total serum levels IgG and AChR-Ab after efgartigimod administration weekly.
MG-ADL: MG Activities of Daily Living, QMG: Quantitative Myasthenia Gravis, AChR-Ab: acetylcholine receptor antibody

EP.14B MESOTHELIOMA, THYMOMA, AND OTHER THORACIC TUMORS - THYMUS
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EP.14B.03 Predictive Value of Neutrophil-to-Lymphocyte Ratio (NLR) and Absolute Lymphocyte Count (ALC) In Thymic Epithelial Tumors

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Introduction: High NLR is associated with increased mortality and decreased immunotherapy benefit in several malignancies. NLR was previously associated with thymic epithelial tumor (TET) recurrence after resection; however, its predictive value in metastatic TETs treated with immunomodulatory treatments is unknown. We examined the association of NLR with treatment outcomes in metastatic TETs.

Methods: This single-institution, retrospective analysis was conducted on data obtained between 05/2012 and 03/2023 from four phase II clinical trials evaluating immunomodulatory treatments in metastatic TETs: avelumab (A), bintrafusp alfa (B), PT-112 (P) and sunitinib (S). Baseline NLR and ALC were assessed via logistic regression in relation to duration of benefit for the overall group, for S alone, and for A, B and P combined. Kaplan-Meier curves compared patients with baseline NLRs and ALCs at various levels.

Results: Eighty-eight patients were enrolled in A, B, P or S trials (four patients participated in more than one trial; median age: 57 years old; female: 41; White/African-American/Other: 63/14/11; thymoma: 41; S trial: 43, A/B/P trials: 49). There was no association between pre- or on-treatment NLR or ALC and treatment response or duration of clinical benefit (Table 1). Elevated NLR (cutoff of 3 or 5) and low ALC (> grade 1 or > grade 2) were not associated with duration of clinical benefit (Figure 1).

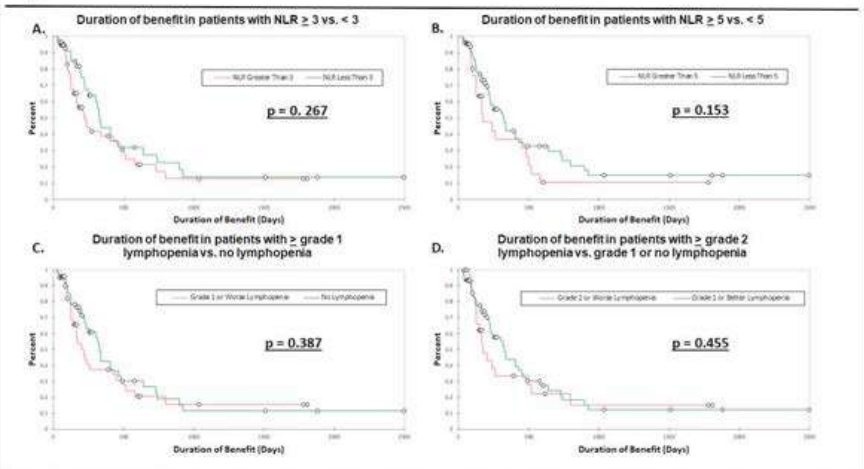
Conclusions: No association was observed between baseline or on-treatment NLR and treatment outcomes in patients with advanced TET patients. Potential reasons include small cohort size and heavy pretreatment affecting immune response. Long term follow-up in a larger cohort is needed.

Table 1. NLR and ALC Levels During Treatment with Immunomodulatory Therapies

	All (S, A, B, P)		S		A, B, P	
	# of Patients*	Median (Range)	# of Patients	Median (Range)	# of Patients	Median (Range)
Neutrophil-Lymphocyte Ratio						
Pre-Treatment	92	3.70 (0.21 - 25.68)	43	3.79 (0.21 - 25.68)	49	3.54 (0.80 - 19.29)
Best Response**	84	2.89 (0.32 - 47.05)	39	2.26 (0.32 - 13.71)	45	3.60 (0.50 - 47.05)
Progression	58	3.28 (0.37 - 32.27)	30+	3.33 (0.37 - 32.27)	28	4.27 (0.39 - 23.08)
Off Study^	80	3.85 (0.37 - 37.45)	43	3.71 (0.37 - 32.27)	37++	3.98 (0.39 - 37.45)
Absolute Lymphocyte Count ($x10^3/\mu l$)						
Pre-Treatment	92	1.06 (0.22 - 12.48)	43	1.06 (0.24 - 12.48)	49	1.07 (0.22 - 5.51)
Best Response**	84	0.97 (0.19 - 5.04)	39	0.83 (0.19 - 5.04)	45	1.09 (0.21 - 4.38)
Progression	58	0.93 (0.15 - 12.21)	30+	0.77 (0.15 - 12.21)	28	1.05 (0.28 - 3.17)
Off Study^	80	0.96 (0.15 - 12.21)	43	0.93 (0.15 - 12.21)	37++	1.08 (0.26 - 6.65)

A = Avelumab; anti-PD-L1 antibody (NCT03076554); B = Bintrafusp alfa; anti-PD-L1/TGFβ-trap fusion protein (NCT04417660); P = PT-112; ribosomal biogenesis inhibitor and immunogenic cell death inducer (NCT05104736); S = Sunitinib; multi-kinase inhibitor with immunomodulatory activity (NCT01621568); *Includes four patients who participated on two separate trials; **Calculated for patients who were evaluable for response and whose disease did not progress at first restaging; +Some patients came off study for adverse events, patient choice, or death unrelated to disease and are not included here; ++Patients on A, B, and P were able to continue treatment beyond progression; some remain on treatment; ^Patients not receiving clinical benefit were taken off study for the following reasons: adverse event, progressive disease (for S, treatment was stopped at first progression; for A, B, and P, treatment beyond first progression was allowed with stoppage of treatment at second progression), patient choice, or death.

Figure 1. Duration of clinical benefit at different baseline NLR and ALC cutoffs.



(A) Duration of benefit for NLR ≥ 3 (median 168 days; 95% CI, 73.1 – 263) and NLR < 3 (median 255.5 days; 95% CI, 75.5 – 435.5; p=0.267). (B) Duration of benefit for NLR ≥ 5 (median 150.5 days; 95% CI, 17.1 – 283.9) and NLR < 5 (median 220 days; 95% CI, 104.2 – 335.8; p=0.153). (C) Duration of benefit with ≥ grade 1 lymphopenia (median 167.5 days; 95% CI, 42.4 – 292.6) and no lymphopenia (median 224 days; 95% CI, 93.6 – 354.4; p=0.387). (D) Duration of benefit with ≥ grade 2 lymphopenia (median 148 days; 95% CI, 0 – 307.4) and grade 1 lymphopenia or no lymphopenia (median 224 days; 95% CI, 112.8 – 335.2; p=0.455).

EP.14B MESOTHELIOMA, THYMOMA, AND OTHER THORACIC TUMORS - THYMUS
SATURDAY, SEPTEMBER 7, 2024 - 11:58 - 11:59

EP.14B.04 Nomogram for Predicting the Prognosis of Metastatic Thymic Epithelial Tumors

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Introduction: Patients with thymic epithelial tumors (TETs) are often in advanced stage when they are first diagnosed. This study aimed to develop a nomogram to predict the prognosis of metastatic TETs.

Methods: Patients with metastatic TETs treated in Sun Yat-sen University Cancer Center from July 2000 to November 2021 were retrospectively included. A nomogram model predicting the prognosis of metastatic TETs was established based on the independent prognostic factors. Performance of the nomogram model was assessed by using the concordance index (C-index), calibration curves and decision curve analysis (DCA) curves. Based on the nomogram scores, patients were divided into different prognostic groups.

Results: A total of 254 cases, including 129 thymoma and 125 thymic carcinoma patients were enrolled into this analysis. Characteristics of the patients are shown in Table 1.The median follow-up time was 40.27 months and the median OS was 53.03 months (95% CI: 40.56-65.51 months). After univariate analysis and multivariate analysis, the results showed that WHO histologic classification type C, Masaoka-Koga stage IVb, KPS score 70-80 and baseline serum albumin level <40g/L were independent poor prognostic factors of OS. The independent prognostic factors of OS were taken into the establishment of nomogram model. The C-index was 0.68 (95% CI: 0.59-0.79), indicating good performance. The risk groups were categorized by nomogram scores, using a threshold at 112 score. The median OS in the high-risk group was much shorter than the low-risk group (28.60 vs 74.17 months, HR: 2.44; 95 % CI: 1.65-3.62; p=0.000002).

Conclusions: WHO histologic classification, Masaoka-Koga stage, KPS score and baseline serum albumin level were identified as independent prognostic factors for OS in the patients with metastatic TETs. This study developed a nomogram model which can effectively predict the prognosis of metastatic TETs.

Keywords: thymic epithelial tumors, prognostic prediction model, nomogram

Characteristics	Number	Percentage
Age (years)		
Median age (range)	49 (10-78)	
≤50	135	53.15%
>50	119	46.85%
Gender		
Male	156	61.42%
Female	98	38.58%
Myasthenia gravis history		
No	233	91.73%
Yes	21	8.27%
KPS score		
90-100	203	79.92%
70-80	51	20.08%
WHO histologic classification		
A-AB	23	9.06%
B1-B3	106	41.73%
C	125	49.21%
Masaoka-Koga stage		
IVa	110	43.31%
IVb	144	56.69%
Metastatic site		
Intrathoracic only	146	57.48%
Intrathoracic and extrathoracic	108	42.52%
Albumin		
<40 g/L	69	27.17%
≥40 g/L	185	72.83%

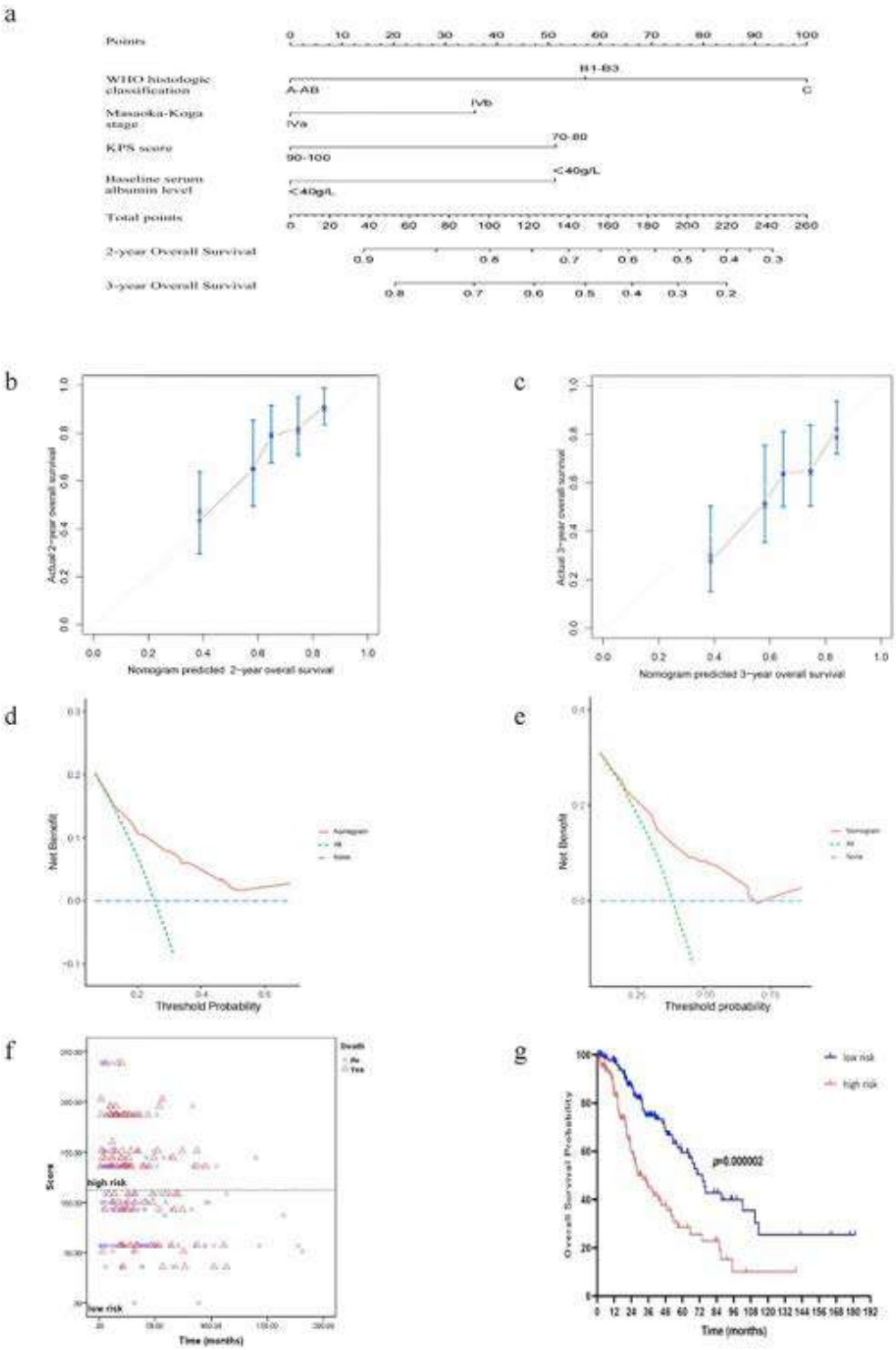

Figure 1 Nomogram for prediction of 2-year and 3-year overall survival (a). Calibration curves of the nomogram-predicted 2-year (b) and 3-year (c) overall survival. Decision curve analysis of the nomogram-predicted 2-year (d) and 3-year (e) overall survival. Death across time in patients with metastatic thymic epithelial tumors (f) and the overall survival analysis of patients after risk-stratification (g).

EP.14B MESOTHELIOMA, THYMOMA, AND OTHER THORACIC TUMORS - THYMUS
SATURDAY, SEPTEMBER 7, 2024 - 11:58 - 11:59

EP.14B.05 What Do We Know About Thymic Epithelial Tumors? Demographic and Survival Analysis from a Single Academic Center in Argentina

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Introduction: Thymic epithelial tumors (TET) are rare malignant neoplasms of unknown etiology with high survivorship at 5 and 10 years. Different types have been described, including thymomas and thymic carcinoma. Thymomas have been related to autoimmune disorders, such as Myasthenia Gravis (MG). Open surgery remains the gold standard of treatment, although new minimally invasive techniques are considered for specific cases. This study aimed to analyze the incidence and survival rate of this uncommon pathology in a tertiary centre in South America.

Methods: We retrospectively studied all patients diagnosed with any type of TET who underwent surgical treatment from 2007 to 2024 at a single academic center.

Results: A total of 27 cases were included. Fourteen (52%) were males, and the average age was 50 (SD±13). Thymoma (22/27 81.5%) was the most frequent type, followed by Thymic Carcinoma (5/27 18.5%). All patients had a CT scan before surgery, and only nine patients had PET TC, which was indicated in high-stage TETs. A high proportion of patients with thymoma (9 41%) were presented baseline paraneoplastic syndromes such as: MG (6 27%) positive ACRA and one thrombophlebitis associated with carcinoma (4%).We found just one patient with thymic carcinoma with clinical signs of MG that disappeared after surgery.From 22 thymoma patients; 19 underwent total thymectomy, and only one required preoperative induction therapy due to an initial non-resectable tumor. Ten patients were resected by sternotomy, five by thoracotomy, and four underwent minimally invasive procedure by VATS. The remaining five patients were treated with systemic therapy due to non-resectable conditions. Radical surgery with free margins was achieved in 95% of cases. The mean size of the tumor was 7.6 cm (SD±3.4). According to the Masaoka-Koga classification, most Thymomas (73%) were classified as Stage I-II, and only 27% were Stage III-IV. Two thymic carcinoma patients were resected by sternotomy, and one underwent minimally invasive procedure by VATS. The mean size of the tumor was 4 cm (SD±3). Radical surgery with free margins was achieved in only one patient, all thymic carcinomas were classified as Stage III-IV according to the WHO classification. No mortality was reported 90 days after surgery. The median survival time of thymoma and thymic carcinoma was 45.6 and 27 months, respectively.

Conclusions: TETs are rare tumors with Was - a good prognosis and high five and ten-year overall survival. The correct multidisciplinary approach is essential to achieving successful results since the initial therapeutic plan is based on the resectability of the injury. Patients with complete resections (R0) and initial stages of classification (EI/II) have greater overall survivorship.

Keywords: Thymic epithelial neoplasms, Mediastinum, Survival

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EP.14B.06 A Retrospective Multicenter Study Evaluating Experience of Perioperative Treatment for Thymic Squamous Cell Carcinoma

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Introduction: Thymic carcinomas (TC) are rare tumors of prevascular mediastinum. Squamous cell carcinoma is the most common histological subtype. TC are invasive and often present as metastatic disease. Their 5 year-overall survival is only 55%. Complete surgical resection (R0 resection) and postoperative radiation therapy (PORT) has been shown to improve survival. In borderline resectable disease, neoadjuvant treatment helps downsize the tumor to allow resection. In this study, we aimed to review our long-term experience of perioperative treatment for patients with thymic squamous cell carcinoma (TSCC).

Methods: We included 50 patients with a diagnosis of TSCC from 1997 to 2023 with an intention for surgical resection. Demographic and clinical data was collected by retrospective chart review. Continuous variables were described as median. A multivariate logistic regression model was performed to test the association of age, gender, smoking status, resection margins, receipts of neoadjuvant treatment and PORT with and without chemotherapy. Overall and progression-free survival, was calculated using Kaplan-Meier method.

Results: We identified 46 patients who underwent surgical resection. 28(60.87%) patients achieved R0 resection. Neoadjuvant treatment was administered in 22 of the 50 cases (44%). Six patients received neoadjuvant concurrent radiation and chemotherapy. Five patients developed disease progression during or following neoadjuvant treatment of which one was salvaged by surgery. Two patients who received neoadjuvant concurrent radiation and chemotherapy achieved complete pathological response. Adjuvant treatment was given in 35 cases (76%). 19 patients received PORT alone and the remaining patients received post operative chemotherapy in addition to PORT. Median overall survival (OS) and median progression free survival (PFS) for the study population was 7.1 years and 18.28 months, respectively. Achievement of R0 resection was associated with receipt of neoadjuvant treatment and it was statistically significant (p=0.03). Only R0 resection was found to have a significant association with OS. None of the variables were significantly associated with PFS.

Conclusions: Amongst all the factors that have been found to be associated with overall survival, R0 resection is the only factor that has been reported in literature to be consistently associated with improved survival. Our study showed that neoadjuvant treatment can improve the probability of achieving R0 resection. Complete pathological response is uncommon after neoadjuvant treatment in TC. Recent studies have shown that perioperative immunotherapy improves pathological response and event free survival in resectable Non-Small Cell Lung Cancer. Studies should explore the role of perioperative immunotherapy in addition to chemotherapy in carefully selected borderline resectable TSCC.

Keywords: Thymic squamous cell Carcinoma, Thymic epithelial malignancies, Mediastinal malignancies

EP.14B MESOTHELIOMA, THYMOMA, AND OTHER THORACIC TUMORS - THYMUS
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EP.14B.07 Does Surgical Incision Affect Quality of Life in Masaoka Stage 1-2 Thymomas?

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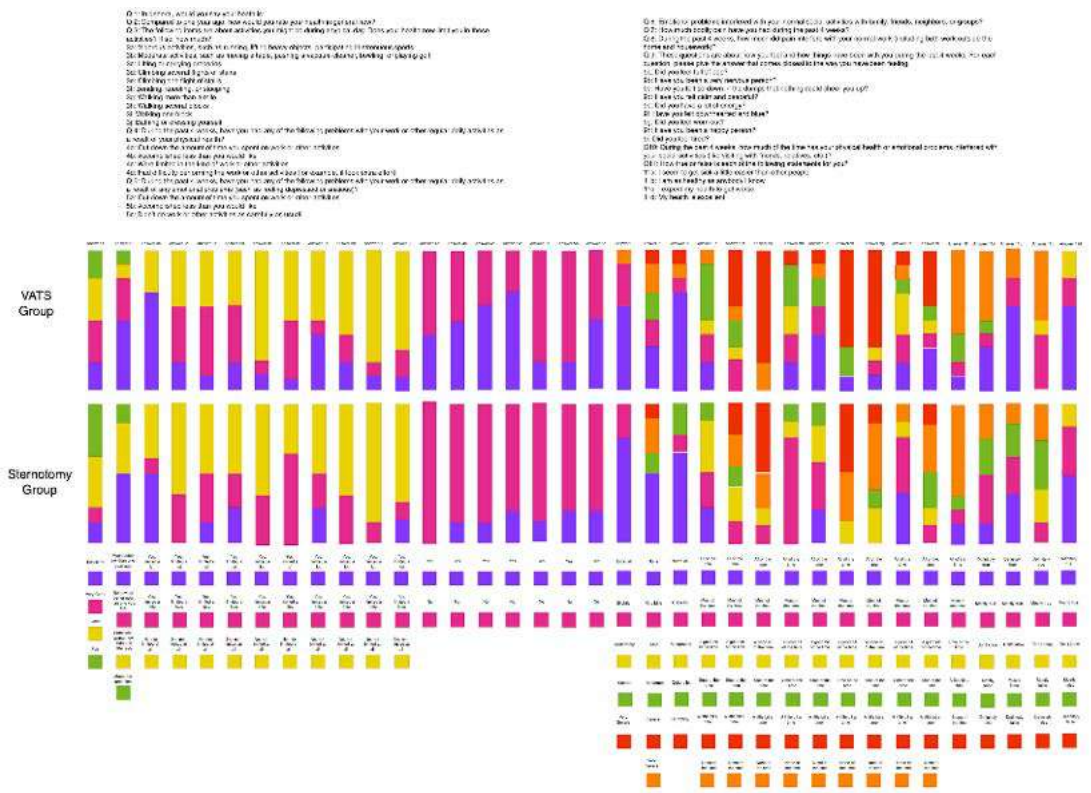
Introduction: Thymoma is a neoplastic disease originating from the epithelial cells of the thymus gland. TNM staging and Masaoka-Koga staging are often used. Complete removal of the thymus tissue and surrounding fatty tissue with extended thymectomy complies with oncological principles. Surgery can be performed by open method (sternotomy) or minimally invasive methods (VATS/RATS). In our study, we aimed to investigate the effect of surgery on the quality of life in patients who underwent surgery with a diagnosis of Masaoka stage 1-2 thymoma.

Methods: Patients who were operated on in our clinic with the diagnosis of Masaoka stage 1-2 thymoma between 2007 and 2022 were included in the study. 8 patients were accepted as exitus during follow-up. 18 out of 25 patients could be reached. 10 patients were operated with VATS and 8 patients were operated with sternotomy. SF-36 survey was administered to the patients to evaluate their quality of life.

Results: The VATS group reported that their general health was better and that they were better at a higher rate compared to the previous year (80% and 90%). There were similar restrictions in general activities in the VATS and sternotomy group. Individuals in the two groups rated the effects of emotional problems on their daily activities as similar. While the VATS group stated that they were better in the evaluation of pain, mood and physical activity in the last 4 weeks, they rated their health holistically as good at a higher rate (Figure 1).

Conclusions: In our study, the quality of life of patients who underwent thymectomy with VATS or sternotomy due to stage 1-2 thymoma was evaluated with the SF-36 test. In the late-term life evaluation survey after surgery, the group who underwent VATS stated that their general health and general life activities were better. Although the application of minimally invasive surgeries has increased with technological developments, minimally invasive methods remain important in thymoma surgery due to the concern of residual tissue remaining. Considering the superiority of VATS in the evaluation of general quality of life, it should be preferred in appropriate patients.

Keywords: Thymoma, Masaoka Staging, Minimal Invasive Surgery



EP.14B MESOTHELIOMA, THYMOMA, AND OTHER THORACIC TUMORS - THYMUS
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EP.14B.08 Thymic Carcinoma with Treatment-Related Leukemia Showing Complete Response to Bcl-2 Inhibitors: A Case Report

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Introduction: Thymic carcinoma is a rare malignancy with poor prognosis.The existing systemic chemotherapy regimens for thymic carcinoma are primarily based on limited evidence from phase II clinical trials and retrospective studies. Due to the rarity of this cancer, gathering a sufficient number of cases for comprehensive research is challenging, highlighting the need for further studies on more effective treatments. Many thymic carcinomas express Bcl-2, a protein known to play a role in the regulation of cell death. However, the effectiveness of Bcl-2 inhibitors in the treatment of these carcinomas remains unclear.

Methods: A 48-year-old man, initially diagnosed with stage I thymoma, underwent surgical excision but later experienced local recurrence and disseminated lesions, leading to a revised diagnosis of thymic carcinoma. Despite attempting surgical resection, complete removal was not achieved. The patient underwent first-line chemotherapy with cisplatin and etoposide, resulting in a temporary reduction in the primary lung mass. However, six months post-treatment, left pleural dissemination increased, indicating disease progression.

Five years after thymic carcinoma diagnosis, the patient developed treatment-related acute myeloid leukemia (AML). Initial AML treatment with idarubicin and cytosine arabinoside yielded limited therapeutic response. Persistent left lower extremity pain and uncontrolled treatment-related AML warranted consideration of alternative chemotherapeutic strategies.

Due to the patient's non-complete remission status for thymic carcinoma and contraindications for intensive AML therapy, 5-azacytidine and venetoclax were chosen as second-line AML treatment. Two months after initiation, the patient achieved complete remission for AML, with no detectable peripheral blood blasts. Simultaneously, significant regression of thymic carcinoma occurred, reaching complete remission after the third treatment cycle. Subsequently, there has been no recurrence of either thymic carcinoma or leukemia since completing this treatment.

Results: In this patient, the pathological specimen showed high Bcl-2 expression, suggesting a potential association with the observed therapeutic response to the Bcl-2 inhibitor. The favorable response of the patient's thymic carcinoma to Venetoclax combined with 5-azacytidine underscores the necessity for further research on this novel treatment approach, particularly for thymic carcinomas characterized by high Bcl-2 expression.

Conclusions: A complete response has been observed in thymic carcinoma during chemotherapy with 5-azacytidine and Venetoclax, which were initially administered for the management of treatment-related leukemia. This finding suggests that the combination of 5-azacytidine and venetoclax may be effective for direct treatment of thymic carcinoma. The involvement of high Bcl-2 expression in thymic carcinomas may be a key factor in the mechanism of action of this therapeutic approach.

Keywords: thymic carcinoma, Bcl-2 inhibitors, venetoclax

EP.14C MESOTHELIOMA, THYMOMA, AND OTHER THORACIC TUMORS - OTHER THORACIC CANCERS
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EP.14C.01 Coexisting Pulmonary Tuberculosis and Primary Lung Cancer: Prevalence of Diagnostic, Treatment and Outcome

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Introduction: Vietnam ranks 11th among 30 countries that suffer from the highest tuberculosis (TB) burden around the world. Lung cancer (LC) has become the second most common cancer in our country. Both diseases coexist producing a diagnostic dilemma and affecting treatment efficacy.

Methods: We retrospectively reviewed 52 medical records of patients with coexistent lung cancer and pulmonary tuberculosis at Vietnam National Cancer Hospital and National Lung Diseases Hospital between 2008 and 2022. The clinical features, diagnosis, treatments, and OS were evaluated.

Results: The mean age was 59,2 years (age range: 46,4-72 years); the ratio of male/female was 2,3/1; 86.4% of patients had ECOG PS scores ranging from 0 to 1. The prevalence of stage I, II, III, and IV due to AJCC version 8 staging classification were 9.6%, 13.4%, 38.5%, and 38.5%, respectively. The most common symptom at admission was chest pain (55%), and 91.9% of patients had a regular history of smoking with a mean 46 pack-year. The most common imaging feature on CT was an enhanced cavitary mass in the upper lobes (65.4%). Squamous cell carcinoma (50%) was the most common pathology type followed by small cell carcinoma (23.1%) and adenocarcinoma (21.2%). Tuberculosis detected by lung tissue cultured and H&E staining the biopsy specimens were 25%, and 48.1%, respectively. The simultaneous and sequential presentation of pulmonary TB and lung cancer within the same patient were 51.2%, and 48.8%, respectively. In our study, treatments included curative intended and palliative, with proportions of 28.3%, and 71.7%, respectively. The mean period of time for diagnosis is delayed by 3,6 months. The median survival time of those who had curative intended was 18,3 ± 3,6 months. Median survival times of those treated by palliative therapy were 11,3 ± 4,1 months.

Conclusions: Pulmonary TB coexisting with lung cancer can mask the underlying disorder resulting in a delay in diagnosis, treatments will affect the patient's outcome. Tuberculosis should be a significant concern, especially in male patients with heavy cigarette smoking and located in TB-endemic areas.

Keywords: Tuberculosis, Lung Cancer, Co- existence

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EP.14C.02 Identification and Isolation of Cancer Stem Like Cells in Pulmonary Sarcomatoid Carcinoma

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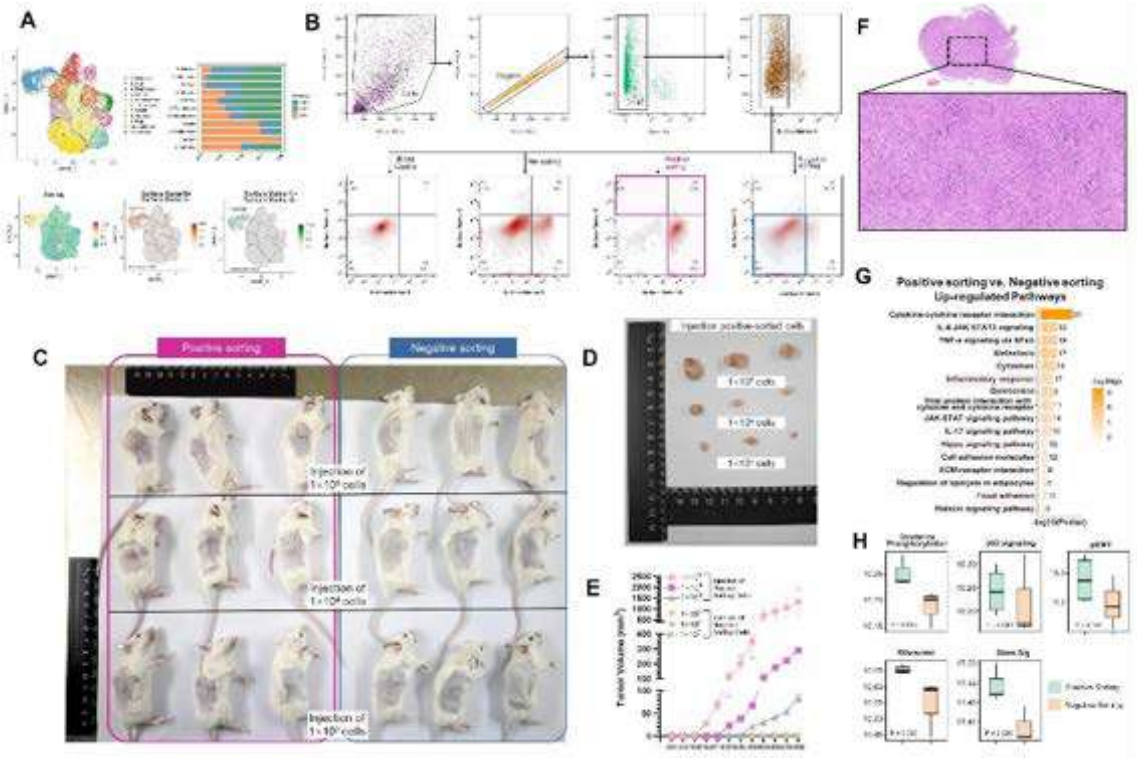
Introduction: Pulmonary sarcomatoid carcinoma (PSC) represents a rare subset (0.4%) of highly aggressive and poorly differentiated NSCLC, characterized by sarcoma-like or sarcoma (spindle- or giant-cell) elements. The scarcity of PSC cases has limited the exploration of atlas and heterogeneity, while the efficacy of current NSCLC treatments is constrained by tumor heterogeneity. Our study utilized snRNA-seq to unveil the 'Plasticity' of PSC cells, marked by a prominent expression of a stemness signature (WCLC 2023, P2.22-01), thus confirming the existence and signature of cancer stem cells (CSCs) in PSC, offering insights into its malignant nature and drug resistance.

Methods: Single nuclei were isolated from frozen tissues using an isolation kit following the manufacturer's protocol (Sinotech Genomics Co., Ltd). PDX models were established by subcutaneously implanting small tissue fragments from PSC patients into NOG mice. 'Plasticity' cells from patient-derived xenograft (PDX) tumors were sorted via Fluorescence-activated cell sorting after dissociation into single-cell suspension. Both positive-sorted ('Plasticity' cells) and negative-sorted cells were inoculated subcutaneously into the right flank of NOG mice.

Results: Based on our previous snRNA-seq findings, we identified a PSC-enriched cancer cell 'Plasticity' exhibiting elevated expression of the stemness signature Stemsig. We defined a signature of three surface markers for 'Plasticity' subtype with an accuracy of 0.874 to 0.849 (Fig. 1A). 'Plasticity' cells isolated from PSC PDX tumors via FACS (Fig. 1B) were successfully implanted into NOG mice in varying quantities from 103-105, revealing that all positive-sorted cells initiated tumor growth, irrespective of cell number, while negative-sorted cells failed to generate tumors (Fig. 1C). Meanwhile, tumors injected with a higher number of 'Plasticity' cells exhibited a notably accelerated growth rate compared to those injected with lower numbers (Fig. 1D and 1E). Moreover, tumors derived from 'Plasticity' cells exhibited typical PSC characteristics upon histological examination (Fig. 1F). Pathways associated with metastasis, inflammatory response, Hippo signaling, and focal adhesion were upregulated in positive-sorted cells ('Plasticity', Fig. 1G), along with elevated expression of the stemness signature Stemsig (Fig. 1H).

Conclusions: CSCs, known for their role in tumor recurrence and progression through self-renewal and regeneration, are pivotal in cancer biology. The 'Plasticity' cells we identified met gold standards of CSCs, displaying the capacity to differentiate into complete malignant tumors with minimal cell numbers (102~103 cells) and histological similarities to primary tumors. Our established signature for CSC identification in PSC, validated in vivo, offers promising avenues to combat the malignant nature and drug resistance associated with PSC.

Keywords: pulmonary sarcomatoid carcinoma, Cancer Stem Cell



EP.14C MESOTHELIOMA, THYMOMA, AND OTHER THORACIC TUMORS - OTHER THORACIC CANCERS
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EP.14C.03 Long-Term Outcomes of Unresectable Tracheobronchial Tumors Treated with Radiotherapy- Analysis from a Tertiary Cancer Centre

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Introduction: Tracheo-bronchial (TB) malignant tumors constitute an uncommon malignancy of the thorax. Radical radiation therapy (RT) is the standard treatment for unresectable or in margin-positive cancers. Here, we report our institutional data of TB tumors treated with RT.

Methods: From 2012 to 2024, we retrospectively collected data of TB tumors treated with radiation therapy at our tertiary cancer care centre. Data was collected from electronic medical records and case files. Clinicopathological and demographic variables were collected. Categorical and numerical variables were summarized using descriptive statistical methods. Overall Survival (OS) and progression-free survival (PFS) were calculated from the date of diagnosis until the date of progression or death, respectively, whichever is earlier. Both were analysed using the Kaplan-Meier method.

Results: Twenty-eight patients of TB tree tumors received RT. The median age was 44 years (range, 19-63), with slight male preponderance. The clinicopathological characteristics and treatment options are summarised in Table 1. The most common histology was adenoid cystic carcinoma in 23 patients and majority of the tumors were within 2cm from the carina. The most common presenting symptoms were cough and breathlessness. Debulking surgery was done in 18 (3 with stent placement). Twenty-two patients received definitive RT and 6 received adjuvant RT (margin positive). The median RT dose was 60Gy (50 - 66Gy). All patients received conformal RT and 3 received intraluminal brachytherapy boost post-definitive RT. All radical RT patients received concurrent chemotherapy. The median follow-up period was 29 months (IQ range, 4-57 months) with 23 patients alive at the data cut-off. The disease relapse was seen in 10 patients (local-4, distant-6). The median and 3-year PFS and OS were 26 months & 65% and 42 months & 87%, respectively. Acute ≥ Gr 2 toxicity was seen in 4 patients (14%) and late ≥ Gr 2 in 7 (25%) as cough and dysphagia. One patient developed tracheo-esophageal fistula, two developed symptomatic tracheal stenosis requiring dilatation.

Conclusions: Unresectable tracheobronchial tumors treated with radical CTRT demonstrated good local control and overall survival. Late toxicity is a concern, which requires frequent intervention.

Keywords: Tracheobronchial tumors, Adenoid cystic carcinoma, Unresectable tumors

PATHOLOGICAL CHARACTERISTICS	NUMBER OF PATIENTS
HISTOLOGY	-
Adenoid cystic carcinoma (ACC)	23 (82.5%)
Neuroendocrine tumors (small cell carcinoma)	2 (7%)
Mucoepidermoid carcinoma	1 (3.5%)
NUT midline carcinoma	1 (3.5%)
Squamous cell carcinoma (SCC)	1 (3.5%)
GRADES (in ACC)	-
I	3 (13%)
II	11 (48%)
III	2 (8.6%)
NA	7 (30.4%)
PDL-1	-
Positive	1 (3.6%)
Negative	3 (10.7%)
NA	24 (85.7%)
RADIOLOGICAL FEATURES	**NUMBER OF PATIENTS**
EPICENTRE	-
>2cm proximal to Carina	7 (25%)
<2cm proximal to Carina/ at Carina	13 (46.5%)
Right/ Left Main Bronchus	8 (28.5%)
BHATTACHARYYA T STAGE	-
T1	3 (10.7%)
T2	6 (21.4%)
T3	14 (50%)
T4	5 (17.9%)
BHATTACHARYYA N STAGE	-
N0	19 (68%)
N1	9 (32%)
TREATMENT MODALITIES	**NUMBER OF PATIENTS**
DEBULKING SURGERY	-
Yes, with stent	3 (10.7%)
Yes, without stent	15 (53.5%)
No	10 (35.7%)
RADICAL SURGERY	-
Yes	6 (21.4%)
No	22 (78.6%)
RADIOTHERAPY	-
Adjuvant	6 (21.4%)
Definitive	22 (78.6%)
CHEMOTHERAPY	-
Yes	22 (78.6%)
No	6 (21.4%)

Table 1: Clinicopathological features summary and treatment modalities used for tracheobronchial tree malignancies in 28 patients between 2012 to 2024 at Tata Memorial Hospital, Mumbai, India

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EP.14C.04 Micro Neck Incision Combined with VATS for Resection of Superior Mediastinal Neoplasms

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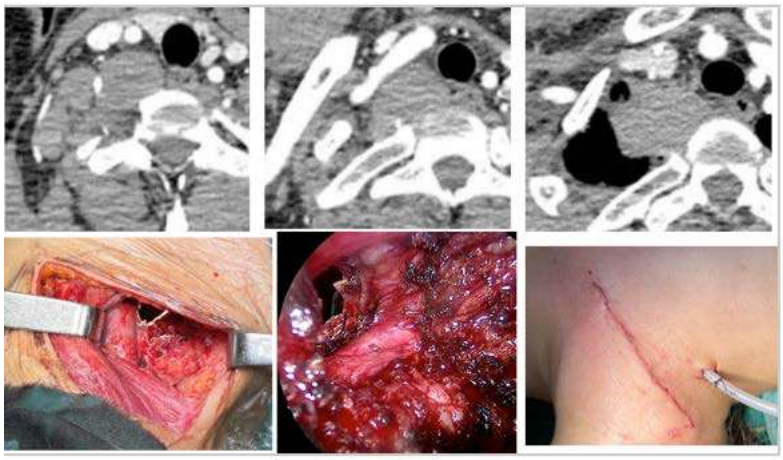
Introduction: Treat superior mediastinal neoplasms through micro neck incision combined with VATS.

Methods: Patients with huge mediastinal mass underwent complete examination of whole body. Patients with no metastasis were selected to perform this novel minimally invasive approach. We select the specific incision location according to the main location of the tumor. We choose necklace incision or collar incision for the neck approach. We choose intercostal thoracoscopy or subxiphoid thoracoscopy for the thoracoscopic approach.

Results: Nine cases of high mediastinal tumors were treated with cervical micro incision combined with video-assisted thoracoscopic surgery. No patient was converted to open surgery. Pathological types include aggressive fibroma, goiter, thymoma, angioma, teratoma and paraganglioma. There was no Horner syndrome. There were no vagus nerve injury, recurrent laryngeal nerve, or phrenic nerve injury. None of brachial plexus injury or major vessel injury were reported. All patients are well after a short-term follow-up.

Conclusions: Cervical micro incision combined with thoracoscopic surgery is a safe and effective technology for the treatment of high mediastinal tumors. This technology can avoid unnecessary thoracotomy when it is difficult to expose upper mediastinal tumors.

Keywords: mediastinal neoplasm, VATS



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EP.14C.05 The Management of Solitary Fibrous Tumors of Chest in a Center

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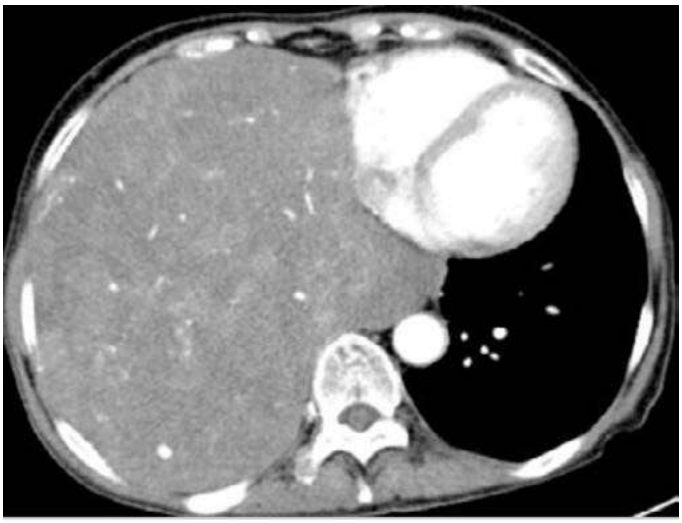
Introduction: SFTs comprise a histologic spectrum of rare tumors which originate from mesenchymal cells. Most of them are slow-growing and asymptomatic. Males and females are affected at equal frequencies. They are most common seen in the fifth to seventh decade. CT is considered the gold standard examination. An SFT is comprised of randomly arranged cells with spindle shape within a collagenous stroma. The biomarkers CD34, Bcl-2 and STAT6 are specific for SFT. The standard of care is the complete surgical resection. The prognosis is good and the survival rate is more than 85% after five years.

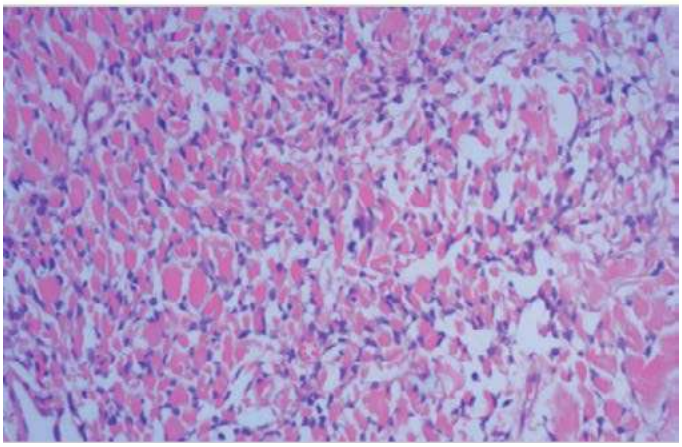
Methods: A number of ten patients with SFT had been treated in the Department of Thoracic Surgery of the General Hospital of Athens «Sotiria» from January 2019 to June 2023. The statistical analysis is based on gender, age, days of hospitalization, location of the tumor, size, histopathologic examination and immunochemistry evaluation. Demicco score was calculated for each patient.

Results: The mean age of patients in the sample is 65,4 years. Half of them are men. The mean reported length of hospital stay is 7,8 days. In five patients the tumor was localized in the right hemithorax and in the rest of the patients was in the left hemithorax. Four out of ten patients were treated with open surgery and six of them with video-assisted thoracoscopy. The mean size of the tumor was 6,57 cm. Based on Demicco score, six patients have low metastatic risk, three patients have intermediate metastatic risk and one patient has high metastatic risk.

Conclusions: SFT are well defined rare neoplasms. They are asymptomatic in early stages. CT is the gold standard examination. Complete surgical resection is the treatment of choice. The majority of SFT do not recur locally or distantly. Most of them are benign with high overall survival rate.

Keywords: Solitary fibrous tumor, Surgery, Mesenchymal tumor





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EP.14C.06 Surgical and Local Treatment of Pain in Tietze Syndrome: Our Experience in University Hospital "Shefqet Ndroqi"| Tirana Albania

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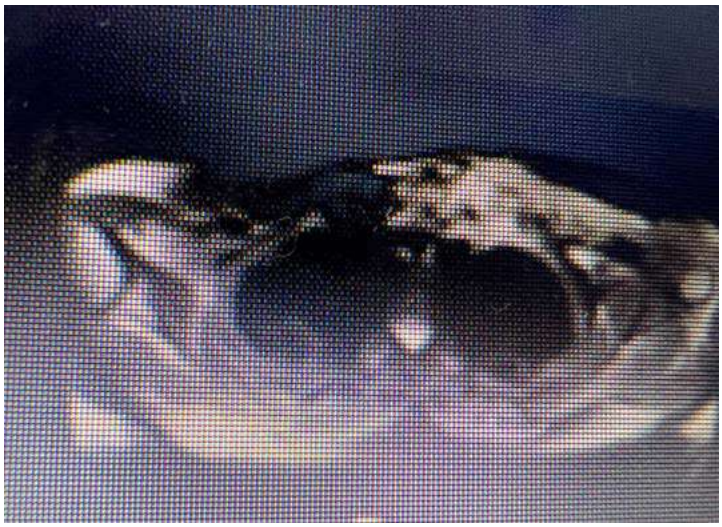
Introduction: In this study, we present our experiences with local treatment and surgical treatment in patients diagnosed with Tietze syndrome.

Methods: Between January 2008 and January 2023, a total of 17 patients (6 males, 11 females; median age: 33 years; range, 27 to 67 years) who were diagnosedand treated with TS in our clinic. Pain killer were injected into painful joints.Pain sensation of the patients was recorded using the Pain Rating Scale developed. Pain was also assessed atseveral weeks after injections qualitatively and based on physical examination. All patients were medicaly treated. Only one patient intervented d medically. Steroids and local aesthetic were used. In 8 patients, oral or i/m and i/v antibiotics were also used, and systemic anti-inflammatory drugs were also used.

Results: At two weeks, the patients felt calmer and performed better.

Conclusions: Patients diagnosed with Tietze syndrome and local steroids or anesthetic injection provides a rapid relief from pain, or employment status. Surgical treatment was used only in selected case.

Keywords: Atralgy, Tietze syndrome, Chest pain



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EP.14C.07 Hyperossosis of the Right 10th Rib the Osteochondral Part that Compresses the Dexter Lobe of the Liver

F. GRADICA[1], A. Cani[2], L. Lisha[2], I. Peposhi[2], F. Kokici[2], A. Leka[3], D. Xhemalaj[4], M. Rama[5], S. Gradica[6], L.G. Matmuja[5], F. Hoxha[7], [1]University Hospital "Shefqet Ndroqi", Tirane/AL, [2]University Hospital "Shefqet Ndroqi", Sauk Tirane/AL, [3]Imagery Service Lezha Hospital, Lezhe/AL, [4]University Hospital "Mother Theresa", Tirane/AL, [5]SUT, Trauma Hospital/AL, [6]Publik Pharmacy Service, Kamez Tirane/AL, [7]Managament of human resource, Kamez Tirane/AL

Introduction: Rib hyperostThe rib hyperostosis can be suspicious for malignancy.Hyperostosis has previously been described in conjunction with disorders causing excessive rib ossification due to osseous bridging across the costocondrial joint, such as in diffuse idiopathic skeletal hyperostosis. Hyperostosis is believed to be a reactive process due to altered forces across the affected rib as bridging osteophytes decrease mobility at the respective costocondrial joint.

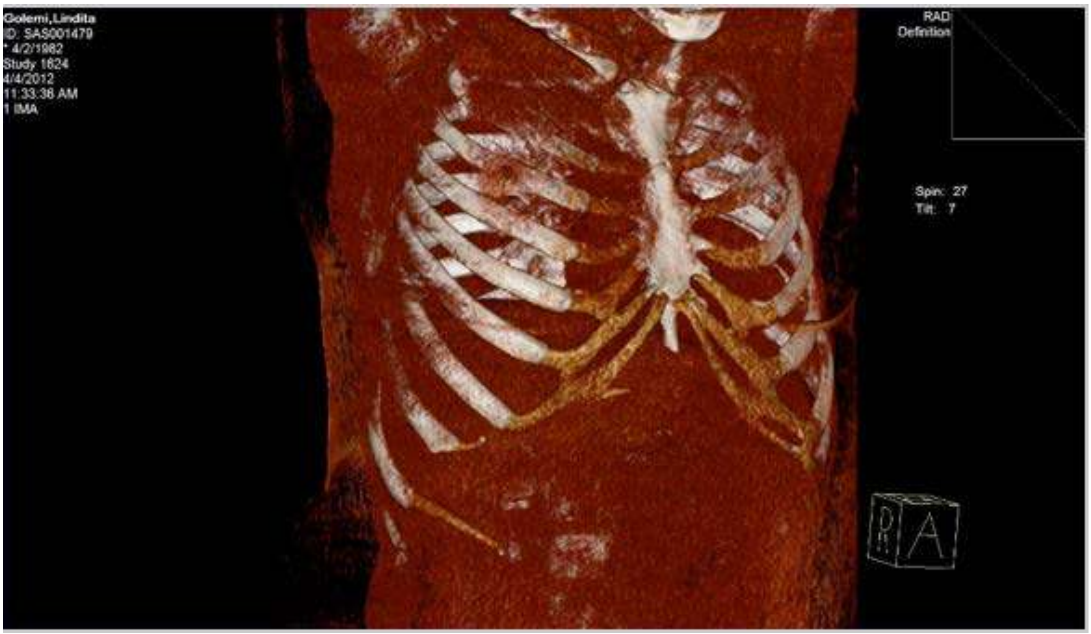
Methods: A 37-year-old female patient. She presented to the consultation with severe pain in the upper abdominal quadrant and at the level of the right rib cage. She had these concerns for several months, but in the last few weeks the pain became stronger and more stable, related to the movement of the trunk. It was treated with tranquilizers, but again it did not find stability. In the thoracic Ct scanner, the 10-th rib on the right anterior segment is evident, ossified and elongated, going in the direction of the liver.

Results: After completing the appropriate examinations, the patient underwent surgical intervention with x-rays of the hyperostosis part. During the intervention, the compressed area in the right lobe of the liver was clearly visualized due to the pressure exerted by the part of the hyperostosis rib on the liver. It left many traces on the surface. of the liver but without damaging it in the shape of a furrow about 7-8 cm. The biopsy result shows hyperostosis of the 10-th right rib, the anterior costochondrial part, about 7-8 cm.

The patient is calm and without worries.

Conclusions: Hyperostoses of the ribs have high suspicions of malignancy and can give clinical signs of severe pain when they grow in the direction of the parenchymal organs, as in our case, growing in the direction of the liver and continuously. Surgical resection is the right solution.

Keywords: Hyperostosis, Ribs Benign, Malignancy, Diffuse Idiopathic Skeletal Hyperostosis



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EP.14C.08 Challenges in Diagnosis and Management of Epithelioid Inflammatory Myofibroblastic Sarcoma - Case Report

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Introduction: Epithelioid inflammatory myofibroblastic sarcoma (EIMS) is a rare subtype of inflammatory myofibroblastic tumour (IMT). EIMS typically presents with sheets or loose fascicles of epithelioid cells mixed with inflammatory cells in a variably myxoid background. Notably, approximately 50% of typical IMTs harbour ALK gene rearrangement and overexpress ALK, often showing diffuse cytoplasmic staining. However, recent findings suggest that specific staining patterns of ALK may indicate malignant behaviour in these tumours.

Methods: A case report.

Results: : A 45-year-old patient underwent a right upper lobectomy in December 2018 for an epithelioid variant of inflammatory myofibroblastic sarcoma with ALK expression. In March 2020, he presented to the neurosurgical clinic with persistent headaches and double vision. Brain MRI revealed an extensive tumour in the right frontoparietal region, resulting in calvarial destruction and compression of the right cerebral hemisphere. On March 24, 2020, surgical excision of the tumour mass involving the calvarium was performed, with histological examination confirming metastasis of the epithelioid inflammatory myofibroblastic tumour. Till then, the patient hasn't received any oncological treatment; an oncologist has observed him. In general, the patient hasn't had any significant complaints; he has been using anticonvulsive therapy with a small dose of corticoids. On May 5, 2020, the patient was admitted to a department due to weaknesses. Upon admission, we conducted an MRI of the brain, revealing multiple nodular and patchy lesions in the frontoparietal region bilaterally. According to the consulted neurosurgeon's opinion, the findings were inoperable, so we were considering external radiotherapy to the brain. As literature sources indicated that the patient could benefit from ALK-TKI (tyrosine kinase inhibitors), we requested compassionate use approval from the ministry. Meanwhile, the patient, experiencing persistent weakness and headaches, initiated external radiotherapy to the brain and completed one session. Subsequently, upon approval of the medication, treatment with alectinib was undertaken on June 6, 2020, and external radiotherapy was interrupted. The patient was doing very well; he continued going to work. In May 2021, a left parietal tumour was found on a follow-up CT scan. The patient underwent reoperation, revealing a fibrous meningioma with a high MIB-1 index. The patient, undergoing alectinib treatment, attained postoperative stability. In June 2023, a seizure occurred at home, prompting a CT scan revealing a right frontal high tumour. Subsequent neurosurgical resection confirmed it as a metastasis of epithelioid inflammatory myofibroblastic sarcoma. The patient, remaining stabilised, continues alectinib therapy and anticonvulsant treatment.

Conclusions: This case underscores the diagnostic and therapeutic complexities of epithelioid inflammatory myofibroblastic sarcoma (EIMS), a rare inflammatory myofibroblastic tumour (IMT) variant. Despite initial treatment with alectinib and surgical intervention, disease progression and metastasis occurred, highlighting the aggressive nature of EIMS. Accurate diagnosis and targeted therapy guided by ALK expression patterns remain crucial for managing this challenging malignancy. Further research and collaborative efforts are needed to enhance outcomes for patients affected by EIMS.

Keywords: Myofibroblastic Sarcoma, Alectinib, Brain Metastasis

EP.14C MESOTHELIOMA, THYMOMA, AND OTHER THORACIC TUMORS - OTHER THORACIC CANCERS
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EP.14C.09 Lung Metastasis of Clear Cell Renal Carsinoma Mimicking Primary Lung Cancer Following Nephectomy in 30 Years Old Women: A Case Report

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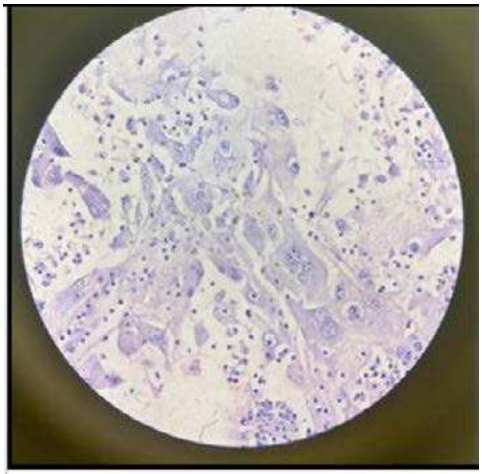
Introduction: It is possible that five years after a long gap radical nephrectomy, lung metastases from clear cell renal cancer will develop. According to data from the International Agency for Research on Cancer, Indonesia has a crude fatality rate of 1.3 cases per 100,000 people and a cumulative risk of 0.17% for kidney cancer. 635 instances of kidney cancer were reported between January 2013 and December 2017, with a male to female ratio of 2:1 and the largest age group being 51-65 years (42%). We describe a unique example of lung metastases in this case report, including a thirty years old lady after nephrectomy.

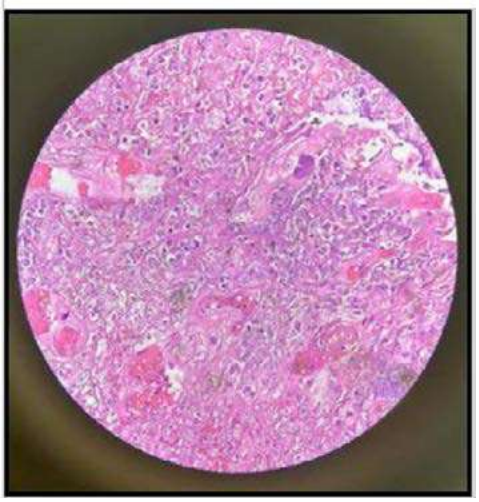
Methods: An x-ray of the chest taken of a 30-year-old woman who had been experiencing dyspnea and chest pain for three months. And chest ct scan revealed bilateral opacity in the left medial temporal lobe and right upper lobe, as well as several lung nodules in the left lung's medial and basal lobes. A soft tissue mass with central necrosis infiltrated around the superior mediastinal and superior cava vein, as well as complex pleural effusion a type of subpleural pulmonary metastasis with histopathology results from biopsy forceps sample fron bronchoscopy methods indicating clear cell renal carsinoma lung metastasis. The masses measured 7.3 x 4.9 x 6.6 cm.

Results: Renal cell carcinoma (RCC) is the sixth most common malignant tumor in men and the tenth most common tumor in women. the lung is one of the most common sites of metastasis. This is the first documented case of clear cell renal cell carcinoma related lung metastases in woman 30 years old after nephrectomy from Lampung.

Conclusions: Clear Cell Renal Carsinoma is the tenth most common malignant tumor in women and mostly metastasis to the lung although after nephectomy with the metastasis mimicking primary lung cancer.

Keywords: Clear Cell Renal Carsinoma, Mimicking, Lung Cancer





EP.14C MESOTHELIOMA, THYMOMA, AND OTHER THORACIC TUMORS - OTHER THORACIC CANCERS
SATURDAY, SEPTEMBER 7, 2024 - 11:58 - 11:59

EP.14C.10 Clinical and Pathoanatomical Characteristics of Rare Pulmonary Neuroendocrine Tumors in Greek Population

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Introduction: Pulmonary neuroendocrine tumors (PNETs), including lung carcinoids (typical and atypical), and large-cell neuroendocrine carcinoma (LCNEC), are rare entities with distinct clinical and pathological features. Due to its rarity, clinical and molecular characterization of PNETs and LCNECs is not well elucidated. About 50-60% of patients with LCNECs present with stage IV disease, and no large randomized clinical trial data are available to determine the optimal treatment strategy. In this study, we report the first analysis of the clinical and pathoanatomical characteristics of PNETs and LCNECs in patients treated at the National and Kapodistrian University of Athens, Sotiria Hospital.

Methods: Data were collected from the medical records of patients diagnosed with PNETs or LCNEC between May 2017 and July 2023, focusing on clinical presentations, diagnostic methods, and pathoanatomical findings.

Results: The cohort comprised 80 patients, with a median age of 59 years for NET and 66.5 for LCNEC. Notable findings included a significant difference in sex distribution and smoking status between the NET and LCNEC groups. There was no correlation between smoking status and NET incidence, while the majority of patients with LCNEC were active smokers. The primary symptoms leading to the diagnosis differed, with most patients diagnosed as asymptomatic in the NET cohort and breathlessness and persistent coughing in the LCNEC cohort. The average primary tumor size upon diagnosis was 2.1 for NET and 3.5 for LCNEC. Patients with NET were more likely to be diagnosed at an earlier stage. In contrast, patients with LCNEC are mainly diagnosed with stage IV disease. NET and LCNEC patients showed distinct Ki67 expression levels; NET patients expressed Ki67 at 7%, while LCNEC patients expressed it at 70%. Immunohistochemistry of neuroendocrine markers, immune markers, and transcription factors (ASCL1, NEUROD1, and POU2F3) is currently ongoing and will be correlated with clinical outcomes.

Conclusions: Our study provides valuable insights into the clinical and pathoanatomical landscapes of PNETs and LCNECs. In-depth molecular characterization and investigation into larger cohorts are currently ongoing to validate our observations and further explore treatment efficacy and patient outcomes.

Keywords: Neuroendocrine tumors, pathoanatomical, pulmonary

EP.14D MESOTHELIOMA, THYMOMA, AND OTHER THORACIC TUMORS - CLINICAL TRIALS IN PROGRESS
SATURDAY, SEPTEMBER 7, 2024 - 11:58 - 11:59

EP.14D.01 Cadonilimab Plus Bevacizumab and Chemotherapy as First Line Therapy in Unresectable Pleural Mesothelioma: A Single-Arm Phase II Study

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Introduction: Pleural mesothelioma is usually diagnosed at an advanced, unresectable stage at which systemic therapy is the only treatment option. Platinum-pemetrexed chemotherapy with or without bevacizumab is standard, with median survival of 12-18 months. The immunotherapies nivolumab and ipilimumab improved survival compared with platinum-pemetrexed, particularly in non-epithelioid histology. Nevertheless, there is still a strong unmet need to improve systemic therapy in pleural mesothelioma. Cadonilimab, a bispecific IgG-single-chain Fv fragment (ScFv) antibody that simultaneously targets PD-1 and CTLA-4, has shown encouraging anti-tumor activity and a favourable safety profile in advanced solid tumors. We aim to investigate the activity of cadonilimab in combination with bevacizumab and chemotherapy as first line treatment in unresectable pleural mesothelioma.

Methods: This is a prospective, single-arm, multicenter, investigator-initiated phase 2 study (NCT05930665). Eligible adult patients (aged ≥18 years) have histologically confirmed unresectable pleural mesothelioma; no previous systemic therapy for advanced disease; an ECOG performance status score of 0 or 1; measurable disease according to the Response Evaluation Criteria in Solid Tumours version 1.1 modified for use in pleural mesothelioma (mRECIST v1.1). Patients will receive carboplatin AUC 5, pemetrexed 500 mg/m^2, bevacizumab 7.5 mg/kg, cadonilimab 10 mg/kg intravenously on day 1 of a 3-weekly schedule for a maximum of six cycles. Bevacizumab and cadonilimab are continued for a maximum of 24 months. The primary endpoint is objective response rate (ORR) per mRECIST v1.1. Secondary endpoints include progression-free survival (PFS), disease control rate (DCR), duration of response (DOR), overall survival (OS) and safety. Simon's two-stage design is applied, with 19 evaluable patients recruited in the first stage and 13 evaluable patients to be continued in the second stage. A total of 38 patients will be recruited to account for dropout. Enrolment began in November 2023 and the study is currently ongoing.

Keywords: Pleural mesothelioma, immunotherapy, bispecific antibody

EP.15A MULTIDISCIPLINARY CARE: NURSING, ALLIED HEALTH AND PALLIATIVE CARE - NAVIGATION AND MULTIDISCIPLINARY TEAMS
SATURDAY, SEPTEMBER 7, 2024 - 11:58 - 11:59

EP.15A.01 Lung Cancer Patients in a Nationwide Oncology Navigation Program

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Introduction: Navigation in oncology has demonstrated benefits for people at risk for or diagnosed with cancer. These include a shorter time to diagnosis and start of treatment, better adherence to recommended care, and improved quality of life. Implementing a nurse navigation program can be challenging in developing countries, especially with nationwide healthcare networks. Lung cancer (LC) is the leading cause of cancer deaths worldwide. This study describes the characteristics and outcomes of lung cancer patients in a pioneering oncology navigation program in Brazil.

Methods: Rede D'Or São Luiz (RDSL) is Brazil's largest integrated private healthcare network, comprising 63 general tertiary hospitals and 50 oncology clinics in 13 states. A comprehensive oncology navigation program was started in 46 facilities in 2018, and a web-based system was implemented in 2020. The first phase focused on following suspected or diagnosed cancer patients who attended general hospitals. After identification, a trained nurse was allocated to improve their care coordination. Epidemiological, social, and clinical data were obtained, including time to establish a cancer diagnosis and start of treatment. Every two weeks, a national virtual meeting is organized to present anonymous data, compare results, and create solutions to address national and local barriers. Here, we report data for LC patients included in the program from 2020 to 2023.

Results: The navigation program identified a total of 28,977 cancer patients. Of these, 1,897 (6.5%) had a diagnosis of LC. Most patients were newly diagnosed (54.7%) and identified at Inpatient Clinical Units (33.9%) after LC diagnosis. The emergency room was the second most frequent admission facility (22.6%). Females accounted for 55.9% of the patients. Surgery was performed in 533 patients (28.0%). Only 54 patients progressed to death during hospitalization, and 78 of them were readmitted to the hospital before outpatient consultation. A total of 285 patients (15%) required an inpatient oncology treatment approach supported by the oncology team.

Conclusions: The goal of the navigation program is to reduce cancer morbidity and mortality by eliminating barriers to timely access to cancer care, which may be financial, social, logistical, or related to communication and equity of health care delivery. These results show that the RDSL National Oncology Navigation Program is feasible. After this implementation phase, the program will measure outcomes such as pathology reports turnaround time, staging workouts, and treatment initiation intervals. In the future, we expect that data collected from this project may help individual patients and families and address cancer care disparities nationwide.

Keywords: lung cancer, navigation, care coordination

EP.15A MULTIDISCIPLINARY CARE: NURSING, ALLIED HEALTH AND PALLIATIVE CARE - NAVIGATION AND MULTIDISCIPLINARY TEAMS
SATURDAY, SEPTEMBER 7, 2024 - 11:58 - 11:59

EP.15A.02 Prospective Evaluation of A Single-Day Multidisciplinary Clinic for Patients with Locally Advanced Non-Small Cell Lung Cancer

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Introduction: Approximately one-third of patients with non-small cell lung cancer (NSCLC) will present with locally advanced disease. Treatment options vary and are made based on multiple factors, including resectability and medical fitness. This workup and consensus requires complex coordination of care among the multidisciplinary team. We hypothesized that earlier multidisciplinary intervention would enhance care and clinical trial enrollment, including in those patients without an established diagnosis or full staging of lung cancer. To this end, we initiated a single-day multidisciplinary clinic for patients with confirmed locally advanced NSCLC or clinically suspected but yet to have biopsy-confirmed disease.

Methods: Patients with imaging and clinical history suggestive of locally advanced lung cancer, +/- confirmatory biopsy, were invited to participate in a multidisciplinary clinic between April 2023 and March 2024 with a maximum of 3 patients per day. Patients who accepted were scheduled for coordinated appointments with a thoracic surgeon, medical oncologist, and radiation oncologist, with consensus recommendations given at the end of the visit. Patient satisfaction data was collected prospectively. Patient demographics, retention, time to treatment start, and clinical or biospecimen protocol enrollment were also collected.

Results: Sixty-seven patients underwent evaluation in the single-day lung cancer multidisciplinary clinic. Of these, 55% were men, the median age was 67 years old (range 39 - 88). At the time of consult, 72% of patients needed additional workup including biopsy and/or imaging to complete their staging. Upon completion of all staging workup, 87% were histologically confirmed to be NSCLC and 58% were AJCC 8th edition stage II or III. Of the patients with a cancer diagnosis who were evaluated in clinic, 92% chose to continue care at the same institution. Of these patients, 70% received systemic therapy, 44% were treated with radiation, and 26% underwent a non-bronchoscopy surgery. Eighty seven percent of patients evaluated in multidisciplinary clinic were enrolled in a biospecimen or clinical research protocol. Patient satisfaction surveys indicated that 98% of patients were very likely to recommend the multidisciplinary clinic to family/friends and 87% of patients indicated the clinic helped them arrive at a final treatment decision.

Conclusions: Despite the lack of an established diagnosis or full staging at presentation, a single-day multidisciplinary clinic for clinically suspected locally advanced NSCLC facilitated high patient retention and enrollment on institutional biospecimen and clinical research protocols. Additionally, the vast majority of patients rated the experience highly, including facilitating a final treatment decision. These data imply that multidisciplinary visits are beneficial even in the context of incomplete diagnosis or staging. Expansion of this model is planned at regional facilities and for alternative clinical contexts requiring multidisciplinary input.

Keywords: Multidisciplinary clinic, Locally advanced NSCLC

EP.15A MULTIDISCIPLINARY CARE: NURSING, ALLIED HEALTH AND PALLIATIVE CARE - NAVIGATION AND MULTIDISCIPLINARY TEAMS
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EP.15A.03 Lung Cancer Multidisciplinary Teams in China Show Multi-faceted Similarities and Differences Compared to Europe and Canada

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Introduction: China, with approximately 820,000 new patients with lung cancer in 2020 accounting for 37% of the total number in the world, bears the responsibility of treating the largest lung cancer patient population worldwide. Medical care in China represents a different mode with that in Europe and Canada. The objective of this study is to compare the differences and similarities in lung cancer MDT management between China, Europe and Canada, in order to better understand and summarize the characteristics and advantages of MDT management in different regions, so as to support on the improvement of the outcome and cost-efficiency of global LC MDT.

Methods: We initiated a global MDT study in LC to gather insights on the similarities, and differences of China LC MDT processes compared to other countries. In this study, we conducted virtual semi-structured interviews, on-site masterclasses, and internal data analysis with 20+ leading hospitals in LC across China, the Netherlands, Italy, Spain, Switzerland, Denmark, Norway, and Canada. Literature review has been used as general information supplement. To build a global collaboration on LC MDTs, 4 international knowledge exchange (IKE) sessions with were organised with an average of 15 LC experts attending each.

Results: We identified seven main differences between China, Europe and Canada, the most significant and fundamental of which was the enrolment criteria of patients in MDT that China MDTs focus on challenging cases such as resistance to multi-lines of therapy, multiple primary lung cancer and stage III lung cancer, while Europe and Canada MDTs mainly for routine patients. Secondly, there was also a 3x difference shown in time per patient spent in MDT, from 30-60 minutes per patient from historical records collection to patient's follow up in China due to the challenging cases discussed, to 10-20 minutes spent per patient in Europe and Canada. Thirdly regarding the setup of LC cancer and composition of MDT teams, the advanced large-scale Chinese hospitals are able to effectively integrate multiple specialists into one single unit to utilize the strength of the team more efficiently, while the specialists are often distributed separately in Europe and Canada. Other differences include leadership culture, digitalization of MDTs, incentives and reimbursement for MDT attendance, cross-institutional patient referral to the MDT, patient follow-up after MDT discussion. Similarities identified include the MDT development model from both hospital and national level, experience sharing to educate junior physicians, hospital willingness to learn at global level, and challenges of high pressure with limited medical resources.

Conclusions: Further global collaboration to identify synergies within LC MDT communities can help China and other regions learn from each other and share China expertise in large-volume data-based practices globally, so as to improve the MDT outcome and cost-efficiency globally.

Keywords: Multidisciplinary teams, China Lung Cancer, Global comparison

EP.15A MULTIDISCIPLINARY CARE: NURSING, ALLIED HEALTH AND PALLIATIVE CARE - NAVIGATION AND MULTIDISCIPLINARY TEAMS
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EP.15A.04 A Tripartite Care Model for Home Care of Lung Cancer Patients Based on the Theory of Tripartite Care Led by Specialist Nurses

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Introduction: To explore the challenges and countermeasures of family care for cancer patients, propose a family care plan for cancer patients based on the hospital-community-family tripartite care model led by specialist nurses, and provide new perspectives and ideas for the development and innovation of cancer care.

Methods: Through literature review, analyze the current situation, problems, and needs of family care for cancer patients, summarize the experience and models of family care for cancer patients at home and abroad, and construct the theoretical framework and implementation steps of the hospital-community-family tripartite care model led by specialist nurses.

Results: The hospital-community-family tripartite care model includes three aspects: coordination mechanism, training and guidance, support and evaluation. Under the leadership of specialist nurses, it can achieve information sharing, resource integration, and service connection between hospitals, communities, and families, improve the nursing ability and self-management level of family caregivers, provide personalized psychological, social, and economic assistance, and regularly monitor and feedback the nursing effects and satisfaction of patients and families.

Conclusions: The hospital-community-family tripartite care model led by specialist nurses is an effective countermeasure for family care of cancer patients. It is of great significance for improving the quality of life of cancer patients, alleviating symptom distress, reducing medical costs, enhancing family resilience, etc., and is worth promoting and applying in cancer care practice.

Keywords: lung cancer, Trinity Care, specialist nurse

EP.15B MULTIDISCIPLINARY CARE: NURSING, ALLIED HEALTH AND PALLIATIVE CARE - SUPPORTIVE CARE INTERVENTIONAL STUDIES AND OUTCOME RESEARCH
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EP.15B.01 Effect of Mindfulness-Based Stress Reduction Psychological Intervention on Anxiety and Depression in Patients with Lung Cancer Radiotherapy

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Introduction: To explore the effects of mindfulness-based stress reduction on anxiety and depression in lung cancer patients during radiotherapy.

Methods: 86 patients with lung cancer treated with radiotherapy in our hospital were divided into control group and observation group by random number table method. The control group received routine nursing care of lung cancer radiotherapy after admission, including the introduction of relevant knowledge of lung cancer disease, respiratory function exercise, diet and rest precautions during radiotherapy, and the use of related drugs, and psychological reassurance for patients to reduce their anxiety. On the basis of routine nursing, the observation group implemented mindfulness-based decompression psychological intervention after admission, and formulated corresponding training plans and contents according to the content of mindfulness-based decompression and the actual situation of patients during radiotherapy. The self-rating Anxiety Scale (SAS), self-rating Depression Scale (SDS) and the incidence of radiotherapy complications were observed before and after the intervention. The specific measures to implement mindfulness-based stress reduction psychological intervention in the observation group were as follows: ①A mindfulness-based stress reduction psychological intervention group was established, including 1 deputy chief physician in the radiotherapy department and 4 nursing staff with more than 5 years of nursing experience. ②Before the implementation of the mindfulness-based stress reduction psychological intervention program, the group members all learned and were familiar with the concept and specific content of mindfulness-based stress reduction psychological intervention. When the content of mindfulness-based stress reduction was uncertain, they promptly consulted the national second-level psychological counseling teachers. ③After the patient was admitted to the hospital, a wechat group was established to guide the patient to conduct 30min independent exercises once a day for the patient for 4 weeks. Family members were encouraged to attend the training once a week and assist the patient to actively participate in the training. The guidance manual for relevant training content was distributed at the first training session, and the relevant concepts, contents and matters requiring attention of MBSR therapy were regularly pushed to the wechat group. Patients improve their self-control while relaxing, thereby regulating their own response to bad emotions and improving the mood of patients. ④Through wechat video call and other forms of communication training, there is a person in person or wechat group every day to prompt mindfulness-based stress reduction therapy training punched, actively encourage the completion of training personnel, can not complete the personnel timely telephone communication reasons, to help solve difficulties, in the case of the day after surgery or other special circumstances can not tolerate training, reduce the training content or cancel the training.

Results: The scores SAS and SDS of the observation group were significantly lower than those of the control group (t=11.276, 13.155; P<0.05). The incidence of radiation complications, such as radiation pneumonia and radiation esophagitis, also decreased significantly after radiotherapy.

Conclusions: Psychological intervention program based on mindfulness-based stress reduction can reduce the anxiety and depression of patients with lung cancer radiotherapy, and reduce the complications of lung cancer radiotherapy.

Keywords: Psychological, Anxiety, Radiotherapy

EP.15B MULTIDISCIPLINARY CARE: NURSING, ALLIED HEALTH AND PALLIATIVE CARE - SUPPORTIVE CARE INTERVENTIONAL STUDIES AND OUTCOME RESEARCH
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EP.15B.02 Real-World Data from Advanced Practice Nurse Care in Lung Cancer in a Private Clinic in Brazil.

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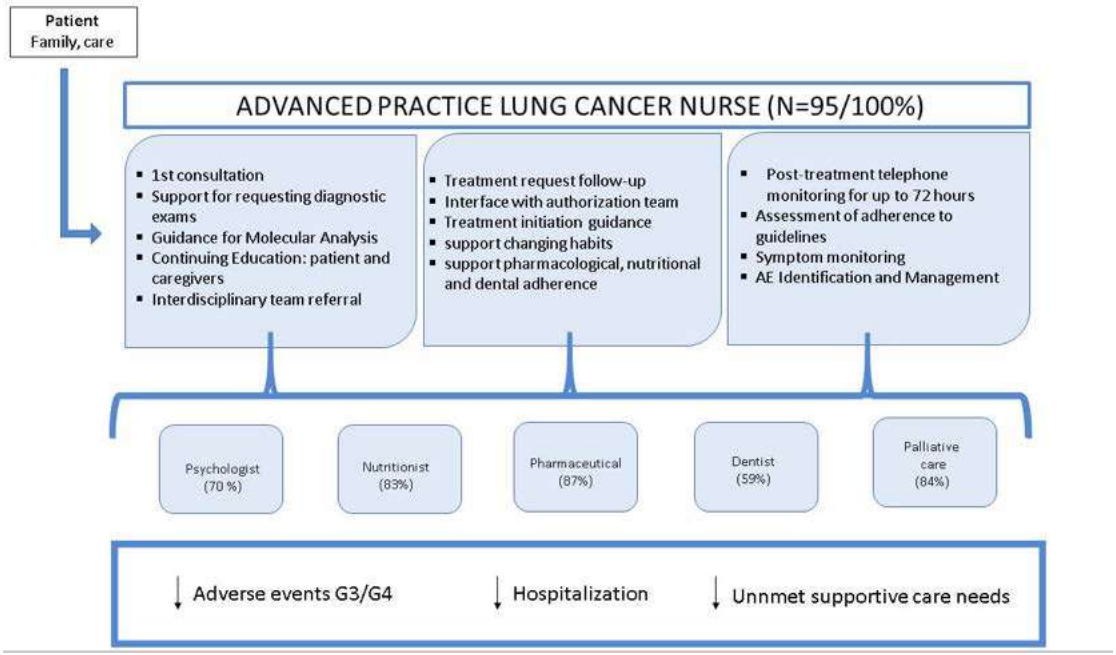
Introduction: The treatment of lung cancer (LC) has made important advances in recent years, increasing the complexity of care and the need for support by advanced practice nurses (APN) specialized in LC. The objective of this study is to identify the profile and outcomes related to APN care in patients with PC in a private center in Brazil.

Methods: This is a cross-sectional study carried out from 2022 to 2023 with patients diagnosed with LC at a cancer center in Brazil. The data consisted of clinical and epidemiological variables, actionable mutations, therapeutic modalities and detection and intervention of adverse events (AE) by APN. AE were classified according to (CTCAE) and data were presented descriptively.

Results: A total of 95 patients were evaluated, 78% female, 63% elderly, 95% NSCLC, 71% adenocarcinoma, 64% smokers, 84% with TNM III-IV, 27% patients had actionable mutations, with a predominance of 23% in EGFR. Regarding therapeutic modalities, 56% received systemic treatment with chemotherapy and/or immunotherapy, 27% tyrosine kinase inhibitors, 25% radiotherapy and 21% underwent lobectomy. 100% of patients were monitored (Figure 1) by APN. AEs of any cause and degree occurred in 70% of patients and were identified, managed, guided and referred to the interdisciplinary team. Among them we can highlight the management of fatigue, paronychia, diarrhea, neutropenia, anorexia, anemia, constipation, nausea, rash, thrombocytopenia, mucositis. AE with grades 1 and 2 were 92%, while grade 3 were 8%. Outpatient and home management was 96% and 4% with hospital admission. Referral to the interdisciplinary team occurred in 100% of patients with follow-up of 87% for pharmaceutical, 83% nutritional, 70% psychological and 59% dental care.

Conclusions: Our data found a low occurrence of G3 AE and hospital admission in patients with compared to literature data, demonstrating the importance of APN action. APN plays a fundamental role in managing patient care throughout their treatment journey. APN navigation operates at all stages of the therapeutic process, thus contributing to the early detection of toxicities, facilitating management, intervention and guidance for the interdisciplinary team. Personalized care favors better outcomes and should be encouraged.

Keywords: Lung cancer, advanced practice nurse, real world data



EP.15B MULTIDISCIPLINARY CARE: NURSING, ALLIED HEALTH AND PALLIATIVE CARE - SUPPORTIVE CARE INTERVENTIONAL STUDIES AND OUTCOME RESEARCH
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EP.15B.03 Pilot Web-Based Study of Functional Status and Quality of Life Benefits Associated with Darbepoetin Alfa Use in Anemic Patients with Lung Cancer

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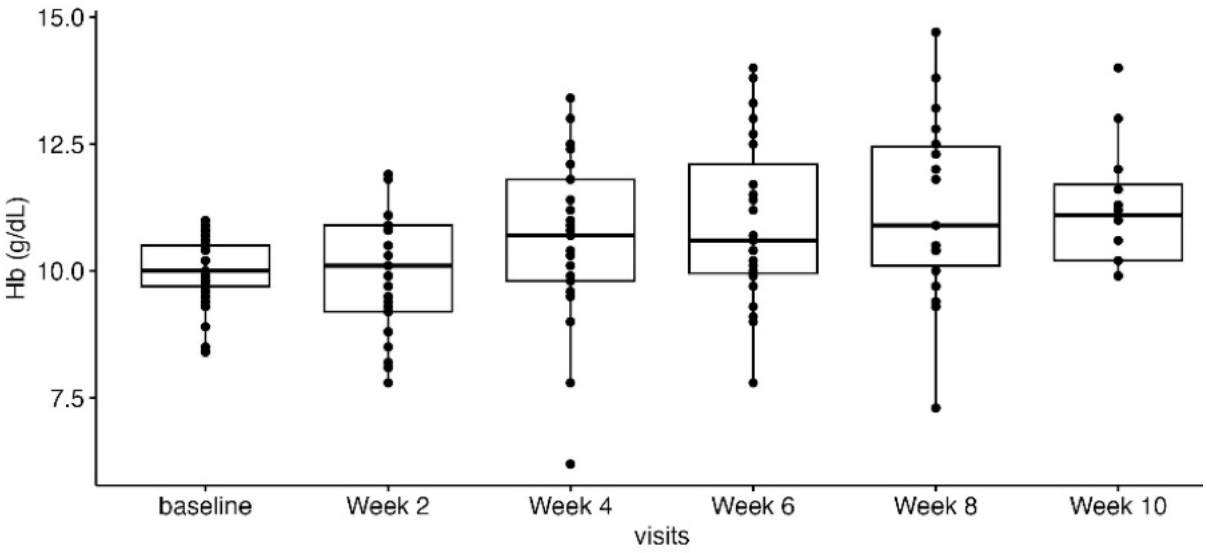
Introduction: Patients with lung cancer often present with symptomatic anemia at diagnosis. Moreover, platinum-based chemotherapy with or without immunotherapy, induces anemia through myelosuppression and impaired renal erythropoietin release. Erythropoietin-stimulating agents have shown efficacy in chemotherapy-induced anemia (CIA) but concerns regarding potential tumor-promoting effects have curtailed their use. Improvements in cancer-related symptoms have been reported in paper-based surveys. We conducted a pilot study to explore a web-based platform to evaluate the clinical symptom benefits associated with darbepoetin alfa (DPO) administration in anemic patients with lung cancer and assess for correlation with changes in hemoglobin (Hb) concentrations.

Methods: This is an open-label, single-arm pilot trial in patients with NSCLC/SCLC with Hb≤11.0g/dL(NCT00153868). Patients were treated with DPO 200mcg subcutaneously Q2W or DPO 300mcg Q3W for 12 weeks. Hb concentrations were obtained every 2 or 3 weeks. Patients with <1.0g/dL increase in Hb after 6 weeks required DPO dose escalation. Endpoints included time of Hb response (increase Hb≥2.0g/dL over baseline) and time of Hb correction (Hb≥12.0g/dL). We conducted posthoc pairwise comparisons under a paired T-test framework at each visit after Bonferroni correction for significance. Before DPO administration, patients completed a secure web-based assessment of cancer-related symptoms (LCSS), functional status (SF-36), and QoL (FACT-An and PFS).

Results: 29 patients were included in the analysis; 14 were men (48.3%) and 15 female (51.7%) with a median age of 64 years. Most of the patients presented with advanced disease (n=21, 72.4%); 23 (79.3%) had NSCLC, and 6 (20.7%) had SCLC. More than half were treated with platinum-based chemotherapy (n=17, 58.6%). Only 4 patients (13.4%) required blood transfusions. The trial completion rate was 51.7% (n=15). Hb response was observed in 13 patients (44.8%) and Hb correction in 9 patients (31%)(Fig.1). Pairwise comparisons between Hb concentrations at baseline and weeks 6 and 8 were statistically significantly different at PBonferroni=0.018 and PBonferroni=0.008, respectively. The platinum-based chemotherapy group showed an earlier Hb effect on DPO at week 6 (PBonferroni=0.012) compared to the non-platinum-based chemotherapy group at week 8 (PBonferroni= 0.046). Updated results for the assessments of the functional status, and QoL will be presented at the meeting.

Conclusions: Results from this study confirmed that DPO increases Hb concentrations in lung cancer patients with CIA. In patients receiving myelosuppressive platinum-based chemotherapy, Hb concentrations improved earlier on DPO compared with other regimens. After week 6 on DPO, Hb>8g/dL was more frequently observed. Proper DPO use is crucial to its efficacy in lung cancer.

Keywords: Chemotherapy-induce anemia, Darbepoetin alfa, Advanced lung cancer



EP.15B MULTIDISCIPLINARY CARE: NURSING, ALLIED HEALTH AND PALLIATIVE CARE - SUPPORTIVE CARE INTERVENTIONAL STUDIES AND OUTCOME RESEARCH
SATURDAY, SEPTEMBER 7, 2024 - 11:58 - 11:59

EP.15B.04 High-Fiber Intake Predicts Overall Survival in Lung Cancer Patients - Real-World Analyses

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Introduction: The treatment of lung cancer (LC) has advanced with the use of targeted therapies and checkpoint inhibitors, however, the responses are still unsatisfactory in some individuals. Therapeutic modalities are influenced by the intestinal microbiome, which depends on a series of factors, including dietary fiber intake, with current dietary recommendations of 30g/day, also indicated after cancer diagnosis, if possible. The current analysis aimed to evaluate whether dietary fiber consumption at diagnosis is predictive of LC treatment outcomes.

Methods: This is a prospective observational cohort carried out with LC patients served from January to December 2019 from a private center in Rio de Janeiro, Brazil. This study was approved by the Ethics in Human Research Committee and was conducted following the Good Clinical Practice Guidelines. Clinical variables, first-line therapeutic modalities as well as nutritional risk screening for patients cancer and anthropometric data were used. Information on food consumption at the time of diagnosis was analyzed using a 24-hour recall. The Kaplan-Meier method was used to estimate overall survival (OS) according to fiber consumption.

Results: A total of 50 individuals were included, with a mean age of 71.2 [48, 88] years, 62% female, and 88% had non-small cell LC, 88% with stage III and IV disease, 82% ECOG perfomance status 1, 64% (current or former) smokers. First-line therapeutic modalities consisted of 90% chemotherapy and/or immunotherapy, 6% targeted therapy, 12% radiotherapy, and 10% surgery. Regarding nutritional status, 76% were at risk at screening, a median body mass index of 23.7kg/m^2 [21.08, 28.18], and 60% were classified as eutrophic and/or overweight according to with age. The median consumption of dietary fiber was 13.15 g/day with interquartile ranges [10.32, 19.05]. Individuals with fiber consumption greater than 19.05 g/day had a higher median OS than those with lower intake, 56.5 versus 33.9 months, respectively (p=0.008)(Figure 1).

Conclusions: In the current study, the median consumption of dietary fiber at diagnosis was lower than recommended, reflecting unsatisfactory consumption of a plant-based diet. The fiber intake was a predictor of the treatment results of LC patients. Dietary fibers have been postulated as a possible modulator of the intestinal microbiome and antitumor immunity. Nutritional interventions are simple, practical, accessible measures that allow a personalized approach that can reverse these findings and thus contribute to better clinical results. Nutritional care should be part of the LC patient's journey.

Keywords: Lung cancer, Total fibers, Overall survival

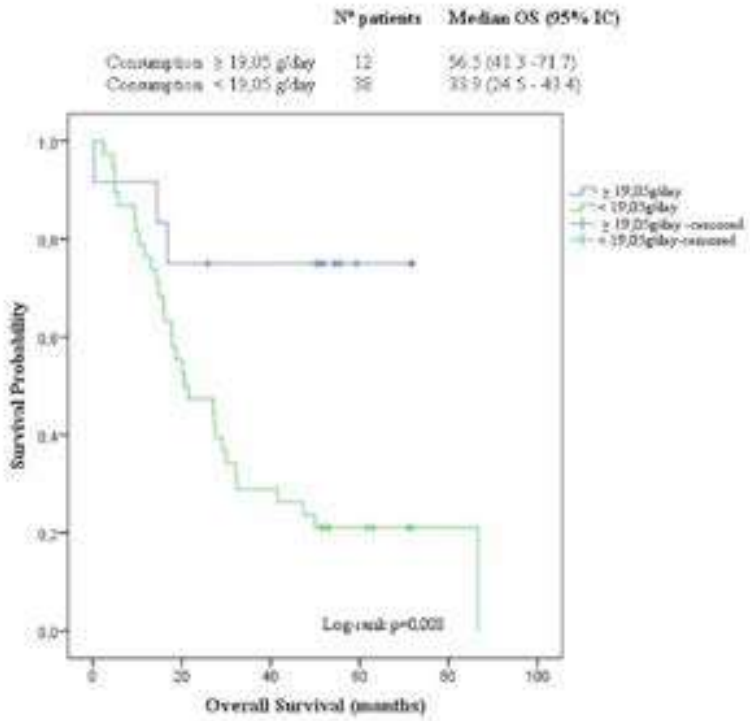

Figure 1: Kaplan-Meier plot comparing overall survival intervals according to total fiber intake in patients with lung cancer

EP.15B MULTIDISCIPLINARY CARE: NURSING, ALLIED HEALTH AND PALLIATIVE CARE - SUPPORTIVE CARE INTERVENTIONAL STUDIES AND OUTCOME RESEARCH
SATURDAY, SEPTEMBER 7, 2024 - 11:58 - 11:59

EP.15B.05 Predictors of 30-Day Mortality after Systemic Therapy in Hospitalized Lung Cancer Patients: A Retrospective Single-Center Observational Study

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Introduction: Due to the aggressive nature and high incidence of disease-associated symptoms, hospitalization is often required for lung cancer patients in order to receive oncologic treatment. An accepted threshold for late systemic therapy administration is 30 days before death, but data regarding potential predictive factors of 30-day mortality following anticancer treatment are still limited.

Methods: This is a retrospective single-center observational study aimed at investigating potential predictors of 30-day mortality since systemic therapy start in lung cancer patients admitted to receive anticancer treatment at the Oncology ward of University Hospital of Parma from January 2017 to January 2022. Baseline clinicopathological features, laboratory values and immunological scores were collected. Prognostic nutritional index (PNI) was calculated using the albumin level and lymphocyte count.

Results: A total of 144 lung cancer patients were consecutively enrolled; 14 (9.7%) patients did not start anticancer treatment and were excluded from the study. Among 130 included patients, median age was 68 years (Range, 30-86), 79 (60.8%) patients were men and 112 (89.6%) current/former smokers. ECOG Performance Status was 0/1 in 100 (76.9%) cases. Median body mass index was 25.3 (Range, 15.3-42.9). The most frequent histology was small-cell carcinoma (n = 60, 46.2%), followed by adenocarcinoma (n = 41, 31.5%), and most of the patients had stage IV disease (n = 107, 82.3%). Baseline median hemoglobin was 12.1 g/dL (Range, 7–16.8) and median albumin was 3.3 g/dL (Range 2.4-4.4). At admission, median values of platelet-to-lymphocyte ratio, neutrophil-to-lymphocyte ratio (NLR) and derived NLR were 177.1 (Range, 25.1–836.0), 4.4 (Range, 0.4–23.9) and 2.8 (Range, 0.3–11.4), respectively. PNI had a median value of 41.4 (Range, 28.3–59.8). Median time from hospitalization to treatment start was 5.0 days (95% Confidence Interval [CI] 3.0–6.0). Chemotherapy was the most frequent administered treatment (n = 76, 58.5%), followed by chemoimmunotherapy (n = 33, 25.4%). The majority of patients (n = 115, 88.5%) received therapy in first-line. After a median follow-up of 30.5 months (95% CI 26.2–Not Reached), median overall survival from anticancer therapy was 6.4 months (95% CI 4.3–7.8). The 30-day mortality rate from therapy was 10% (n = 13). Age was significantly associated with 30-day mortality from therapy (≥ 65 vs < 65: 15.9% vs 0%, p = 0.002). Baseline laboratory predictors of 30-day mortality were low hemoglobin (low vs in range vs high: 18% vs 2.9% vs 0%, p = 0.013), low albumin (low vs in range: 17.7% vs 0%, p = 0.008) and low pseudocholinesterase (pCHE) (low vs in range: 22.7% vs 3.9%, p = 0.002). Among immunological scores, PNI showed a negative impact on 30-day mortality in our study population (< 45 vs ≥ 45: 16.4% vs0%, p = 0.030).

Conclusions: Older age and baseline low values of hemoglobin, albumin, pCHE and PNI were associated with increased 30-day mortality from therapy in hospitalized lung cancer patients. Special caution should be addressed when treating in-hospital lung cancer patients with the above-mentioned features.

Keywords: lung cancer, 30-day mortality, systemic treatment

EP.16A PATIENT ADVOCACY - BIOMARKERS
SATURDAY, SEPTEMBER 7, 2024 - 11:58 - 11:59

EP.16A.01 Patient Experiences of Biomarker Testing: Insights from a Global Patient Experience Survey

K. Clayton[1], M. Daniels[2], J. Fox[3], B. Gaspar[4], M. Hennink[5], J. Mayans[4], A. McNamara[6], L. Pretorius[2], M. Rigney[7], M. Dohr[8], [1]Lung Cancer Nursing UK, London/GB, [2]Campaigning for Cancer, Randburg/GB, [3]Roy Castle Lung Cancer Foundation, Liverpool/GB, [4]Asociación Española de Afectados de Cáncer de Pulmón, Valencia/ES, [5]Longkanker Nederland, Utrecht/NL, [6]Irish Cancer Society, Dublin/IE, [7]GO[2] Foundation for Lung Cancer, Washington, D.C./DC/USA, [8]Incisive Health, London/GB

Introduction: Looking for changes in tumour cell DNA, biomarker testing plays a crucial role in tailoring optimal treatment plans for individuals with lung cancer. As biomarker testing becomes more widely available, more patients can now benefit from targeted therapies tailored to their unique tumour type. The Global Lung Cancer Coalition (GLCC), a partnership of 43 patient organisations across 30 nations, sought to understand the experience of patients across the world in receiving access to biomarker testing, and to see whether patients understood what biomarker testing is.

Methods: In the GLCC's fifth annual survey, the coalition commissioned Censuswide to conduct a global survey of lung cancer patients. The survey is currently in the field across 18 countries (Australia, Argentina, Bulgaria, Canada, Denmark, Greece, Ireland, Israel, Italy, Japan, Mexico, Portugal, Netherlands, South Africa, Spain, Taiwan, UK, USA). As part of this survey, the GLCC included questions regarding respondents' personal experience with biomarker testing.

Results: 92% (346/375) of respondents with non-small cell lung cancer [or those who did not know what type of lung cancer they had] reported having been spoken to about biomarker testing.

However, nearly 40% (129/346) of those who reported having been tested did not understand what was meant by 'biomarker testing' when they first heard about it. Similarly, one-third of respondents (129/346) reported having to subsequently do their own independent research to learn what was meant by the term.

Conclusions: While the majority of respondents eligible for biomarker testing reported having been spoken to about it, four out of ten reported not understanding the term when it was first discussed - highlighting a significant gap in patient communication and understandingabout these tests.

The GLCC patient charter states patients have a right to informed self-determination. Therefore, it is important that people who undergo biomarker tests have the tests (and subsequent results) clearly communicated. Healthcare professionals, serviceproviders and patient support groups provide important education about biomarker testing. They should be supported to improve the clarity of this communication to help more patients access personalised treatment, support and care.

Keywords: patient experience, patient information, biomarker testing

EP.16B PATIENT ADVOCACY- CLINICAL COMMUNICATIONS
SATURDAY, SEPTEMBER 7, 2024 - 11:58 - 11:59

EP.16B.01 UK and US Patient Preferences for Anaplastic Lymphoma Kinase Positive Advanced Non-Small Cell Lung Cancer Tyrosine Kinase Inhibitors Treatments

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Introduction: We aimed to explore patient experiences, expected treatment benefits, and treatment-related risks associated with anaplastic lymphoma kinase positive (ALK+) tyrosine kinase inhibitors (TKIs) in the 1L setting for patients in the UK and US, to understand key treatment attributes for decision-making.

Methods: Thirty semi-structured interviews (US: 20; UK: 10) were conducted with patients with advanced ALK+ non-small cell lung cancer (aNSCLC). Interviews (90 min with an online survey) utilized qualitative and quantitative methods. Qualitative interview data was analyzed using an inductive thematic approach, while the quantitative responses were analyzed descriptively.

Results: The mean age of patients in the US was 52 years (range 38-69), with 60% having brain metastases (BM). In the UK, mean age was 48 (range 31-62), with 40% having BM. Most patients in the US were on 2L (40%) or 3L+ (35%) treatments, while most UK patients were on 1L treatment (70%). Most US patients indicated they were restricted in strenuous activity (85%), as opposed to UK patients where most reported being fully active (70%). The treatment benefits most desired by patients in the US and UK were improving overall survival (90%, 70% respectively), improving progression-free survival (85%, 70%), and preventing metastases (55%, 50%). Patients without BM were concerned about BM development, particularly those from the UK, as it may significantly affect their daily activities such as driving. Quality of life improvements were primarily described as coming from cancer control. Patients in the US and UK reported experience with fatigue (85%, 60%), and weight gain (65%, 60%). The third most reported side effect was muscle pain in the US (65%) and constipation in the UK (60%). While there were slight variations in treatment side effect experiences, both US and UK patients were concerned about cognitive effects (50%, 50%), weight gain (35%, 40%), and fatigue (30%, 30%). All patients were willing to tolerate adverse events in exchange for efficacy. Patients in the UK had less experience with multiple TKIs in their treatment sequence than patients in the US (30%, 70%). Patients in both countries expressed a preference for a regimen that was infrequent (e.g., once a day) and without dietary restrictions, but a few individuals conveyed dissatisfaction with their treatment due to administration requirements. Patients from both countries indicated that the treatment selection and change in treatment decision were based on discussion with their doctors. The shared decision-making process was described to evolve over time, with patients initially relying solely on doctors' advice, and later gaining confidence in conducting independent research to be "very involved in all the decisions".

Conclusions: While the priorities of US and UK patients were similar, some differences in TKI treatment preferences were detected between countries. Most patients prioritized treatment efficacies (i.e., improving overall survival, lung cancer control, and controlling BM progression or development) over side effects. Overall, this study highlights the importance of considering patient preferences and experiences when developing treatment strategies in ALK+ aNSCLC patients.

Keywords: Patient Advocacy, NSCLC, ALK

EP.16B PATIENT ADVOCACY- CLINICAL COMMUNICATIONS
SATURDAY, SEPTEMBER 7, 2024 - 11:58 - 11:59

EP.16B.02 Lung Cancer Patients' Preferred Methods of Receiving Information from their Treatment Teams: Insights from a Global Patient Experience Survey

K. Clayton[1], M. Daniels[2], J. Fox[3], B. Gaspar[4], M. Hennink[5], J. Mayans[4], A. McNamara[6], L. Pretorius[2], M. Rigney[7], M. Dohr[8], [1]Lung Cancer Nursing UK, London/GB, [2]Campaigning for Cancer, Randburg/ZA, [3]Roy Castle Lung Cancer Foundation, Liverpool/GB, [4]Asociación Española de Afectados de Cáncer de Pulmón, Valencia/ES, [5]Longkanker Nederland, Utrecht/NL, [6]Irish Cancer Society, Dublin/IE, [7]GO[2] Foundation for Lung Cancer, Washington, D.C./DC/USA, [8]Global Lung Cancer Coalition, Liverpool/GB

Introduction: The Global Lung Cancer Coalition (GLCC), a partnership of 43 patient organisations across 30 nations, reaffirms in its charter the right of all lung cancer patients to be treated with dignity and respect and to have access to quality health care, including informed self-determination and physical and mental integrity.

How patients engage with and receive information from their treatment teams is essential for these patient rights. GLCC therefore sought to understand patients' preferences for receiving information from their treatment teams in different clinical contexts.

Methods: In the GLCC's fifth annual survey, the coalition commissioned Censuswide to conduct a global surveyof lung cancer patients. The survey ran from 28 March 2024 - 18 April 2024. It received 905 responses across 18 countries (Australia, Argentina, Bulgaria, Canada, Denmark, Greece, Ireland,Israel, Italy, Japan, Mexico, Portugal, Netherlands, South Africa, Spain, Taiwan, UK, USA).

Results: When asked what is your preferred format for receiving information, there was variation in response, with cancer support hotlines (33%: 297/905), print materials (29%: 261/905) and apps (14%: 128/905) all ranking highly.

Participants were also asked how they felt about the information they received. The majority of respondents felt they got the information they needed at the right time: at diagnosis (82%: 745/905); when starting treatment (78%: 638/813); when changing treatment (76%: 615/813); when ending treatment / follow-up (76%: 615/813); when accessing palliative care (73% 656/905).

Conclusions: While the majority of respondents reported getting the right information at the right time, there is still scope for improvements in when and how information is shared, particularly as patients journeythrough their care pathways. Healthcare providers should tailor their approaches to providing patient information, fostering more effective patient-provider relationships and ultimately enhancing the delivery of patient-centric care.

Keywords: patient experience, health information, treatment

Questions	Answer options			
Doctors can take a sample of a tumour to test for biomarkers (also known as mutation, genomic, or molecular testing). Has anybody spoken to you about this topic?	Yes, and the cancer has been tested.	Yes, but the cancer has not been tested.	No, nobody has mentioned this to me.	I am not sure.
If you were spoken to about biomarker testing, do you feel you understood what it is?	Yes, I understood what biomarker testing meant before or after someone spoke to me about them.	No, I did not understand what it meant when they spoke to me about it, but I since have learned what it means on my own.	No, I did not understand what it meant when I first heard about it, and I still do not know.	I am not sure.

What best describes how you feel about the information you received from your treatment team about your lung cancer? Please choose the option that best describes you.

			*Those who are currently having treatment or have finished treatment			*Those who are currently having treatment or have finished treatment			*Those who are currently having treatment or have finished treatment					
At diagnosis	All	Count	**When starting treatment**	All	Count	**When changing treatment**	All	Count	**When ending treatment / follow-up**	All	Count	**When accessing palliative care**	All	Count
N	905		N	813		N	813		N	813		N	905	
I got the information I needed at the right time	82.32%	745	I got the information I needed at the right time	78.47%	638	I got the information I needed at the right time	75.65%	615	I got the information I needed at the right time	75.65%	615	I got the information I needed at the right time	72.49%	656
The information wasn't helpful	1.66%	15	The information wasn't helpful	2.71%	22	The information wasn't helpful	1.85%	15	The information wasn't helpful	1.48%	12	The information wasn't helpful	2.76%	25
The information came too late	6.63%	60	The information came too late	9.23%	75	The information came too late	8.86%	72	The information came too late	8.49%	69	The information came too late	9.39%	85
The information wasn't helpful and it was also given too late	0.88%	8	The information wasn't helpful and it was also given too late	0.49%	4	The information wasn't helpful and it was also given too late	1.72%	14	The information wasn't helpful and it was also given too late	1.60%	13	The information wasn't helpful and it was also given too late	1.66%	15
I had to look for other information on my own	1.77%	16	I had to look for other information on my own	1.60%	13	I had to look for other information on my own	1.97%	16	I had to look for other information on my own	2.09%	17	I had to look for other information on my own	1.77%	16
I didn't understand the information provided	1.10%	10	I didn't understand the information provided	0.86%	7	I didn't understand the information provided	0.86%	7	I didn't understand the information provided	0.98%	8	I didn't understand the information provided	0.66%	6
I didn't get any information	0.22%	2	I didn't get any information	0.37%	3	I didn't get any information	0.62%	5	I didn't get any information	0.98%	8	I didn't get any information	1.10%	10
I didn't want to know any information	0.77%	7	I didn't want to know any information	0.86%	7	I didn't want to know any information	1.23%	10	I didn't want to know any information	1.35%	11	I didn't want to know any information	1.22%	11
Other way	0.66%	6	Other way	0.86%	7	Other way	0.74%	6	Other way	0.62%	5	Other way	1.10%	10
No way in particular	1.22%	11	No way in particular	1.48%	12	No way in particular	2.46%	20	No way in particular	2.83%	23	No way in particular	2.54%	23
Not applicable	2.76%	25	Not applicable	3.08%	25	Not applicable	4.06%	33	Not applicable	3.94%	32	Not applicable	5.30%	48

EP.16C PATIENT ADVOCACY - CLINICAL TRIALS IN PROGRESS
SATURDAY, SEPTEMBER 7, 2024 - 11:58 - 11:59

EP.16C.01 The INSPIRE (INformation Support through Patient Involvement for Research and Education) Project

M-L. Meyer[1], K. Lê Van[1], S. Peters[1], [1]CHUV - Centre Hospitalier Universitaire Vaudois, Lausanne/CH

Introduction: Communication is a critical element in the relationship between patients and the healthcare system, influencing patient satisfaction, reducing anxiety levels, and preventing medical errors. The Swiss Cancer Patient Experiences (SCAPE) study identified areas in communication that specifically require enhancement, especially concerning the delivery of treatment information, including the management of side effects. Consequently, a program was developed to bolster services for patients, including the creation of a mobile app currently used for general information. Our research project aims to address the gaps identified in the clinical information exchange between healthcare providers and patients in thoracic oncology by developing personalized information tools.

Methods: This study proposes a qualitative analysis in collaboration with expert patients (individuals who have developed significant knowledge about their condition and treatment through their lived experience) to identify deficits in clinical information content. Focus groups and semi-structured interviews will be conducted to understand detailed specific needs. Informational supports will be written in collaboration with the oncologists, nurses, pharmacists, and communication experts at the University hospital. The project will develop personalized information supports detailing treatment plans, medications, administration modalities, schedules, common side effects, and urgent consultation needs. These supports will be designed for digital and printable access and will be integrated into the mobile app. They will be accessible at all times by patients and relatives and also aim to serve as references during medical and specialized nursing consultations, as well as for teaching purposes. Expert patients and healthcare professionals will formally evaluate their effectiveness.

Keywords: Communication, Expert Patient, Personalized Information

EP.16D PATIENT ADVOCACY - DISPARITIES
SATURDAY, SEPTEMBER 7, 2024 - 11:58 - 11:59

EP.16D.01 Call Me by My Pronouns: Ethnic Disparities in Self-Reporting Gender Identity in Patients with Cancer

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Introduction: To promote inclusivity, the term LatinX has emerged in recent years to incorporate all gender identities in the LatinX population. However, its use is not common practice in this population, as only 24% of LatinX adults report having heard the term and only 3% has ever used it. This raises suspicion for the perceptions of the LatinX population regarding the use of self-identifying pronouns. In our study, we assess the trends on self-reporting gender identity in the LatinX population with cancer. We hypothesized that LatinX are less likely to report their pronoun of preference in their medical records than other ethnicities.

Methods: We performed a single institution study at the University of Miami. All subjects with cancer seen from 2020-2021 were included in the analysis. Demographic information including age, sex at birth, gender identity, race, and ethnicity were obtained. Our variables of interest were responses to gender identity. Options to choose from included: she/her/hers, he/him/his, they/them, not listed, unknown, or decline to answer. A chi-square comparison was conducted to compare responses to pronoun identification question and ethnicity.

Results: We reviewed the charts of 90,110 participants of which 38.7% self-identified Hispanic/LatinX, 56.5% non-Hispanic/LatinX and 4.8% unknown/other ethnicity. Of the total cohort, only 12.5% selected an answer to the gender preference question, whereas the rest left the question blank. Hispanic patients were significantly less likely to select their pronoun of preference and more likely to choose 'decline to answer' than any other ethnic group. Almost one third (29%) of the Hispanics that selected an answer to the gender identity question, selected 'decline to answer' compared to 19% and 18% of non- Hispanics and unknown/other ethnicity, respectively (chi sq 184.9; $p < 0.00001$) [Table 1].

Conclusions: Despite Hispanic/LatinX comprising only approximately one third of the patients analyzed, they accounted for almost half of the patients who selected 'decline to answer' as their response to the gender identity question, much more frequently than other racial and ethnic groups. It is unclear the premises under which Hispanic/LatinX refused to select their pronoun of preference. Presumable, some of the reasons could be fear of judgement, a lack of understanding of the terms, and/or adamancy towards the use of self-identifying pronouns. Further studies to understand the LatinX awareness and perceptions towards gender identity is needed to best promote inclusion, self-acceptance, and overall satisfaction with cancer related care.

Keywords: disparities, gender identity, hispanic

	Hispanic/LatinX (N = 3726)	Non-Hispanic/LatinX (N = 5515)	p
Selected 'Decline to answer'	1081	1002	< .00001
Selected an actual response	2645	4513	

EP.16E PATIENT ADVOCACY - LUNG CANCER EDUCATION
SATURDAY, SEPTEMBER 7, 2024 - 11:58 - 11:59

EP.16E.01 Advancing Patient Empowerment: The Growth and Impact of Educational Lung Cancer Patient Groups

D.J. Donaldson[1], L. Abbott-McCloud[2], [1]LiveLung, High Point/NC/USA, [2]LiveLung, Charlotte/NC/USA

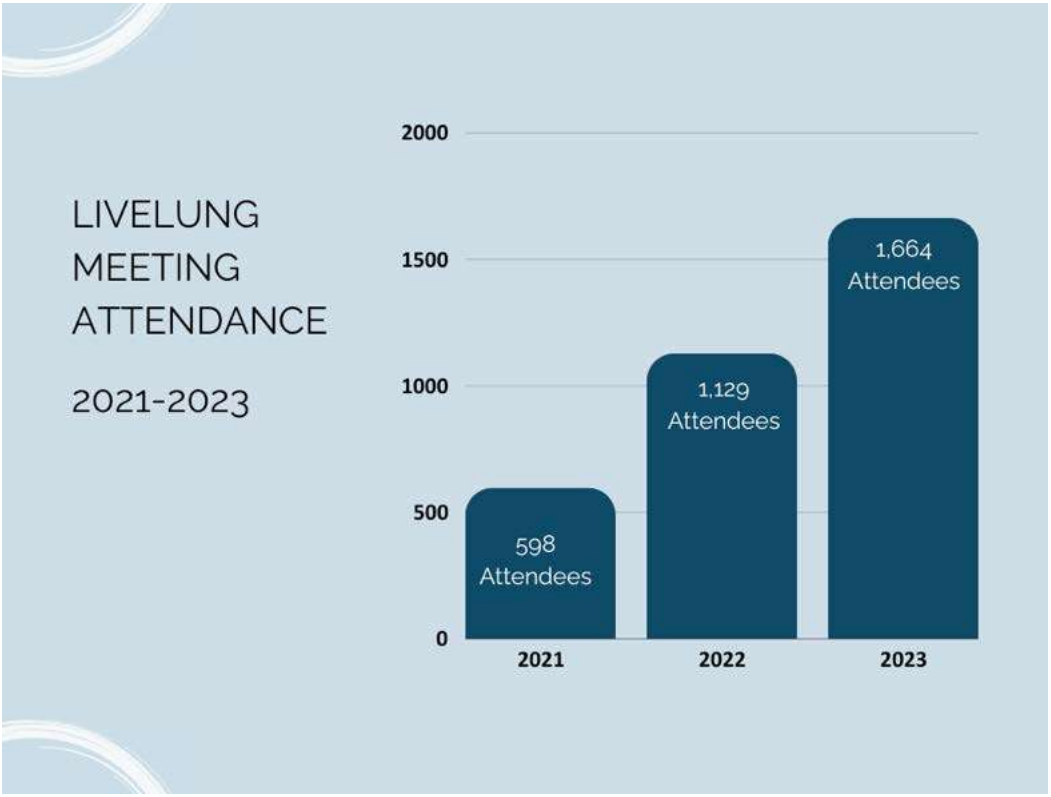
Introduction: Introduction: Impact of a Lung Cancer Diagnosis and the Role of Patient Groups Lung cancer patients face multifaceted challenges upon diagnosis, including emotional turmoil, financial strain, and social stigma. In response to these challenges, educational lung cancer patient support groups have emerged as crucial resources for patients and their families. These groups provide a platform for sharing experiences, accessing information, and fostering community. Martina Jablotschkin's research on cancer self-help groups (CSHGs) in European Journal of Cancer Care emphasizes the benefits of such groups for patients and their partners. "Benefits and challenges of cancer peer support groups: A systematic review of qualitative studies," the authors state that "All included studies consistently indicate that participation in a peer led CSHG leads to multiple perceived benefits, that is, informational support, shared experience, learning from others, helping others as well as cultivating humour as a coping strategy." LiveLung educational patient groups bring expert speakers to address many concerns of patients and their partners. One of the primary objectives of the programs is to share knowledge that empowers patients.

Methods: Methods: The objective of this abstract is to highlight growth and impact of educational lung cancer patient groups over the past three years. Examining the expansion of these groups underscores the positive impact such programs bring in addressing the needs of lung cancer patients nationwide. We conducted a retrospective analysis of the growth and development of LiveLung educational patient groups from January 2021 to December 2023. Data were collected from program records, participant feedback, and community outreach efforts. We also included data from a new patient group exclusively for Small Cell Lung Cancer patients.

Results: Results: Over the past three years, LiveLung educational patient groups have experienced substantial growth expanding their reach to serve an increasing number of lung cancer patients and their families across the country. Total attendees were 598 in 2021, 1,129 in 2022; and 1,664 in 2023—a 278 percent increase from 2021 to 2023. The SCLC program grew from 271 attendees in 2022, when the program started, to 666 in 2023.

Conclusions: Conclusion: The growth of LiveLung educational patient groups highlights the critical need for accessible and comprehensive support services for lung cancer patients nationwide. By providing education, community, and empowerment, these programs play a vital role in improving the quality of life and outcomes for individuals affected by lung cancer.

Keywords: Peer-Led Support Group, Patient Empowerment, Lung Cancer Community



EP.16E PATIENT ADVOCACY - LUNG CANCER EDUCATION
SATURDAY, SEPTEMBER 7, 2024 - 11:58 - 11:59

EP.16E.02 15 Years of the Lung Cancer Living Room Expert Speaker Series Provides Critical Education to Global Audience

N.M. Phipps, D. Hicks, M. Zeh, GO² for Lung Cancer, SAN CARLOS/CA/USA

Introduction: Lung cancer remains the deadliest cancer in the United States and around the world. In 2009, The Bonnie J. Addario Lung Cancer Foundation, now GO2 for Lung Cancer, began a monthly expert speaker series called the Lung Cancer Living Room to educate and empower people facing a lung cancer diagnosis. Over the years, the program has evolved and expanded to reach a global audience, bringing conversations with lung cancer thought leaders directly into people's living rooms via live stream on Facebook and YouTube and via video library on Vimeo and YouTube. Topics for these 200+ Living Room episodes have included early detection, biomarker testing, targeted therapies, small cell lung cancer, pulmonary health, palliative care, financial toxicity, survivorship, and so much more. Although based in the US, the Living Room has become a trusted source of education and information around the world, particularly in countries where advocacy groups like GO2 for Lung Cancer are fewer and farther between.

Methods: Data was reviewed regarding Living Room views on YouTube between 2000 and 2024. There were approximately 1.4 million total views during that time.

Results: Across approximately 1.4 million total views on YouTube, approximately 20% - or 280,000 views - have come from people located outside of the United States. The top countries outside the US are - in approximate order - Philippines, Japan, China, India, the UK, Australia, Canada, Singapore, Mexico, Spain, Taiwan, and Hong Kong.

Conclusions: Over the past 15 years, the Lung Cancer Living Room has become a source of critical lung cancer education across the globe for people experiencing a lung cancer diagnosis, with especially strong viewership in countries where support from advocacy groups may not exist at all or may be insufficient to meet the needs of the lung cancer community.

Keywords: lung cancer, education, global advocacy

EP.16F PATIENT ADVOCACY - NEEDS OF PATIENTS AND CAREGIVERS
SATURDAY, SEPTEMBER 7, 2024 - 11:58 - 11:59

EP.16F.01 Priorities and Support Needs for People Impacted by Lung Cancer in Ireland

J. Byrne[1], T. Byrne[1], B. Carpenter[1], D. Staunton[1], M. O'Sullivan[1], C. Dowling[1], A-M. Baird[1], S. Cotter[1], [1]Irish Lung Cancer Community, Dublin/IE

Introduction: While more general European data is available in relation to the needs of the wider lung cancer community, there is little known specifically in relation to Ireland. The aim of this study was to find out demographical information and identify key educational needs and priorities in Irish people impacted by lung cancer.

Methods: Following a review of the literature, a brief survey was developed concentrating on three key themes (i) demographics, (ii) supports available and how people access existing information, and (iii) educational priorities. The survey was active for approximately 1 month and delivered through Microsoft Forms with no identifiable information collected. The survey was socialised through the Irish Lung Cancer Community (ILCC)'s social media platforms and our closed Facebook group as well at the Irish Lung Cancer Alliance (ILCA).

Results: Forty-six people responded to our survey, although all participants did not respond to all questions. Participants were mainly people diagnosed with lung cancer (29/44), female (38/46) and 50-65+ years of age (29/42). Most were living with Stage IV disease (32/46) and were diagnosed with non-small cell lung cancer (NSCLC) - adenocarcinoma (27/46). Although 15% of participants did not know what type of lung cancer they had (7/46). In terms of biomarker testing, a significant 29% did not know if their tumour was tested (13/45), with a further 56.5% stating that their tumour had been tested. The most common markers were EGFR (10/27) and ALK (10/27). Participants stated that a range of supports were accessible to them from psychosocial to financial. The top three supports that were available were psychosocial/counselling, patient organisation support and physical therapy, which were the same top three that people accessed and prioritised. Participants primarily accessed disease information through their care team and the internet, with their care team ranked as the most important place to get information. In terms of preferences in receiving information - something that could be read either physically or digitally and chatting to other people, were the top three. There were a large number of expectations in what the ILCC should deliver with the top three relating to information on the latest research and treatments, information, and guidance on how to navigate the system/care pathway and facilitating peer to peer support. These same three items were given the highest priority ranking. Interestingly raising awareness to destigmatise the disease was the least priority. The top channels to receive the information and support from the ILCC was evenly spread over webinars, our website and social media channels and in person events.

Conclusions: While this is a small study, it is to our knowledge, the first and largest study within the lung cancer patient community in Ireland. It demonstrated a key need for further information and support particularly in terms of research/treatments and navigating the complex care pathway. In person peer to peer support is also highly valued.

Keywords: Advocacy, Ireland, Support

EP.16F PATIENT ADVOCACY - NEEDS OF PATIENTS AND CAREGIVERS
SATURDAY, SEPTEMBER 7, 2024 - 11:58 - 11:59

EP.16F.02 Availability of Supportive Care in Lung Cancer: A Global Perspective

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Introduction: People with lung cancer experience high rates of distress and have greater unmet psychological and physical needs compared to those with other cancers. Lung cancer remains the leading cause of cancer deaths in most parts of the world with an estimated 2+ million diagnoses and up to 1.8 million deaths in 2020. Worldwide, those in need of comprehensive and culturally appropriate care to help understand the disease and treatment options; cope with the diagnosis; relieve symptoms and side-effects; and even just connect with others who will understand face considerable barriers to care and gaps in services. Even in relatively resourced countries, these services remain all too unavailable or out of reach. Founded in 2001, the Global Lung Cancer Coalition (GLCC) serves as the international voice of the lung cancer community, connecting charitable organisations that focus solely on lung cancer; service all cancers; address all respiratory diseases; or work on primary and secondary prevention. All have a special focus on lung cancer. GLCC unites small, volunteer-led groups all the way through large multi-country organisations. With a dedication to understanding how those diagnosed, and their loved ones get their information, cope with the disease, and find/utilize psychosocial services, GLCC has conducted multiple country-wide patient surveys. The goal of the current effort is twofold. First, to augment existing knowledge and identify gaps by surveying members. Second, to develop a repository of psychosocial care and beyond, available across the globe.

Methods: A subgroup of psychosocial professionals from the UK, US and Ireland developed a 22 question, mixed-methods survey. Questions were related to the psychoeducational, psychosocial, and supportive care services offered by members or available in their countries or regions. Questions around pandemic-related changes, willingness to mentor other organisations, and related to data collection were also included. The survey was open to the 33 GLCC organisations from 26 February to 4 April 2024.

Results: The response rate was 85%. Countries represented were Argentina, Brazil, Bulgaria, Canada, Denmark, Europe, Greece, Ireland, Israel, Italy, Japan, Mexico, Portugal, Slovenia, South Africa, The Netherlands, Taiwan, the United Kingdom, and the United States. These initial results focus on the 24 organisations that provide supportive care services. Over 60% offer, alone or in partnership, professional counseling. Nearly 50% offer in-person support groups with 60% offering support specific to carers. Nearly 25% offer or partner on activities to improve breathing. For 68%, services changed when the pandemic hit with 87% adding services. 50% of organisations that lost services hope to return to full operation.

Conclusions: GLCC is uniquely positioned to inform and to help expand services across the globe through collaboration and mentorship. GLCC organisations range in size and scope, but clear similarities in purpose were highlighted in this survey. While an encouraging breadth of programs and services were found, the many needs of those living with lung cancer internationally demand more. The thoracic oncology community can best serve their patients and families by referring to, collaborating with, and supporting the efforts of patient advocacy organizations.

Keywords: Psychosocial, Survivorship, Advocacy

EP.16F PATIENT ADVOCACY - NEEDS OF PATIENTS AND CAREGIVERS
SATURDAY, SEPTEMBER 7, 2024 - 11:58 - 11:59

EP.16F.03 Lung Cancer Patients' Preferred Methods of Involvement with their Treatment Teams: Insights from a Global Patient Experience Survey

K. Clayton[1], M. Daniels[2], J. Fox[3], B. Gaspar[4], M. Hennink[5], J. Mayans[4], A. McNamara[6], L. Pretorius[7], M. Rigney[8], M. Dohr[9], [1]Lung Cancer Nursing UK, London/GB, [2]Campaigning for Cancer, Randburg/ZA, [3]Roy Castle Lung Cancer Foundation, Liverpool/GB, [4]Asociación Española de Afectados de Cáncer de Pulmón, Valencia/ES, [5]Longkanker Nederland, Utrecht/NL, [6]Irish Cancer Society, Dublin/IE, [7]Campaigning for Cancer, Randburg/GB, [8]GO[2] Foundation for Lung Cancer, Washington, D.C./DC/USA, [9]Incisive Health, London/GB

Introduction: The Global Lung Cancer Coalition (GLCC), a partnership of 43 patient organisations across 30 nations, reaffirms in its charter the right of all lung cancer patients to be treated with dignity and respect and to have access to quality health care, including informed self-determination and physical and mental integrity. How patients engage with their treatment teams is essential for these rights.

Methods: In the GLCC's fifth annual survey, the coalition commissioned Censuswide to conduct a global survey of lung cancer patients. The survey ran from 28 March 2024 - 18 April 2024. It received 905 responses across 18 countries (Australia, Argentina, Bulgaria, Canada, Denmark, Greece, Ireland, Israel, Italy, Japan, Mexico, Portugal, Netherlands, South Africa, Spain, Taiwan, UK, USA).

As part of this survey, the GLCC included questions regarding respondents' preferences for engagement with their treatment teams and their involvement in decision-making.

Results: Almost all (98%, 885/905) of the respondents answered that they did feel involved in decisions about their treatment and care, and nearly half of respondents (48%, 438/905) answered that they had been fully involved. A small group (2%, 20/905) did not feel involved in decisions about their treatment and care, with all but one of these respondents saying they would have liked to be.

When asked about preferences around engaging with their treatment teams, throughout the care pathway most participants preferred face-to-face meetings in all situations. Telephone calls were respondents' secondary preference in all situations, except for when finding out about the diagnosis (where video was preferred).

Conclusions: The findings of the survey highlight that despite changes in the availability of tele-health, patient preferences can vary. Treatment teams should take care to better understand and cater to their patients' preferences, ensuring that they involve patients in decisions about their care in a way that is appropriate for that individual.

Keywords: patient experience, decision-making, treatment

Questions	Answer options									
When talking to your treatment team, did you feel involved in the decisions about your treatment and care? Please choose the option that best describes you.	Yes, I've been fully involved	Yes, I've been involved mostly, but wanted to be more involved	Yes, I've been involved mostly, and didn't want to be more involved	Yes, I've been involved sometimes, but wanted to be more involved	Yes, I've been involved sometimes and didn't want to be more involved	Yes, other please specify	No, but I would like to be involved	No, but I didn't want to be involved	No, but my caregiver was involved	No, other please specify
What do you think is the best way to have a conversation with your treatment team in the following situations? [Matrix: Rows provided are: • Finding out the diagnosis • The first consultation • Regular check ups • If there is a change to treatment • If there is a change in my disease • If I'm worried about something	Video	Telephone	Face-to-face	Not sure						

What do you think is the best way to have a conversation with your treatment team in the following situations?

Finding out the diagnosis	All	Count
N	905	
Video	24.09%	218
Telephone	17.68%	160
Face-to-face	57.35%	519
Not sure	0.88%	8

The first consultation	All	Count
N	905	
Video	7.62%	69
Telephone	17.13%	155
Face-to-face	74.59%	675
Not sure	0.66%	6

Regular check ups	All	Count
N	905	
Video	13.37%	121
Telephone	12.38%	112
Face-to-face	72.93%	660
Not sure	1.33%	12

If there is a change to treatment	All	Count
N	905	
Video	8.73%	79
Telephone	22.54%	204
Face-to-face	67.73%	613
Not sure	0.99%	9

If there is a change in my disease	All	Count
N	905	
Video	12.38%	112
Telephone	26.96%	244
Face-to-face	59.56%	539
Not sure	1.10%	10

If I'm worried about something	All	Count
N	905	
Video	9.94%	90
Telephone	27.18%	246
Face-to-face	61.55%	557
Not sure	1.33%	12

EP.16G PATIENT ADVOCACY - SCREENING
SATURDAY, SEPTEMBER 7, 2024 - 11:58 - 11:59

EP.16G.01 Ready, Set, Screen: Evaluating Community Readiness for Lung Cancer Screening Among Non-Hispanic Black Populations in Florida

S. Monestime[1], R. Theodore[2], D. Harris[3], A. White[4], [1]GO[2] for Lung Cancer, Washington/DC/USA, [2]CLT Business Solutions, Homestead/FL/USA, [3]Villages at NorthStar Community Development Corporation, Detroit/MI/USA, [4]University of North Texas Health Science Center, Fort Worth/TX/USA

Introduction: In Florida, only 2.4% of high-risk individuals undergo lung cancer screening (LCS), emphasizing a critical need for targeted interventions, particularly among the non-Hispanic Black (NHB) population, who experience the highest incidence of lung cancer compared to other racial/ethnic minority groups. While existing literature examines individual factors influencing LCS rates, a gap remains in understanding community awareness and resources dedicated to increasing LCS rates. Therefore, this study will utilize the Community Readiness Model (CRM) to assess NHB community readiness to increase LCS.

Methods: The CRM integrates theories of community-level processes and social action to improve public health concerns across five dimensions: community efforts, leadership, climate, knowledge, and resources. This model was utilized to guide qualitative semi-structured interviews in Broward County, FL with community leaders, high-risk smokers, and individuals with lung cancer (LC) self-identifying as NHB or predominantly working with the NHB population. Systematic gathering of qualitative responses for each dimension included assigning scores from 1 to 9, indicating the extent of awareness—ranging from no awareness to a high level of community ownership. Content analyses were used to further understand knowledge gaps in LC and LCS awareness.

Results: Participants (n = 24) were primarily 50-80 years old (45.8%), NHB (60%), female (62.5%), and from community-based organizations (47.4%). Scores for community knowledge of efforts, leadership, community climate, community knowledge, and resources were 1.24, 1.92, 1.61, 1.82, and 3.03 respectively. The overall score for readiness was 1.92, indicating “no awareness” of LCS. Of the participants, 53.8% considered LCS a “low priority,” 70% noted community members knew “nothing” or “little” about signs and symptoms of LC, 64.7% reported “some” knowledge about the causes of LC, and 55.6% cited “no knowledge” of LC prevalence in the NHB community. Community leaders were perceived as not prioritizing LCS, often due to a lack of awareness or other pressing community issues. While resources exist to increase LCS in NHB communities, respondents identified various obstacles hindering community prioritization of screening, including limited knowledge, financial constraints, lack of health insurance, transportation issues, and competing daily responsibilities.

Conclusions: Readiness to address LCS in NHB communities in Broward County, FL is low. These findings underscore the critical need to increase education and awareness among community leaders who serve as crucial gatekeepers to reach NHB communities. Additionally, interventions to increase LCS should target multiple factors that address social determinants of health to foster a comprehensive approach to mitigate low LCS rates in diverse communities.

Keywords: Screening, Community Engaged Research, Health Equity

EP.17A GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS - CLINICAL MANAGEMENT
SATURDAY, SEPTEMBER 7, 2024 - 11:58 - 11:59

EP.17A.01 The Cumulative Incidence of Brain Metastases in US Medicare Patients with ALK+ mNSCLC Treated with Second-generation ALK TKIs

L. Bazhenova[1], D. Abrahami[2], K. Ramaswamy[2], B. Li[2], M. Davis[3], A.J. Epstein[3], Z.A. Marcum[3], N. Rifi[2], J. Kelton[2], K. Duncan[2], D. Uprety[4], [1]UC San Diego Moores Cancer Center, San Diego/CA/USA, [2]Pfizer, New York/NY/USA, [3]Medicus Economics, Boston/MA/USA, [4]Karmanos Cancer Institute, etroit/MI/USA

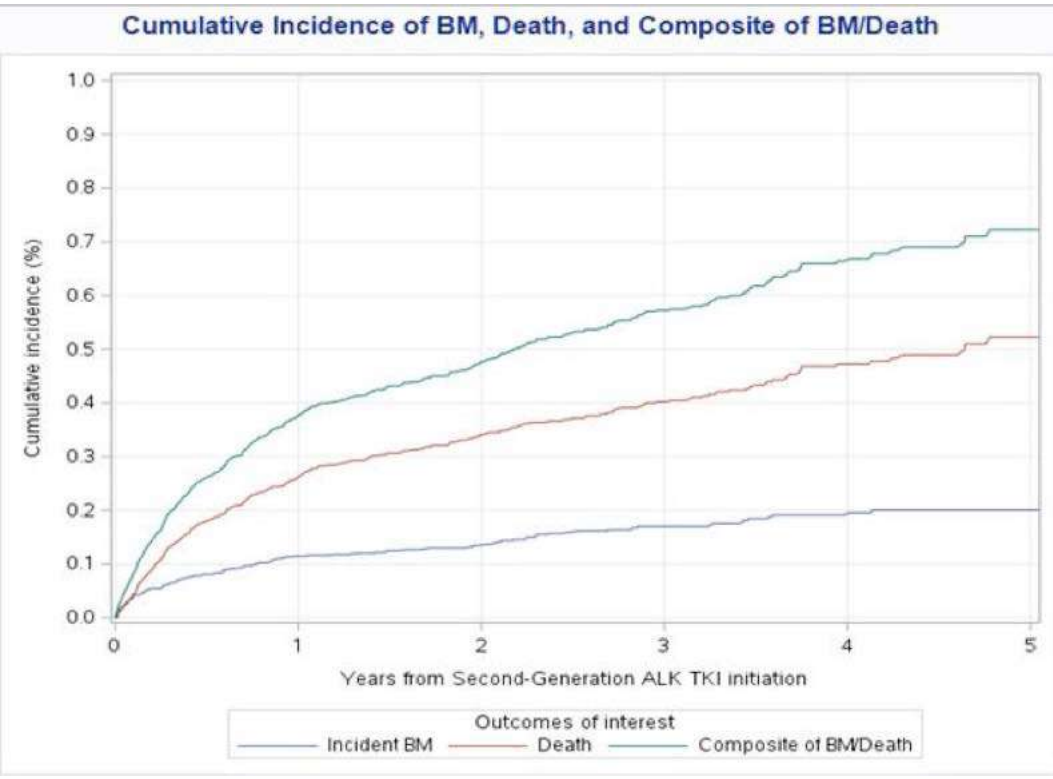
Introduction: Brain metastases (BM) are a major concern for patients with non-small cell lung cancer (NSCLC) and may be present at diagnosis (baseline) or during disease progression (incident). However, limited epidemiological evidence exists on the burden of BM in patients treated for oncogene-driven lung cancers like ALK+ NSCLC. The objective of this study was to quantify the cumulative incidence of BM and death in patients with ALK+ NSCLC in the US whose first ALK-targeted systemic treatment was a second-generation (alectinib, brigatinib) ALK TKI in the first-line setting

Methods: The study cohort was the 100% sample of Medicare fee-for-service and Medicare Advantage beneficiaries (January 1, 2016 - December 31, 2022). Adult patients (>65 years old) with a new pharmacy claim for a second-generation ALK TKI (index date, proxy for ALK+ status) and a history of lung cancer in the year before the index date were included. Patients were excluded if they had <1 year of continuous enrollment in the dataset or a history of ALK TKIs (to capture new first-line use) or EGFR TKIs (to avoid secondary ALK mutations) in the year before the index date. The primary outcome was the cumulative incidence of BM (among those without BM at baseline), calculated using a cumulative incidence function and accounting for the competing risk of death.

Results: The study cohort included 1041 patients (median age, 74 years; 60% female; 68% Non-Hispanic White). The median (interquartile range [IQR]) follow-up was 20 (8-36) months. 290 (28%) patients had baseline BM. Of the 751 patients without BM at baseline, 126 (17%) developed an incident BM over a median (IQR) follow-up of 22 (11-38) months and 377 (50%) died. Of the 126 patients with an incident BM, 76 (60%) were receiving first-line second-generation ALK TKIs when the incident BM was observed. The cumulative incidences of all outcomes are shown in the Figure. The cumulative incidence of BM was 20% after approximately 5 years of follow-up, accounting for the competing risk of death.

Conclusions: In this cohort study of US patients with ALK+ NSCLC treated with second-generation ALK TKIs in the first-line setting, we found that close to 30% had BM at baseline and an additional 20% developed a new BM following second-generation ALK TKI initiation at 5 years. Future research should examine the impact of third-generation ALK TKIs on BM incidence in patients with ALK+ NSCLC.

Keywords: Brain Metastases, ALK fusion



EP.17A GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS - CLINICAL MANAGEMENT
SATURDAY, SEPTEMBER 7, 2024 - 11:58 - 11:59

EP.17A.02 Diagnostic and Treatment Gaps in NSCLC Management Compared to NCCN Recommendations: An Audit Analysis of 214 Cases.

P.K. Singh, A. Ahuja, G. Arya, J. Grover, Pt BDS Post Graduate Institute of Medical Sciences, Rohtak/IN

Introduction: Despite the evidence and recommendations, NSCLC management remains heterogeneous. Financial disparity and lack of access remains a major concern in developing countries. We have analyzed the divergence of the local practice from global guidelines (NCCN) in NSCLC management, at a state-sponsored university teaching hospital in India, catering mainly to rural population.

Methods: Data of lung cancer patients managed at the Thoracic-Oncology-Clinic from September-2022 till March-2024 was retrieved. Inclusion criteria were NSCLC patients' with either squamous or adenocarcinoma histology, stage IIIA or higher (8thTNM) and ECOG-PS 0-2. We collected data only till first line therapy use. Subsequently we compared the NCCN recommendations for individual subjects for testing and treatment. Only category 1 and preferred recommendations were considered. Deviations were recorded as minor or major depending upon, if the deviation was from preferred or category1 recommendation, respectively. Number of deviations was calculated as number of cases in which modality was recommended minus the numbers in which it was done.

Results: Out of 542 cases, data of 214 cases was retrieved (excluding other histologies, PS>2, and incomplete data cases). 108(50.5%) were squamous, 148(69.2%) were males and 157(73.4%) were smokers. The staging distribution was as follows: IIIA-8(3.7%), IIIB-73(34.1%), IIIC-10(4.7%), IVA-88(41.1%), and IVB-35(16.3%), and the PS distribution was as follows- ECOG0-15(7%), ECOG1-117(54.7%), and ECOG2-82(38.3%). Out of the 106 patients of adenocarcinoma, 100 were tested for genetic alterations with 34, 8, 2 and one showing EGFR-mutation, ALK-rearrangement, ROS1-rearrangement, and BRAF-mutation, respectively. • Regarding deviation-in-testing (DT)- NCCN recommends the use of FDG-PET and MRI brain for all patients of lung cancer, however, these were done only in 64 and 25 cases. Re-biopsy was indicated in 28-subjects where the tissue previously obtained was insufficient but was done only in 10-subjects. Nodal disease confirmation was recommended in all stage-III cases but was done only in 27-subjects (DT in 64). Broad molecular profiling was recommended in all stage-IV subjects but was done only in 9-subjects (DT in 205). However, for the major deviation only EFGR, ALK and PDL1 testing was considered. DT in EGFRm and ALKr were both 6 (considered only for adenocarcinoma). However, PDL1 was recommended in all but done only in 84 (including in-house assays), making a DT in 130.• Regarding DM (deviations in management, all major)- Surgery was recommended in 12 but done only in 7 (DM in 5). Definitive concurrent-chemoradiotherapy (CTRT) (recommended in 79) was done only in 19 and sequential-CTRT was done in 32 leading to overall deviation in 28-cases. Durvalumab was not used in any patient (79 DM). There were not DM in EGFRm positive group however, only 4 cases in ALKr received the recommended treatment. In the remaining 169 cases, immune-checkpoint-inhibitors (ICIs) were recommended in all (with or without chemotherapy) but used only in 21 (DM in 148).

Conclusions: In 82.3% (626/761 minor DT) and 76% (266/350 major DM) instances, the local practices deviated from NCCN recommendations. All major deviations are associated with survival advantage in clinical trials. Most common reason was lack of financial support and non-availability of the modality.

Keywords: Inequality in Management, NCCN, Non-small cell lung cancer

EP.17A GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS - CLINICAL MANAGEMENT
SATURDAY, SEPTEMBER 7, 2024 - 11:58 - 11:59

EP.17A.03 NOVA: A Conversational Generative Agent for Thoracic Oncology Decision-Making

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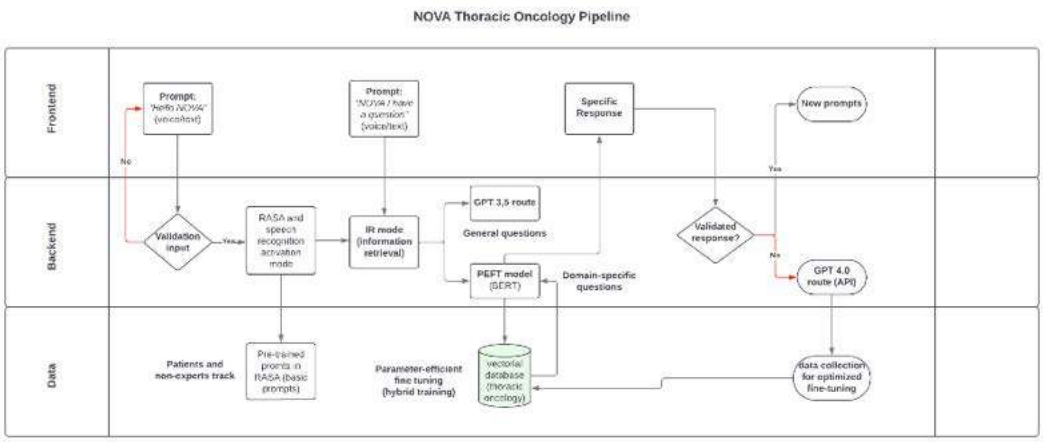
Introduction: Lung Cancer and Mesothelioma are complex neoplastic diseases, and its treatment requires continuous analysis of the abundant clinical information. The inherent complexity of the disease, has created a high demand for refined, contextualized, and rapidly evidenced information.

Methods: A conversational generative agent (NOVA) was trained on lung cancer and mesothelioma using A4I technology that allows dynamic, intuitive, and agile access to state-of-the-art (SOTA) information curated by domain experts, but also facilitates its consultation and aids in drawing conclusions to address decision-making in a timely manner. Our development phases were: 1. Data Preparation: We extracted and curated various primary, secondary, and tertiary sources of SOTA medical literature, followed by preprocessing to convert the information into dense numerical representations of real-world objects and relationships, expressed as vectors. This step was executed by domain expert's thoracic oncologist, thoracic surgeons, and AI. 2. Implementation of the Conversational Model: Implementation of a conversational AI model configured with a pre-trained Transformers Language (TL) model in Spanish language is proposed, allowing the integration of NOVA technology with another complementary Transformer model for question-answering (QA) tasks. This model predicts the response with the highest similarity and extracts related information in a paragraph. 3. LLM Fine-Tuning: With a specific corpus containing relevant and specialized data from this medical domain (questions and answers), as well as vector databases of the document body properly curated by medical domain experts (clinical design) we developed a RAG (retrieval augmented generation) fine-tuning, carefully adjusting its settings to optimize performance in this specific area. 4. Integration of IR with LLM: The output response of the IR model was integrated with a large-scale language model to create a response based on the paragraph output of the IR with the highest accuracy score. This would prevent the generation of text output that may contain "hallucinations" or "biases."5. Development of a User Interface (text-to voice, voice-to-voice, and text-to-text)6. Assistant Deployment: The production deployment was based on Amazon Web Services (AWS) that involves implementing the system in a highly scalable and secure cloud operating environment.

Results: Nova is being implemented in one private clinic in Colombia. Capabilities of Nova are: Rapid and accurate analysis, Decision-making support, Treatment personalization, Continuous and dynamic updating and, Efficiency improvement. Figure 1 shows the operation diagram of NOVA.

Conclusions: NOVA is the first AI-based virtual assistant for decision-making support in the field of lung cancer and mesothelioma applied in Latin America

Keywords: artificial intelligence, lung cancer, Mesothelioma



EP.17A GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS - CLINICAL MANAGEMENT
SATURDAY, SEPTEMBER 7, 2024 - 11:58 - 11:59

EP.17A.04 Real-World Rates of Infusion-Related Reactions in Patients with EGFR-Mutant NSCLC Receiving Amivantamab

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Introduction: Amivantamab is an EGFR-MET bispecific antibody used in the treatment of patients with EGFR-mutant advanced non-small cell lung cancer (NSCLC). In addition to FDA-approved use for patients with EGFR ex20 NSCLC, NCCN guidelines now list a category 1 recommendation for the use of amivantamab after progression on osimertinib in patients with classical EGFR mutations. Infusion-related reactions (IRR) are common with amivantamab, and rates of grade 3 and 4 IRRs reported in clinical trials range from 1 to 5%. We aim to report real-world data on the rates and severity of IRRs with amivantamab as monotherapy and when given in combination in patients with EGFR-mutant NSCLC.

Methods: We performed a retrospective chart review of patients with EGFR-mutant NSCLC, not on clinical trial, treated with amivantamab at Northwestern University's Robert H. Lurie Comprehensive Cancer Center from January 2021 to February 2024. The data analyzed included baseline demographics, amivantamab pre-medications, rate and grade of IRRs based on CTCAE v5, emergency response utilization, and amivantamab discontinuation.

Results: A total of 33 patients received amivantamab. The median age was 62 (36-84) years old. 20 patients (61%) were female, 13 (39%) were male. 15 patients (45%) had an EGFR exon 19 deletion, 6 (18%) had an EGFR L858R mutation, 8 (24%) had EGFR exon 20 insertions, and 4 (12%) had atypical EGFR mutations. Patients received a median of 2 (0-8) lines of therapy prior to amivantamab. 12 patients (36%) received concomitant osimertinib, and 4 (12%) received concomitant carboplatin/pemetrexed. All patients received split first dose amivantamab (350 mg day 1 [D1], remainder D2) along with steroid, antihistamine, and antipyretic premedication before initial dose. IRRs were reported in 27 patients (82%), and all IRRs occurred on cycle 1, D1 (C1D1). Grade 1 IRRs occurred in 1 patient (3%), grade 2 in 10 patients (30%), grade 3 in 12 patients (36%), and grade 4 in 4 patients (12%); grade 3/4 IRRs was 48%. Of patients with a grade 4 IRR, 2 had an emergency response team called, and 2 additional patients had 911 called to the infusion center. C1D2 infusions were completed in 93% (25/27) of patients who had C1D1 IRRs. The 2 patients who did not complete C1D2 infusions discontinued amivantamab, one due to patient preference and the other due to the severity of the IRR.

Conclusions: Contrary to data reported in clinical trials, we observed a markedly higher rate of grade 3 and 4 IRRs at 48% during the administration of amivantamab for EGFR-mutant NSCLC at our institution. Although this was a more heavily pretreated population, this notable difference poses a significant safety concern, particularly for stand-alone infusion centers with limited emergency services. Most patients who experienced IRRs were able to continue therapy. The substantial incidence of grade 3 and 4 IRRs requires considerable resources to administer amivantamab, potentially amplifying healthcare disparities in underserved areas. Our findings call for re-evaluation of administration protocols and further research to develop strategies to mitigate the risk of IRRs, ensuring safe and equitable access to amivantamab across all healthcare environments.

Keywords: Amivantamab, Real-world, Safety

EP.17A GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS - CLINICAL MANAGEMENT
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EP.17A.05 Efficient Lung Cancer Multidisciplinary Team (MDT) Management Strategy for the Hospitals with High-Volume Patients

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Introduction: The increasing number of lung cancer patients in recent years has been influenced by various factors, such as environmental pollution, rising smoking rates, unhealthy lifestyles, and aging populations, posing significant challenges to healthcare systems and lung cancer treatment. The role of MDT management in lung cancer treatment has become increasingly prominent. However, achieving efficient MDT management in the face of a large volume of patients remains a challenge. Therefore, addressing this challenge effectively to improve treatment outcomes and survival rates of lung cancer patients has become an urgent issue. This study aims to explore an efficient MDT management strategy to better meet the needs of a substantial volume of lung cancer patients.

Methods: We conducted brainstorming sessions, and questionnaires with MDT experts to analyze and summarize 32 MDTs from 10 leading lung cancer treatment hospitals in China. We consolidated the experiences from MDT experts at participating hospitals that receive more than 3,000 new lung cancer patients per year and whose lung cancer MDT teams have at least 5 year of management experience.

Results: Our analysis delineated two primary MDT management strategies prevalent in hospitals managing a substantial volume of lung cancer cases (Figure 1): specialized cancer hospitals predominantly adopt Strategy I, while comprehensive hospitals favor Strategy II. A commonality observed in their efficient operation lies in the establishment of standardized quality control and feedback systems. For instance, tailored quality control standards are devised based on patient caseload and specific needs, coupled with feasible evaluation features before, during and after MDT. Over 80% of the surveyed hospitals conduct MDT review meetings at least quarterly, involving all MDT members. These review sessions encompass a spectrum of topics ranging from optimizing MDT operations to the latest advancements in research.

Conclusions: Hospitals should tailor their MDT strategies based on patient demographics and specific management goals. Regardless of the chosen strategy, it is crucial to establish and adhere to quality control standards for MDT design and execution. Regular feedback and optimization across various aspects of MDT implementation play a pivotal role in providing high-quality and efficient services for a large patient population. This nationwide study enhanced lung cancer diagnosis and treatment capabilities in regional hospitals through remote guidance for MDT teams. By doing so, it provided valuable insights and contributed to elevating the overall standard of lung cancer MDT management in China.

Keywords: MDT management, Sustantial volume of patients, Efficiency

Figure 1. Summary of two MDT management strategies for a substantial volume of lung cancer patients

	Patient access and characteristics	*Advantages*
Strategy I	Access to **all** diagnosed lung cancer **patients** ➔ Daily simplified MDT with entry-level physicians from medical oncology, thoracic surgery, and radiation oncology. *If not solved* ➔ Expert-level MDT with more comprehensive specialists	Solve the **problem of process standardization** Define the **initial treatment plan** of each LC patient
Strategy II	**Pre-selected lung cancer patients** in complicated situation ➔ LC MDT for patients with senior/expert-level specialists from pulmonology, thoracic surgery, oncology, radiology, pathology and supporting teams ➔ *Or* specific MDT for specific patients such as stage III, brain metastases, adverse immune reactions with multiple senior/expert-level specialists	Solve **difficult problems**, **serious illnesses**, or any special individualized needs. (E.g., patient with unclear resectability)
Ideal Model	**Fusion of Strategy I and II** ➔ All patients with access to a primary MDT ➔ Complicated cases with access to specialized MDTs	

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EP.17A.06 Real-World Trends in Screening and Evaluation of Paraneoplastic Syndromes among Patients with Small Cell Lung Cancer

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Introduction: Neurologic paraneoplastic syndromes (PNS), including Lambert-Eaton myasthenic syndrome (LEMS), affect approximately 10% of patients with small cell lung cancer (SCLC). Beginning 2020, the National Comprehensive Cancer Network (NCCN) SCLC guidelines recommend considering a comprehensive paraneoplastic antibody panel when neurologic PNS is suspected; however, the impact of this recommendation in real-world settings is unknown. This study investigates longitudinal trends in PNS screening and management among patients with SCLC in the United States.

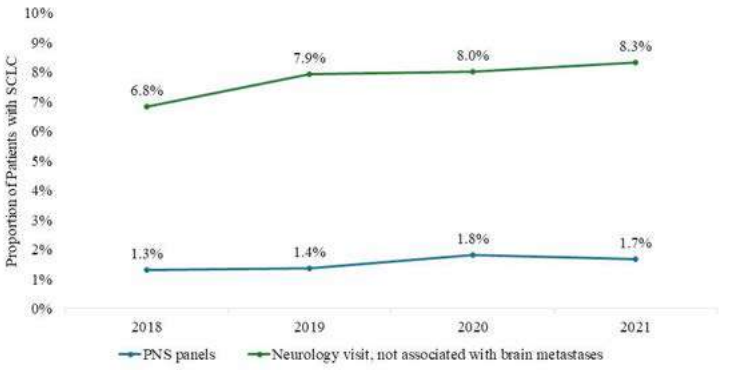
Methods: Healthcare claims between 1/1/2018-12/31/2021 in a longitudinal database representing >300 million US patients were evaluated. Patients with presumed SCLC (ICD-9-CM 162.X excluding 162.0, ICD-10-CM C34.X, + etoposide + platinum therapy) were identified based on ≥2 claims ≥30 days apart. Claims for diagnostic panels for any PNS, including neurologic PNS, and individual antibody tests associated with neurologic PNS were evaluated. The frequency and setting of neurology visits among patients with SCLC with and without associated claims for brain metastases were also evaluated.

Results: Among 38,390 patients with SCLC who received etoposide and platinum-based therapy, 578 (1.5%) patients had claims for PNS tests during the study period. The proportion of patients with SCLC with PNS test claims remained below 2% annually across the study period. Screening rates were 1.3%-1.4% and 1.7-1.8% in the 2 years pre- and post-recommendation, respectively. Most PNS panels during this time were billed as hospital outpatient procedures. During the same period, 12.1% of patients with SCLC had neurology visits and the proportion of patients with visits increased, ranging from 11.2% in 2018 to 13.1% in 2020. Neurology visits were more common among patients with SCLC with claims for comorbid brain metastases (N=1,694/9,402; 18.0%) than without (N=2,953/28,988; 10.2%). 61 patients (0.16% of patients with SCLC) had a comorbid LEMS diagnosis, which was concurrent (±90 days) with SCLC diagnosis in the majority (N=41/61) of SCLC-LEMS patients. 22 patients (36% of patients with SCLC-LEMS) had ≥1 claim for a neurologic PNS test. 65.6% of patients with SCLC-LEMS had neurology visits. Patients with SCLC-LEMS who were not seen by neurologists were more often managed by community oncologists.

Conclusions: This study revealed a low rate of PNS screening persisted among patients with SCLC despite the introduction of screening recommendations in suspected patients. This finding highlights the importance of increased awareness of neurologic PNS among oncologists, including those in the community, as treatment options are available for patients with neurologic PNS.

Keywords: Paraneoplastic syndrome, Small cell lung cancer, Lambert–Eaton myasthenic syndrome

Figure 1. Paraneoplastic Syndrome Screening and Neurologic Evaluation among Patients with Small Cell Lung Cancer (SCLC)[1]



[1]Based on 2 lung cancer diagnoses ≥ 30 days apart and receipt of etoposide and platinum therapy; PNS, paraneoplastic syndrome; SCLC, small cell lung cancer

EP.17A GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS - CLINICAL MANAGEMENT
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EP.17A.07 ROSETTA-LUNG: MultidisciplinaRy Oncology StratEgies for Team-Based Treatment ConcordAnce in Lung Cancer Diagnosis and Treatment Decisions

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Introduction: The ROSETTA-LUNG initiative addresses the imperative demand for improved concordance in decision making of multidisciplinary Teams (MDT) treating lung cancer patients. Addressing the inherent complexity and evolving landscape of lung cancer diagnosis and treatment decisions, our project harnesses a cloud-based portal designed for MDT to assess fictional patient cases. This innovative platform facilitates anonymous, replicable, and compliant comparative decision-making by presenting carefully curated fictional patient cases, based on the cohort of the Danish RING trial. This approach aims to cultivate a robust and safe environment for collaborative analysis and benchmarking of decision-making processes across diverse MDTs worldwide.

Methods: The cloud based MDT platform comprises of 60 patient case descriptions with corresponding PET/CT and CT scan images. Per case, MDTs are queried regarding: cancer stage, treatment intent, and primary treatment choice. Participating MDTs are requested to provided their country of practice, approximate yearly case load, MDT specialty representation and hospital type (academic vs community). This systematic approach anonymously measures and visualizes inter-MDT concordance on a global, regional, and national level. This comparative analysis seeks to provide valuable insights into variations in decision-making practices, fostering a systematic validation of MDT decision making in lung cancer. Primary Objective: The primary goal of the ROSETTA-LUNG project is to measure and enhance the concordance of MDT assessments in lung cancer diagnosis and treatment decisions. The standardized approach and cloud-based platform, will allow for an improved equity, treatment harmonization and improved guideline adherence worldwide. Secondary Objectives: Facilitate Discussions for Improvement: In cases with the lowest concordance, the project facilitates focused discussions between MDT representatives. These sessions identify specific areas for improvement, fostering a collaborative environment where lessons learned enhance patient care outcomes.

Results: “Not applicable”

Conclusions: ROSETTA-LUNG signifies a commitment to harmonize multidisciplinary assessment of lung cancer diagnosis and treatment, acknowledging MDTs as a cornerstone in optimal cancer care. This project not only quantifies concordance, but also allows for avenues of education of healthcare professionals and allows for increased equity among countries that are developing their MDT infrastructure.

Keywords: MDT, Concordance, Lung cancer

EP.17A GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS - CLINICAL MANAGEMENT
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EP.17A.08 Development of the First Lung Cancer Clinical Pathway in Chinese Counties

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Introduction: Lung cancer (LC) remains the leading cause of cancer-related mortality worldwide. In China, it holds the highest incidence and mortality rates among all malignancies, affecting both urban and rural populations. It is imperative to standardize the diagnosis and treatment of LC to enhance patient survival and reduce mortality rates. However, county hospitals face significant challenges in accessing advanced medical technologies, necessitating the development of diagnostic and treatment pathway tailored to their specific circumstances. Under the auspices of the National Health Commission's "Thousand Counties Project (2021-2025)" and "The Belt and Road Initiative," we have formulated the first "Clinical Pathway for Lung Cancer in Chinese Counties" to bolster the comprehensive capabilities of county-level healthcare facilities.

Methods: The formulation of this pathway diverges from conventional guidelines, with Professor Qing Zhou serving as the editor-in-chief, Professor Yi-Long Wu overseeing the review process, and Chinese LC academic celebrities providing guidance. Additionally, LC specialists from county hospitals contribute their expertise as editorial board members. The development of LC clinical pathway was meticulously crafted to align with the diagnostic and treatment technologies available in county hospitals, the approval status of treatment indications, the inclusion of medications in the National Reimbursement Drug List (NRDL), and adherence to existing domestic and international guidelines. The pathway systematically delineates the screening, evaluation, diagnosis, staging, treatment, and follow-up procedures for LC within county hospitals.

Results: The pathway stratify LC treatment strategies into basic and optional approaches (Table 1). Basic strategies represent the essential diagnostic and treatment standards that county hospitals must achieve, while optional strategies provide flexibility and additional choices. The recommendations within the pathway are aligned with existing guidelines and consensus, ensuring both operability and scientific validity. Therefore, the pathway is both operability and scientific.

Conclusions: The creation of first "Clinical Pathway for Lung Cancer in Chinese Counties" represents the diagnostic and treatment recommendations specifically tailored for county-level medical institutions. This initiative not only plays a pivotal role in enhancing the efficiency and cost-effectiveness of LC diagnosis and treatment in county settings, but also providing experiences for establishing County-level Cancer Prevention and Treatment Centers in the world.

Keywords: Chinese County area, Clinical diagnosis and treatment pathway, Basic strategies

Recommended level	Criteria
Basic strategies	Approved by China NMPA for LC and included in the NRDL
Optional strategies	
Level I	Approved by China NMPA for LC but not included in the NRDL
Level II	Based upon high-level evidence, accessible in China, but not China NMPA-approved

EP.17B GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS - DISPARITIES
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EP.17B.01 Timelines of Lung Cancer Pathway in Rural and Regional NSW; A Retrospective Study in Hunter New England LHD

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Introduction: Health disparity among the rural and remote regions of Australia has been an ongoing area of concern and development1. Early diagnosis and treatment have been shown to improve outcomes in lung cancer, a leading cause of death worldwide2. The variations in lung cancer care across Australia have been described in previous reports3. We investigated if the time to diagnosis and treatment of lung cancer in rural New South Wales (NSW) conforms to the recommended guidelines in the Optimal Care Pathway for People with Lung Cancer (OCP).

Methods: A retrospective cohort study, conducted on patients diagnosed with Lung Cancer between January 2021 to December 2022 at Tamworth Hospital in rural NSW. The main outcome measures were time intervals between referral, Lung Cancer Specialist (LCS) review, diagnostic investigations, and treatment.

Results: A total of 106 patients with new diagnosis of lung cancer were identified from the Tamworth Cancer Centre and Local Respiratory Physician Clinics and 76 patients were included in the study. Majority (93.4%) of the patients smoked while similarly adenocarcinoma was noted to be most prevalent among the study population (48.7%, n=37). Moreover, a large proportion (77%) of patients were diagnosed with cancer stage III and above or extensive small cell lung cancer and about 46% (n=35) of the study population have deceased. The median timeframes of care such as LCS to diagnosis and date of first referral (DFR) to treatment were noted to exceed the recommended timeframes. This is especially so in the patients managed with curative intent whereby median time from DFR to treatment was almost double the time taken in those with palliative intent (77 days vs 43 days respectively). However, the time interval from DFR to LCS was within the recommended period. Although only 48.6% (n=37) of patients had multidisciplinary meetings (MDT), majority of patients with curative intent (79.1%) were discussed in MDT. Furthermore, despite the absence of a formal lung cancer care coordinator, the coordination by the cancer center staff was noted to decrease the median timeframes. Overall, as little as 34% (n=26) of the patients were managed within the recommended 42 days pathway.

Conclusions: There are significant delays in diagnosis and treatment of lung cancer faced by the rural patients in our study area. Although most patients are reviewed by an LCS within the recommended time frame, the overall delays in treatment pathway are significant and further efforts are needed to improve resource allocation and understand reasons for delay in diagnosis and treatment to ensure optimum timely care for these vulnerable patients.

Keywords: early diagnosis, Lung Cancer, Optimal Care

EP.17B GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS - DISPARITIES
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EP.17B.02 Racial Disparities in Patients with Lung Cancer Requiring Intubation: A National Inpatient Study

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Introduction: Racial disparities in healthcare refer to differences in health outcomes, access to healthcare services, and quality of care among different racial or ethnic groups. This study aimed to investigate the basic characteristics and clinical outcomes of racial differences in patients admitted with Lung cancer requiring intubation.

Methods: We queried the National Inpatient Sample between 2017-2020 for adult patients of different races hospitalized with Lung cancer requiring intubation using ICD-10 codes. The primary outcome was inpatient mortality. The secondary outcomes were cardiac arrest and total hospital costs. Multivariable logistic, linear, and Poisson regression analyses were used to estimate clinical outcomes with a p-value < 0.05 was significant.

Results: There were 75,115 hospitalizations in patients with Lung cancer requiring intubation. The mean age was 67.7 years and 56.2% were male. Among the admitted patients, Caucasians were 52,775 (70.3 %), Blacks were 12,335 (16.4 %), Asians were 3,875 (5.2%), Hispanics were 2,330 (3.1%) and others were 3,800 (5%). Subgroups with Caucasians, Blacks, Asians, Hispanics, and other races had DM 24.6% vs 30.6% vs 37.3% vs 35% vs 27.9%; Protein calorie malnutrition 25.1% vs 30.5% vs 24% vs 28.6% vs 27.8%; Chronic obstructive pulmonary disease (COPD) 64.5 % vs 52.4% vs 45.7% vs 30.3% vs 56.4%; Tobacco abuse 27.5% vs 24.9% vs 20.8% vs 10.5% vs 28.2% and Pulmonary embolism (PE) 10.6% vs 14.5% vs 11.2% vs 10.7% vs 11%. The secondary outcome of Cardiac arrest in these subgroups was 13.7% vs 20.4% vs 18.3% vs 12.9% vs 17.8% respectively. Total costs adjusted with inflation were highest among Hispanics. All-cause mortality was 39,190, where subgroups with Caucasians, Blacks, Asians, Hispanics, and others were 26,745 (50.7%) vs 6,725 (54.5%) vs 2,125 (54.8%) vs 1,435 (61.6%) vs 2,160 (56.8%).

Conclusions: Minority groups, particularly Hispanics, Asians, and Blacks, experienced higher mortality rates compared to Caucasians, with Hispanics facing the highest mortality. Additionally, these groups also showed varying prevalences of comorbid conditions and were subject to higher instances of cardiac arrest, with Blacks being the most affected. The economic analysis indicated that hospital costs were highest among Hispanics, pointing to a complex interplay of healthcare access, quality of care, and socioeconomic factors contributing to these disparities. The findings signify the urgent need for targeted interventions to address the systemic biases and barriers that contribute to these inequities in healthcare outcomes.

Keywords: Lung cancer, racial disparity, Health Disparity

EP.17B GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS - DISPARITIES
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EP.17B.03 Impact of Social Economic Status on Patient Reported Outcomes (PROs) In Non-Small Cell Lung Cancer (NSCLC)

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Introduction: Patient-reported outcomes (PROs) are a powerful method to assess a patient's well-being as reported directly by the patient without any provider interpretation. PROs in lung cancer have been shown to improve patient quality of life and survival, while decreasing health care utilization. Low socioeconomic status is associated with 13% more advanced lung cancer at diagnosis and carries an inferior prognosis. The impact of social determinants of health on PROs in lung cancer requires more study. We aim to assess the association between socioeconomic status and PROs in NSCLC.

Methods: We conducted a retrospective study of patients diagnosed with NSCLC between 2020 and 2023 who completed their initial PRO survey within 180 days of their diagnosis. NIH PROMIS computer adaptive testing was used as the PRO survey in the cancer clinic. PRO surveys included four domains- physical function, fatigue, pain interference, and depression. Patient demographics including race, gender, ethnicity, marital status, and cancer staging were obtained through electronic medical records. State Area Deprivation Index (ADI) rank was used to assess neighborhood socio-economic status. Statistical analysis was performed using Spearman's correlation test to assess the correlation between ADI and PRO scores.

Results: 491 patients completed their first PRO surveys within 180 days of lung cancer diagnosis. 48.9% of the patients were female (n=194). 21.4% of patients were African American and 71.3% were Caucasian. 48.9% were married. About 40% of the patients in the cohort had a high ADI Rank. Most of the patients had advanced disease (Stage III- 20.4% and Stage IV- 34.8%). The mean PRO scores were 52.8 (depression), 55.6 (fatigue), 57.7 (pain interference), and 37.8 (physical function). Patients with high ADI rank were found to have significantly worse pain scores (p-value- 0.0118) and depression scores (p-0.045).

Conclusions: Socioeconomic status, as measured by ADI, appears to negatively impact PRO scores around the time of diagnosis in NSCLC patients. These findings underscore the importance of considering socioeconomic factors in assessing patient-reported outcomes and developing targeted interventions to address disparities in healthcare access and outcomes among lung cancer patients.

Keywords: Patient reported outcomes, Socioeconomic status

	STATE ADI RANK			
Spearman	correlation	95% CI lower	95% CI upper	P- value
Depression	0.1066	0.0021	0.2088	0.0456
Fatigue	0.0799	-0.0469	0.2042	0.2164
Pain Interference	0.1586	0.0355	0.2770	0.0118
Physical Function	-0.1077	-0.2294	0.0174	0.0912

Table 1. Correlation between state ADI rank and PRO symptom domains

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EP.17B.04 Racial/Ethnic Differences in Risk of Mortality of Men and Women with Lung Cancer

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Introduction: It has been documented that Asian Americans have a reduced risk of lung cancer mortality when compared with white men and Women. It is uncertain if the risk of mortality for Asian Americans is similar across levels of socioeconomic status (SES). The purpose of this study was to assess overall differences in risk of lung cancer mortality by race/ethnicity and within strata of socioeconomic status when Asians are separated into subcategories as well as when combined together into the Asian/Pacific Islander category.

Methods: We identified 362,059 cases of invasive lung cancer from the California Cancer Registry 2000-2021. The Asian ethnicities were classified as, Middle Eastern, Chinese, Japanese, Korean, Filipino, Southeast Asian (SEA), Pacific Islander, or Asian Indian. A second classification combined the Asian ethnicities into the Asian/Pacific Islander (API) category. Cox Regression was used to assess risk of lung cancer specific mortality for each race/ethnicity when compared with non-Hispanic White men and women when adjusted for stage, smoking status, Charlson Comorbidity Index, and treatment with chemotherapy, hormone therapy, immunotherapy, and radiation therapy, and tertile of SES (Lowest, Middle, High). Regression models were conducted with Asians combined into the API category and when Asians remained in separate categories. Analyses within each level of SES were also conducted. All analyses were conducted separately for men and women.

Results: When Asians were combined into the API category, both API men (HR=0.85; 95%CI = .082, 0.89) and API women (HR=0.85; 95%CI = .081, 0.90) had a lower risk of mortality than white men and Women. When Asians remained in separate categories, Japanese men had a higher risk of mortality than white men (HR=1.21; 95%CI = 1.03, 1.41). All other Asian ethnicities had either a lower or equal risk of mortality than white men and women. When stratified by SES, only Japanese men in the highest SES category had an increased risk of mortality (HR=1.38; 95%CI = 1.12, 1.70). All other Asian ethnicities had the same or reduced risk of mortality as white men and women in all SES strata when left separate or when combined into the API category.

Conclusions: Risk of lung cancer mortality is similar among the Asian ethnicities and there is very little variation by socioeconomic status. The combined API category is sufficient for assessing risk of mortality in Asian patients with lung cancer.

Keywords: Racial/ethnic, differences, mortality

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EP.17B.05 Impact of Race and Ethnicity on Financial Toxicity and Outcomes in Lung Cancer

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Introduction: Lung cancer significantly impacts healthcare costs in the United States (US). Despite advancements in cancer treatment, disparities in healthcare costs remain, particularly affecting vulnerable populations. This study aimed to explore the disparities in inpatient hospitalization costs for lung cancer patients in the US.

Methods: A retrospective analysis of cancer-related hospitalizations from 2016 to 2021 was conducted using the National Inpatient Sample dataset. Lung cancer-related hospitalizations were identified using validated ICD-10 Clinical Modification codes. The main outcomes included were hospitalization costs, volume, mortality, length of stay, and disposition status. The cost for each year was adjusted according to 2021 inflation levels released by the US Consumer Price Index.

Results: Among 41,622,004 hospitalizations from 2016 to 2021, 128,624 were primarily due to lung cancer. The study population comprised 76.1% non-Hispanic whites (NHW), 12.2% non-Hispanic blacks (NHB), and 5.1% Hispanics. Medicare access was higher among NHW (66.2%) compared to NHB (57.5%) and Hispanics (56.0%). Total hospitalization costs (standard deviation) were $ 20035 (110.6) for NHW, $ 24892 (188.5) for NHB (OR: 1.21, 95% CI 1.10-1.33), and $ 22231 (361.4) for Hispanics (OR: 1.19, 95% CI 1.07-1.32), respectively (p<0.001). The average length of inpatient stay for NHW was 5.9 (1.5) days, compared to NHB at 6.9 (1.2) days (OR: 1.11, 95% CI 1.07-1.16), and Hispanics at 6.5 (1.8) days (OR: 1.13, 95% CI 1.07-1.19), respectively (p<0.001). The average length of stay was longer for NHB (6.9 days) and Hispanics (6.5 days) than for NHW (5.9 days), with ORs of 1.11 and 1.13, respectively. Mortality rates were highest among NHB at 7.7% (OR: 1.13, 95% CI 1.05-1.20) and Hispanics at 7.6% (OR: 1.10, 95% CI 1.01-1.22), compared to NHW at 6.9% (p<0.001). Disposition to short and long-term facilities was more common for NHB at 50.2% (OR: 1.17, 95% CI 1.12-1.23), compared to NHW at 47.9% and Hispanics at 45.8% (OR: 1.21, 95% CI 1.16-1.28), respectively (p<0.001).

Conclusions: Our data revealed racial disparities in the costs of inpatient hospitalizations, highlighting potential financial toxicity among patients with lung cancer. Additional investigation is warranted to elucidate factors contributing to these inequities, aiming to optimize cancer management and alleviate financial burdens. Addressing these disparities is crucial to prioritize equitable healthcare access and promote systemic change.

Keywords: Financial Toxicity, Racial Disparities, Outcomes Research

EP.17B GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS - DISPARITIES
SATURDAY, SEPTEMBER 7, 2024 - 11:58 - 11:59

EP.17B.06 Survival by Ethnicity and Socioeconomic Status in Patients Diagnosed with Lung Cancer: A 11-year Single Centre Experience

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Introduction: Previous studies found mixed results regarding the impact of ethnicity and socioeconomic status on cancer survival. Few studies include both ethnicity and socioeconomic status in their analysis. Our institution's infrastructure enables sophisticated population-based analysis by leveraging clinical data collected prospectively in a structured and standardised format within the electronic patient record.

Methods: Where available the clinical data of patients diagnosed with NSCLC and treated at a single UK centre between 2013 and 2023 was acquired using the UK Computer Aided Theragnostics framework (Ethics ID: 187386) (n=8260). Survival time was calculated from date seen in a new patient clinic to date last seen or date of death. Ethnicity data was grouped as per Census of England categories. Socioeconomic status was calculated based on the postcode-based Index of Multiple Deprivations (IMD). Median survival was calculated by Kaplan-Meier method. Cox proportional hazards regression models produced hazard ratios (HRs) and 95% confidence intervals (95% CIs).

Results: A summary of results is included in table 1.

*In bold highlights significance ** Not available - multiple potential reasons behind missing data Table 1: Summary of patient characteristics, Kaplan-Meier survival statistics and Cox regression hazards

Conclusions: In this multi-year analysis there is no strong evidence to suggest that social deprivation, ethnicity or age at diagnosis has an impact on the overall survival of patients diagnosed with NSCLC. Patients who are female, have good performance status, are diagnosed with early-stage cancer and are being treated with curative-intent treatments are associated with significantly better overall survival.

Ethnicity data was not available for approximately 50% of patients. Missing data reduces the representativeness of the results and therefore local efforts to improve data capture are required.

Keywords: NSCLC, Ethnicity, Socioeconomic status

n=8260	Frequency	Median OS in months (Log rank)	Hazard ratios for death (95% CI)	Multivariate regression coefficients (95% CI)
Gender:				
Female	3956	16.8		
Male	4302	12.5	**1.17 (1.11 – 1.23)**	**1.27 (1.14 – 1.43)**
Not available**	2	3.79 **(<0.001)**	1.14 (0.16 – 8.13)	0.34 (0.02 – 6.55)
Age at diagnosis:				
25-29	4	10.9		
30-39	24	13.8	1.01 (0.23 – 4.44)	1.44 (0.14 – 15.13)
40-49	162	12.6	1.75 (0.43 – 7.11)	2.13 (0.23 – 19.50)
50-59	813	13.8	2.21 (0.55 – 8.91)	4.11 (0.46 – 36.79)
60-69	2219	12.7	2.55 (0.64 – 10.22)	4.95 (0.55 – 44.13)
70-79	3255	15.3	2.49 (0.62 – 10.01)	5.20 (0.58 – 46.39)
80-89	1666	15.4	2.73 (0.68 – 10.96)	6.55 (0.73 – 58.60)
90-99	117	15.9 (<0.374)	3.10 (0.76 – 12.63)	7.42 (0.79 – 69.48)
Ethnicity:				
White	3723	15.2	0.96 (0.60 – 1.52)	
Not available**	4382	13.0	1.18 (0.74 – 1.88)	**0.78 (0.69 – 0.88)**
Asian or Asian British	83	23.9	0.62 (0.37 – 1.05)	0.60 (0.33 – 1.05)
Black, Black British, Caribbean or African	19	10.5	1.04 (0.53 – 2.05)	2.00 (0.42 – 9.61)
Mixed or multiple ethnic groups	33	19.1	0.77 (0.42 – 1.43)	0.73 (0.31 – 1.72)
Other ethnic group	20	9.0 (<0.233)	0.99 (0.98 – 1.10)	2.71 (0.58 – 12.58)
IMD:				
1 (most deprived)	2134	15.0		
2	1164	14.3	0.97 (0.90 – 1.06)	0.89 (0.74 – 1.08)
3	960	13.5	1.02 (0.94 – 1.12)	0.88 (0.72 – 1.07)
4	695	14.0	0.94 (0.85 – 1.04)	**0.76 (0.61 – 0.94)**
5	624	14.6	0.94 (0.80 – 1.09)	0.82 (0.65 – 1.04)
6	527	12.5	1.00 (0.90 – 1.12)	1.13 (0.87 – 1.47)
7	576	13.5	0.97 (0.87 – 1.08)	0.96 (0.75 – 1.23)
8	655	12.5	0.99 (0.89 – 1.10)	0.78 (0.62 – 0.98)
9	489	14.5	0.97 (0.86 – 1.09)	0.81 (0.63 – 1.05)
10 (least deprived)	436	16.1 (<0.702)	0.91 (0.81 – 1.03)	1.04 (0.79 – 1.37)
ECOG PS:				
0	794	24.8		
1	3051	17.7	**1.55 (1.40 – 1.71)**	**1.69 (1.39 – 2.04)**
2	2475	13.8	**2.21 (2.00 – 2.46)**	**2.42 (1.98 – 2.97)**
3	1449	5.6	**3.01 (2.70 – 3.37)**	**3.13 (2.46 – 3.97)**
4	78	1.5	**2.65 (2.04 – 3.44)**	**2.59 (1.21 – 5.52)**
Not available**	413	12.9 **(<0.001)**	**2.068 (1.801 – 2.374)**	**3.94 (2.82 – 5.51)**
Cancer stage:				
1	1323	48.0		
2	1491	27.9	**1.60 (1.44 – 1.76)**	**2.26 (1.93 – 2.65)**
3	1820	14.0	**2.70 (2.44 – 2.97)**	**3.65 (3.08 – 4.33)**
4	3385	5.6 (<0.001)	**3.56 (3.15 – 4.03)**	**4.26 (3.19 – 5.70)**
Treatment intent:				
Curative-intent	4262	29.7		
Palliative-intent	3998	5.9 (<0.001)	**1.83 (1.67 – 2.01)**	**2.78 (2.16 – 3.56)**

***In bold highlights significance ** Not available - multiple potential reasons behind missing data** *Table 1: Summary of patient characteristics, Kaplan-Meier survival statistics and Cox regression hazards*

EP.17C GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS - EARLY DETECTION
SATURDAY, SEPTEMBER 7, 2024 - 11:58 - 11:59

EP.17C.01 Increasing the Earlier Detection of Lung Cancer: A Toolbox for Change

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Introduction: Most people with lung cancer are currently diagnosed at an advanced stage (Stage III/IV) when outcomes are typically poorer. Earlier detection of the disease at Stages I and II would significantly reduce mortality and improve outcomes. To achieve this, comprehensive early detection strategies must be developed and implemented as part of wider national cancer control plans. While targeted screening using low-dose computed tomography (LDCT) is the most effective means of detecting lung cancer at an early stage, it may not be currently feasible in many countries such as due to limited resources and capacity. Thus, other early detection strategies are available that should collectively be assessed and adopted as appropriate, considering the local epidemiology, health system capacity and available resources.The Lung Cancer Policy Network, a global multi-stakeholder initiative of experts in lung cancer, has developed a comprehensive report exploring the importance of earlier detection for improving outcomes for people with lung cancer.

Methods: The report used a bespoke methodology that combined a review of existing peer-reviewed publications and grey literature, eight qualitative expert interviews from different localities and insights from members of the Lung Cancer Policy Network. This iterative approach led to consensus-driven insights that collectively explore the various existing and emerging earlier detection approaches in lung cancer. The report emphasises the importance of considering the suitability of earlier detection tools with a country's epidemiology and health system to facilitate the implementation of effective and appropriate strategies.

Results: The report explores the utility of various existing and emerging approaches and tools that can be used for the earlier detection of lung cancer and draws these into a toolbox of strategies. These include: public awareness campaigns, symptom-based detection and diagnosis, screening, incidental detection and technological innovation.Throughout the report, 12 case studies from different countries provide real-world examples of earlier detection tools in use from Australia, Denmark, England and Wales, Ireland, Israel, Japan, South Africa, South Korea, and the US.The report concludes with a series of policy recommendations to encourage national decision-makers to act to reduce mortality from lung cancer through the adoption of early detection approaches. This covers prioritisation and promotion of early detection, alignment with broader national policies, health system readiness assessments, engaging with high-risk and traditionally underserved communities, utilisation of technology, investment in research, and monitoring and evaluation.The recommendations emphasise the need to assess key factors such as local epidemiology and health system capacity to inform the development of a unified national strategy using a combination of early detection approaches to detect lung cancer across the population.

Conclusions: The 'Increasing the earlier detection of lung cancer: a toolbox for change' report was made publicly available in November 2023 and to date has been downloaded 960 times.The report aims to support national decision-makers in making earlier detection an integral feature of cancer control plans. It offers the tools needed to start taking ambitious steps towards implementing feasible strategies that serve the differing epidemiology of lung cancer and needs of populations globally.

Keywords: Early detection, Lung Cancer Diagnosis, Outcomes

EP.17C GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS - EARLY DETECTION
SATURDAY, SEPTEMBER 7, 2024 - 11:58 - 11:59

EP.17C.02 Nodule-AFM: Construction and Application of LLM and Multi-Agent Collaborative Based Active Follow-Up Management for Pulmonary Nodule Patients

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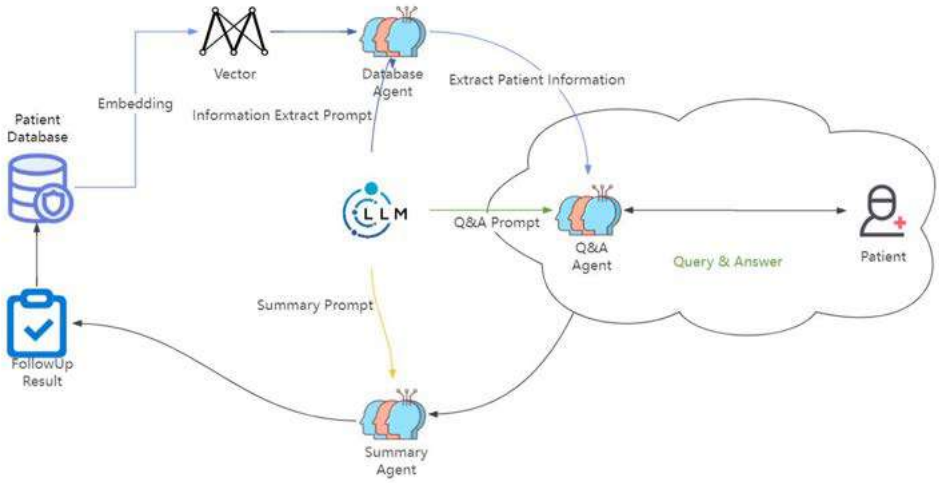
Introduction: Follow-up plays a crucial role in the early screening of lung cancer; however, within the current medical system, follow-up primarily relies on manual intervention. There is a significant need for a personalized and intelligent follow-up management system to enhance the efficiency of proactive follow-up management. Based on open-source large language models(LLM) and the Self-Consistency with Chain of Thought (CoT-SC) concept, an active follow-up management system for pulmonary nodule patients was proposed to improve the follow-up management efficiency and accuracy.

Methods: An open-source LLM(Yi-34b-GPTQ) was adopted and fine-tuned using nearly 1000 clinical follow-up question-and-answer(Q&A) samples. Subsequently, a multi-agent collaborative active Q&A process was constructed. Firstly, a database agent which, based on inquiries, retrieves patient data from the database, extracts patient follow-up information. Then, an active question-and-answer agent, initiating follow-up inquiries with patients, consistently confirming follow-up times through multi-turn conversations in a CoT-SC way. Finally, through a summarization agent, we summarized the above dialogue process to determine if patients could follow up and specified the exact time, updating it in the database. The entire multi-agent collaborative system is implemented based on Langchain and Streamlit, forming a lightweight B/S platform. Ultimately, through testing with 100 cases, four experienced doctors simulated the follow-up management process and evaluated the model's performance, mainly including accuracy of extracting the content of dialogue information(Acc_ext), the accuracy of extracting and summarizing the target words in the dialogue(Acc_sum), and the ability to completion of the conversation(CoC).

Results: The patient dataset of the training and independent testing datasets included age, gender, detection date, pulmonary nodule location, nodule size and nodule Imaging features. The independent testing datasets included 100 individuals with an average age of 46.24 ± 12.97 years and with 36 males(36%) and 64 females(64%). The average size of pulmonary nodules was 8.91±5.27 mm. For the performance evaluation, the completion of the conversation was 94%. The Acc_ext was 84%. The Acc_sum was 79%.

Conclusions: An innovative LLM based nodule active follow-up management solution(Nodule-AFM) is proposed to bring important improvements to traditional nodule follow-up systems. Nodule-AFM could significantly improve the follow up efficiency and reduce the work burden of medical personnel. Future research directions include further optimizing the model's performance and expanding its scope of application to better meet the individual needs of patients and the challenges of healthcare management.

Keywords: Pulmonary nodules management, Artificial intelligence, Large language model



EP.17D GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS - EPIDEMIOLOGY
SATURDAY, SEPTEMBER 7, 2024 - 11:58 - 11:59

EP.17D.01 Trends in Lung Cancer Incidence Among Individuals Under 50: A Retrospective Analysis of the National Inpatient Sample (NIS) Database

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Introduction: Lung cancer (LC) is the second most diagnosed cancer worldwide in men and women, yet it stands as the foremost cause of cancer-related mortality. Nevertheless, incidence has decreased with a proportion of new diagnoses in adults aged 65-years and older from 61% in 1995 to 58% during 2019-2020. Furthermore, data indicates a notable shift in its incidence patterns, particularly among distinct age cohorts. Between 1995 and 2020, there has been a decline in new diagnoses among individuals aged 65-years and older, accompanied by a rise in the proportion of cases among adults aged 50 to 64 years. Conversely, individuals younger than 50 years exhibited a concerning increase in overall cancer incidence during that same period. This retrospective study aims to address the conundrum of this rising entity in the younger population.

Methods: This retrospective cohort study was performed on adults hospitalized in the USA from 2016 to 2020 with LC as their primary diagnosis, identified through ICD-10 codes. Data was sourced from the NIS database. Included were patients aged->= 18 and <50. Socio-demographic factors (age-sex-race-income-insurance-hospital type-bed size-admission type) and outcomes (mortality-incidence-length of stay (LoS)) were analyzed. The impact of care setting (teaching vs. nonteaching-hospitals) and length of stay were studied as surrogates. Chi-Square and Student-T-test were used for categorical and continuous variables, respectively. Statistical significance was set at P<0.05. Logistic-regression assessed the correlation between sociodemographic factors and mortality.

Results: Out of 121, 388 hospitalizations for patients with lung cancer, 4,505 were aged less than 50 years-old, with a median age of 46. The majority were adults aged 41-59 (80%), followed by 29-40 (17%) and 18-28 (2.5%). Males and women were evenly distributed (48% and 52% respectively). Whites comprised 65% of patients, followed by Blacks-(16.6%), Hispanics-(9%), Asians/Pacific Islanders-(6%), Native Americans-(0.5%), and unspecified others (3.2%). <$49,999 income group (32%) and $50,000 - $64,999-(27%) were most prevalent. Private insurance (46%) and Medicaid (34%) were the dominant payers, with Medicare at 8%. Urban teaching hospitals housed 81% of patients, with non-elective admissions at 66% and elective at 34%. Mean LoS was four days. Most deaths occurred outside the hospital (93%). Elective admission had lower mortality compared to emergent (OR: 0.24, 95% CI: - 0.17 - 0.34, p < 0.001). No racial mortality differences were found between white and black patients (OR: 0.84, 95% CI: 0.6 - 1.2, p=0.3). Urban non-teaching hospitals had lower mortality odds than rural ones (OR:0.56, 95% CI:0.3 - 0.99, p=0.04). Income Quartile 3 had lower mortality odds than Quartile 1 (OR:0.7, 95% CI:0.5- 0.99, p=0.04).

Conclusions: This nationwide analysis of LC patients younger than 50-years old reveals that the elective admissions correlate with lower mortality rates than emergent ones, highlighting the importance of timely intervention. Racial disparities in mortality were not significant, indicating equitable outcomes across races. Urban non-teaching hospitals had lower mortality odds than rural ones. Furthermore, higher income quartiles were associated with lower mortality, underscoring socioeconomic influences on health. These findings emphasize the need for tailored interventions to address disparities and optimize outcomes in lung cancer care.

Keywords: Lung cancer, < 50 years old, Disparities.

EP.17E GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS - HEALTH ECONOMICS
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EP.17E.01 Cost-Effectiveness Analysis of Sotorasib vs. Adagrasib in KRAS G12c-Mutated Previously Treated NSCLC

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Introduction: Sotorasib and adagrasib are two FDA-approved KRASG12C inhibitors with demonstrated efficacy in previously treated patients with KRAS G12C advanced non-small cell lung cancer (NSCLC). The registrational phase I/II CodeBreaK 100 and KRYSTAL-1 trials demonstrated similar objective response rate of ~41% and median progression free survival of ~6.3 months. Although no head-to-head clinical trial has been conducted comparing sotorasib with adagrasib, review of the US prescribing information suggests key differences in safety profile, including different rates of dose reductions, rates of gastrointestinal adverse events, and risk of QTc prolongation between both therapies. The comparative cost-effectiveness of both therapies has not yet been assessed.

Methods: To assess the cost-effectiveness between sotorasib and adagrasib from a US private payer perspective a partition survival model (health states: progression-free [PF], post-progression [PP], and death) with a lifetime time horizon and a 1.5% discount rate was applied. The efficacy (overall survival, OS; progression-free survival, PFS) was based on a matching-adjusted indirect comparison (MAIC) of the corresponding Phase 2 trials, using CodeBreaK 100 patient-level data for sotorasib versus KRYSTAL-1 aggregated data for adagrasib. Baseline OS and PFS curves were based on parametric curves from CodeBreaK 100 and relative efficacy (OS, PFS) based on the MAIC. Time-to-death utilities were sourced from CodeBreaK 100. Economic inputs included a treatment specific dose intensity and several costs pertaining to the cost of medication, treatment-related adverse events, comedications, KRAS G12C testing and terminal care. To assess parameter uncertainty, probabilistic sensitivity analysis (PSA) was performed.

Results: Compared to adagrasib, sotorasib was associated with superior health outcomes at lower costs (i.e. in terms of health-economic terminology sotorasib achieved dominance over adagrasib): Quality-adjusted life-years (QALYs) increased by 0.25, costs were reduced by $52,999. Key drivers for cost-effectiveness were efficacy, acquisition costs and adverse events management costs. Compared to deterministic outcomes probabilistic results were consistent. At a willingness-to-pay (WTP) threshold of $150,000, the probability of sotorasib being superior to adagrasib was 73.6%. Yet, dominance of sotorasib over adagrasib persisted, irrespective of the WTP threshold applied.

Conclusions: Among both treatment options, sotorasib compared to adagrasib is more cost-effective. Despite uncertainty on relative OS and PFS outcomes, adagrasib was associated with higher costs to manage the higher adverse event burden. The higher costs of managing adverse events, including higher usage of medications and dose interruptions, led to sotorasib being more cost-effective than adagrasib.

Keywords: Cost-effectiveness, Sotorasib, NSCLC

EP.17E.02 Assessing the True Cost of Lung Cancer Screening - Chargemaster, Payer, And Cash Price Discrepancies for CT Chest Imaging

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Introduction: Patients in the United States (US) often lack information about the price of lung cancer screening services across hospitals and payers. Recent legislation in the US, including the 2021 Hospital Price Transparency Final Rule, requires hospitals to publish standard chargemaster rates, payer-specific negotiated prices, and discounted cash prices for all services, creating a unique opportunity to understand variation in hospital pricing. While uninsured or underinsured patients may be exposed to high chargemaster rates for screening services, those who are able to pay upfront in cash or have negotiated rates through insurance face significantly discounted prices. More research is needed to better understand the relationship between the distinct screening prices facing patients in the United States.

Methods: We extracted standard chargemaster prices, payer-specific negotiated prices, and self-pay cash prices for screening low-dose CT chest imaging (CPT code 71271) from machine-readable files published by eleven top US hospitals. For each hospital, we compared the standard chargemaster rate for low-dose CT chest screening with the average payer negotiated price and determined the chargemaster-payer price ratio. Additionally, we compared the standard chargemaster rates and discounted cash prices for CT chest imaging, and determined the chargemaster-cash price ratio for each hospital.

Results: Across eleven top US hospitals, the average chargemaster rate for low-dose CT chest imaging was $1060. The average cash price for the same service was $515, with an average chargemaster-cash price ratio of 2.5. The average payer-negotiated price for CT chest was $626, and chargemaster rates were also greater than payer-negotiated prices by an average factor of 2.1. The average cash price for lung cancer screening was 82.3% of the average payer negotiated rate for the same service. We observed wide variation across institutions for chargemaster rates, payer-negotiated rates, and discounted cash prices for CT chest imaging, with interquartile ranges of $615, $448, and $409, respectively.

Table 1: Chargemaster Rates, Payer Negotiated Prices, and Cash Rates for Low-Dose CT Chest

Conclusions: Across eleven top US hospitals, the chargemaster price for screening low-dose CT chest imaging was greater than the average payer negotiated rates and discounted cash price for the same service by a factor of 2.1 and 2.5, respectively. This price discrepancy has important consequences for individuals seeking essential lung cancer screening services, with uninsured patients facing prohibitive costs. As curable lung cancers go undetected, the burden on the healthcare system escalates. Policies should aim to improve price transparency, equity, and access to lifesaving lung cancer screening for the most vulnerable populations in the United States.

Keywords: Transparency, Chargemaster, Price

Hospital	*Standard Chargemaster Rate*	*Average Payer Negotiated Price*	*Discounted Cash Price*	*Chargemaster/Payer Price Ratio*	*Chargemaster/ Cash Price Ratio*
Stanford Health Care	$684	$1697	$274	0.4	2.5
Duke Health	$809	$261	$218	3.1	3.7
Northwestern Medical Center	$1043	$515	$730	2.0	1.4
Rush University Medical Center	$300	$259	$150	1.2	2.0
Vanderbilt University Medical Center	$809	$182	$437	4.4	1.9
Houston Methodist Hospital	$2657	$1113	$1328	2.4	2.0
University of Pennsylvania Health System	$1676	$721	$579	2.3	2.9
Massachusetts General Hospital	$1270	$565	$953	2.2	1.3
Cleveland Clinic Health System	$604	$335	$393	1.8	1.5
NYU Langone Health	$560	$462	$106	1.2	5.3
University of Michigan Health	$1248	$771	$499	1.6	2.5
Average Total	**$1060**	**$626**	**$515**	**2.1**	**2.5**
Interquartile Range (IQR)	*$615*	*$448*	*$409*	-	-

EP.17E GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS - HEALTH ECONOMICS
SATURDAY, SEPTEMBER 7, 2024 - 11:58 - 11:59

EP.17E.03 Using Healthcare Claims to Predict Costs by Stage for Medicare and Commercially Insured Patients with Non-Small Cell Lung Cancer

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Introduction: Cancer diagnosis at earlier stages may provide an opportunity to reduce treatment cost burden. This study assessed the relationship between non-small cell lung cancer (NSCLC) stage at diagnosis and healthcare costs post-diagnosis using administrative claims. Since cancer stage is not explicitly available in claims, we applied a validated predictive machine learning model that used claims-derived treatment and demographic variables to assign NSCLC stage at diagnosis. Medicare fee-for-service (FFS) and commercially insured populations were categorized by predicted stage to compare costs over time for patients insured under different coverages.

Methods: Patients newly diagnosed with NSCLC were identified in the 2016-2017 SEER-Medicare linked dataset and Milliman's 2019-2020 Consolidated Health Cost Guidelines Sources Data, for Medicare and commercially insured populations, respectively. Patients without 12 months of continuous enrollment and those with evidence of cancer diagnoses, metastases, or treatment in the year prior to their first date of NSCLC diagnosis (index) were excluded. Claims-derived treatment and demographic variables for included patients were processed using a multinomial logistic regression model (R Statistical Software - v4.1.2 R Core Team 2021; nnet package - Venables and Ripley 2002). Patients were sorted into AJCC stages 0/1/2, 3, or 4, and average monthly allowed medical and pharmacy costs from index through enrollment end or 36 months post-diagnosis (whichever came first) were adjusted to a 2022 basis and summarized. Average costs by predicted stage for Medicare and commercially insured populations were compared.

Results: Average first-year costs for commercially insured patients following NSCLC diagnosis ranged from 1.3x to 2.5x greater than costs for Medicare patients with the same predicted stage at diagnosis. In the first year, stage 4 Medicare patients incurred costs roughly 2x those of stage 0/1/2 patients, while stage 4 commercially insured patients incurred costs 3x those of stage 0/1/2 patients. For patients with stage 3 or 4 disease, costs continued to be higher up to 36 months post-diagnosis for commercially insured patients relative to Medicare patients.

Conclusions: This claims-based analysis demonstrates that higher cancer stage at diagnosis is associated with greater healthcare expenditures for at least three years post-diagnosis for patients with NSCLC. Healthcare cost burden for commercially insured patients is higher than for Medicare patients with similar NSCLC stages. This cost differential is especially pronounced among those diagnosed with stage 3 or 4 disease. Our study highlights the opportunity to use claims data to estimate the potential for NSCLC cost reductions through screening and early diagnosis.

NSCLC Healthcare Costs Post-Diagnosis by Predicted Stage and Insurance Coverage

Keywords: non-small cell lung cancer, cancer stage, healthcare costs

Predicted AJCC Stage	Coverage Type	n	Average Age	% Female	Months Post-Diagnosis			3-Year Costs
					1-12	13-24	25-36	
0/1/2	Medicare FFS	5,343	75	55%	$74,820	$47,103	$35,526	$157,449
	Commercial	2,867	64	59%	$95,812	$44,223	$40,438	$180,474
3	Medicare FFS	1,977	73	44%	$112,920	$76,101	$52,847	$241,867
	Commercial	922	62	45%	$280,944	$152,949	$89,746	$523,639
4	Medicare FFS	6,174	75	51%	$159,206	$125,869	$84,966	$370,040
	Commercial	2,551	62	51%	$312,819	$192,530	$118,940	$624,289

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EP.17E.04 Cost-Effectiveness of PD-L1 Testing for Guiding Immunotherapy in Non-Small Cell Lung Cancer (Stage IIA-IIIB & Stage IV) Patients in China

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Introduction: Accurate PD-L1 testing for non-small cell lung cancer (NSCLC) maximizes the benefits of immunotherapy drugs like Atezolizumab and Pembrolizumab. False test results may lead to patients receiving inappropriate treatment, and worsening clinical and economic outcomes. The treatment pathways for patients with NSCLC vary based on the stage of their disease. This study evaluates the cost-effectiveness of various PD-L1 testing methods for guiding immunotherapy in NSCLC patients with stage IIA-IIIB and stage IV. The findings aim to provide a scientific foundation for selecting the most cost-effective diagnostic testing and guiding immunotherapy for NSCLC patients in China.

Methods: A decision tree model was constructed to evaluate the cost and effectiveness (percentage of patients successfully diagnosed and prescribed the correct therapy per China treatment guidelines) of using Ventana PD-L1 IHC SP263 assay, Dako PD-L1 IHC 22C3 assay, and Dako 22C3 antibody concentrate for stage IIA-IIIB and stage IV NSCLC patients in China, respectively. The model incorporated PD-L1 testing accuracy parameters derived from the external quality assessment (EQA) report, with expert interviews for verification. Testing costs were based on the median charging prices in certain provinces and cities of China. Clinical parameters, health utilities, and medical resource utilization parameters were sourced from published literature and databases. Both one way and probabilistic sensitivity analysis were conducted to assess the model robustness.

Results: When guiding stage IIA-IIIB NSCLC patients to receive adjuvant therapy with Atezolizumab after chemotherapy, the SP263 assay group was cost-effective when compared to the 22C3 assay group and 22C3 antibody concentrate group with an incremental cost-effectiveness ratio (ICER) of RMB 9,449. When guiding immunotherapy for stage IV NSCLC patients, the SP263 assay group had an advantage in guiding multiple immunotherapy monotherapies (e.g., Atezolizumab, Pembrolizumab) over other PD-L1 testing. Compared to the 22C3 assay group and 22C3 antibody concentrate group, the SP263 assay group demonstrated a higher effectiveness of 4.53% and 14.25% and a lower cost of RMB 3,414 and RMB 3,059. Both one-way sensitivity and probabilistic sensitivity analysis proved the stability of the results.

Conclusions: In China, the SP263 PD-L1 testing is the most cost-effective option for guiding immunotherapy in both stage IIA-IIIB and stage IV NSCLC patients.

Keywords: PD-L1 Testing, NSCLC, Cost-Effectiveness Analysis

EP.17F GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS - HEALTH SYSTEM
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EP.17F.01 Care Pathways for Lung Cancer: Building a Foundation for Optimal Care

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Introduction: The Lung Cancer Policy Network, a global multi-stakeholder initiative of experts in lung cancer, has developed a comprehensive report exploring the essential role care pathways play in delivering best-practice lung cancer care. Despite evidence showing that high-quality care pathways can improve outcomes, system processes and resource optimization, only a small number of countries and regions have established formal care pathways for lung cancer. In these cases, improved experiences, outcomes and survival for people with lung cancer have been observed. Widespread adoption of care pathways is needed to advance lung cancer care on a global level.

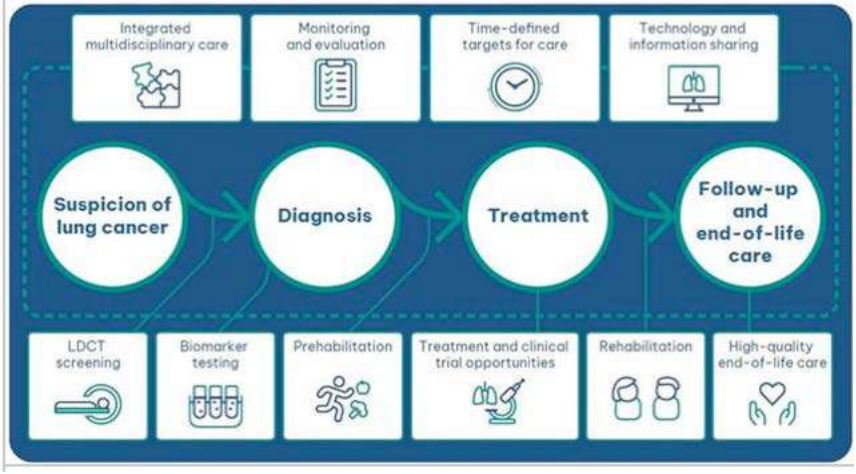
Methods: The report was informed by a review of existing peer-reviewed and grey literature, interviews with nine experts across four continents, alongside insights from members of the Lung Cancer Policy Network. The report incorporates practical case studies from Australia, Brazil, Canada, Japan, Norway, the Netherlands, Spain, the UK and the US.

Results: The report recommends ten key actions to support health system leaders and decision-makers in delivering high-quality lung cancer care through the implementation of effective, consensus-driven care pathways within health systems. It sets out tangible actions to support the development of care pathways in the context of changing approaches to lung cancer care, and the needs of individual health systems. These recommendations include opportunities across and at specific stages of the care pathway (Figure 1). Incorporation of multidisciplinary care across all care pathways is a key facilitator of high-quality care. The multidisciplinary team (MDT) members may change as people transition through the care pathway. However, patient navigation always needs to be part of the MDT to help coordinate care and ensure access to care. This is especially important for people in underserved populations. The report also has actions at specific points along the care pathway such as introducing comprehensive prehabilitation and rehabilitation programs, and readily incorporating new biomarkers and targeted treatments.

Conclusions: Effective care pathways (regularly updated to reflect best practice) have the potential to relieve some of the substantial global burden and poor outcomes of lung cancer, mitigate the current inequalities in access to high-quality lung cancer care, and increase earlier detection. To realize this opportunity, policymakers must assess and identify how to improve current practice, develop care pathways where they do not exist, and optimize these pathways accordingly.

Keywords: lung cancer, care pathways, high quality care

Figure 1. Opportunities across and at specific stages of care pathways for lung cancer to promote high-quality care



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EP.17F.02 Three-Stage Evolution of Lung Cancer Multidisciplinary Team in China

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Introduction: Multidisciplinary Team (MDT) management in lung cancer treatment has become increasingly prominent worldwide. Facing with a large number of lung cancer patients and gap in medical care between city and rural area, how to achieve a high-quality MDT management with more efficient organization and broader patient accessibility remains a challenge in China. Leading chinese lung cancer centers have been working together to achieve a cross-regional, convenient, and efficient MDT over the past 10 years. This study aims to explore the evolution of lung cancer MDT management in China and identify the key developmental elements, so as to provide references for hospitals that are in the process of developing lung cancer MDT.

Methods: We conducted in-depth interviews, brainstorming sessions, and questionnaires with MDT experts from multiple leading lung cancer treatment hospitals in China, such as Guangdong Provincial People's Hospital, West China Hospital of Sichuan University and Xiangya Hospital of Central South University, to analyze the evolution of lung cancer MDT in China.

Results: Consulted leading hospitals have demonstrated commonalities in lung cancer MDT evolution as well as differences in personalized MDT such as psychosomatic MDT for lung cancer patients. We have summarized a three-stage evolution pathway for lung cancer MDT by looking for commonalities in 5 key aspects (Table 1). We also took Guangdong Lung Cancer Institute (GLCI), where the lung cancer MDT was established the earliest in China since 2003, as an example to represent the lung cancer MDT evolution in concrete terms (Fig1).

Table 1. Five key aspects along the lung cancer MDT evolution in China

Conclusions: Lung cancer MDT in China has been evolving towards collaborative, personalized, and intelligent healthcare. Three-stage MDT evolution provide a paradigm for developing regions/countries with significant patient volumes and relatively unbalanced medical resources to elevate the standard of MDT practices and improve patient accessibility. Stage 4.0 of international lung cancer MDT is expected on the way.

Keywords: Lung cancer Multidisciplinary Team, Evolution, China

Aspect	Evolution stage	Stage 1.0	Stage 2.0	Stage 3.0
1	Coverage of patients and MDT experts	In-hospital	Inter-hospital within province	Inter-hospital within country
2	Preparation for MDT cases	Physician's personal style	Standardized process and PPT template	
3	MDT discussion process	No digital	Digital-assisted meeting(e.g., Zoom/Tenccent Meeting)	Digital-assisted whole process(e.g., AI-facilited iMDT tool)
4	Management focus	Treatment quality and MDT efficiency	+ Patients' clinical outcomes after the MDT treatment	+ Longitudinal management and patient follow-up
5	Broadness and depth of educational coverage	• Offline MDT discussion open to all in-hospital physicians and other healthcare professionals (HCPs) •Generation of MDT Book in leading hospital for other doctors to learn	•Offline MDT & limited Online MDT meeting access open to HCPs from other selected hospitals	•Off-line & Online MDT meeting free access open to all HCPs as well as to patients

Fig 1. Example of GLCI Lung Cancer MDT Evolution

EP.17F GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS - HEALTH SYSTEM
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EP.17F.03 An Evidence-Driven Approach to Optimizing Clinical, Operational, And Economic Value in the Lung Cancer Care Pathway

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Introduction: The use of a scalable, real-world, evidence-driven approach to lung cancer care pathway optimisation enables more patients to be diagnosed and treated earlier and in a more personalised and sustainable manner, potentially leading to better outcomes.

Methods: This study measured qualitative and quantitative clinical, operational, and economic data in the lung cancer care pathway in a university hospital in Spain. Structured and unstructured patient data (assisted by natural language processing) were used to identify >250 key variables related to patients, activities, and treatments. A time-driven activity-based costing tool was applied to calculate patient-level direct and indirect costs.

Results: Data were available for 2502 patients (2016-2021). Over a 6-year period, 40,000 hours were dedicated to providing care for these 2502 patients. Total costs were €31.4 million, 62% for hospital-related activities and 38% for drug therapy. Staging (mapped to TNM 8th edition) was available for 767 patients (stage IV, n=307 [40%]; stage III, n=244 [32%]). Costs were highest among patients with stage IV disease (€4.8 million), mainly constituting drug therapy costs (Figure 1). Times to first anti-cancer drugs were similar for patients with stage III or stage IV disease (Figure 2). Early-stage patients took the longest time to move through the care pathway. Time to first computed tomography scan or first hospital visit varied the least across stages and services. Half of cases (52%) were presented to the tumour board multiple times (mean, 3.6 presentations per case). Among patients with a bronchoscopy and a tumour board evaluation, more bronchoscopies were prescribed after (n=941) than before (n=115) the tumour board (105 had bronchoscopies before and after).

Conclusions: This study showed that, through the generation and unification of operational, clinical, and financial evidence, opportunities for pathway capacity optimisation and a reduction in the variability of clinical care can be identified.

Keywords: lung cancer, quality, costs

Figure 1. Total costs of care by stage, 2016-2021 (n=767)

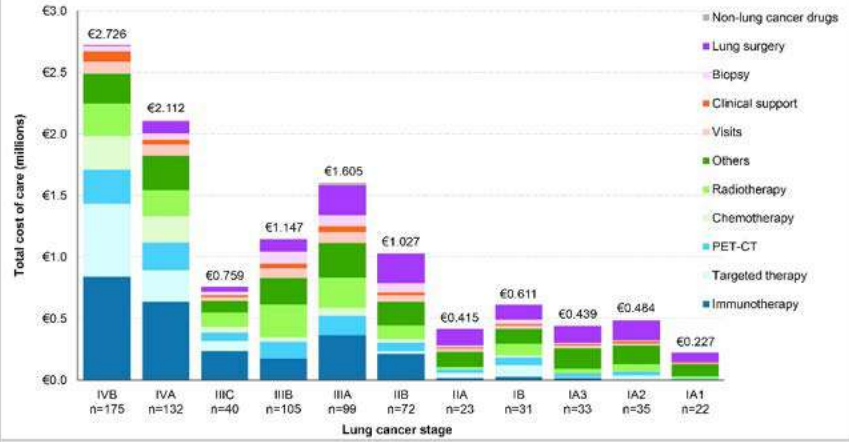
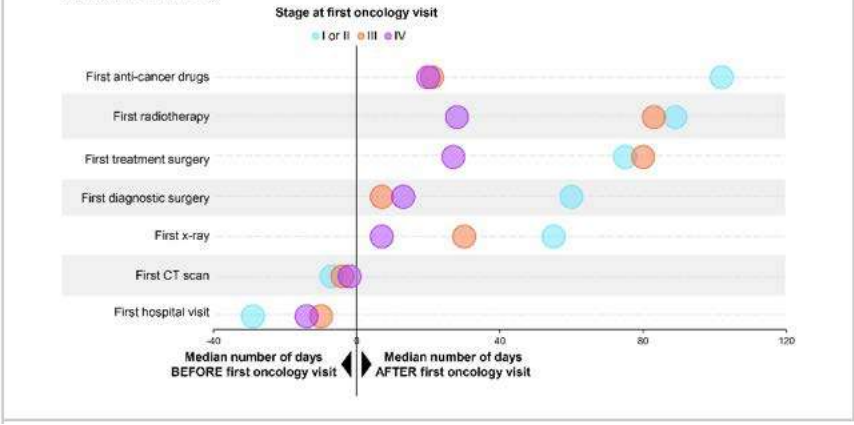


Figure 2. Median time between first oncology visit and key points in the patient care pathway for patients with first visit in 2017 (n=336)



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EP.17F.04 Challenges and Opportunities in Multidisciplinary Team (MDT) Consultations for Advanced-Stage Lung Cancer Patients in China

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Introduction: The high proportion of advanced-stage (stage III or IV) lung cancer patients at initial diagnosis in China, reaching 64.7%, contrasts sharply with a survival rate of only 5.27% for such patients. However, the treatment of advanced-stage lung cancer patients often faces numerous challenges, such as complex conditions and difficulties in selecting treatment plans. MDT meetings offer a promising approach to improve patient outcomes, their application and impact in the context of advanced-stage lung cancer patients remain underexplored. This study aims to explore the demand for MDT consultations among patients with advanced-stage lung cancer and the challenges they face, aiming to provide reference and suggestions for improving the diagnosis and treatment mode of lung cancer patients.

Methods: Through in-depth interviews and cross-institutional MDT consultations, a comprehensive investigation and analysis were conducted on MDTs and advanced-stage lung cancer patients in China. Additionally, data from 102 cases of advanced-stage lung cancer patients were collected to explore their needs, feedback on MDT consultations (including satisfaction with physical, psychological, cognitive, and social role recovery statuses), and subsequent treatment outcomes (including overall quality of life and objective response rates of tumors).

Results: Findings reveal that while specialized MDT teams for advanced-stage lung cancer patients are prevalent (100% consulted hospitals) in Chinese hospitals, they face mainly four challenges such as lengthy time commitments, high frequency of consultations, substantial resource allocation, and limited treatment options (Figure 1). Statistical results from patients' follow-ups indicated: 97.1% (99/102) were satisfied with the MDT treatment recommendations; two main reasons of requiring MDT consultation - 51% (52/102) difficulty on diagnosis and 45.1% (46/102) difficulty on treatment; four ending points after MDT consultation - 9.8% (10/102) enrollment of clinical trials, 11.8% (12/102) maintenance of original treatment regimen, 23.5% (24/102) refinement of the diagnosis, 54.9% (56/102) conduction of adjusted treatment regimen.

Conclusions: Positive feedback from patients indicates that the specialized MDT approach for advanced-stage lung cancer patients is yielding promising results. However, in-depth analysis by experts has identified the key challenges faced by existing MDTs. Despite these challenges, Chinese lung cancer MDTs show considerable potential. By optimizing resource allocation, fostering cross-institutional collaboration, and prioritizing psychological well-being, MDT consultations can be further enhanced for advanced-stage lung cancer patients, ultimately improving prognosis and quality of life.

Keywords: Multidisciplinary Team, Advanced-Stage Lung Cancer, China

	Challenges	Results summary			
1	**Long time commitment per patient**	Patients with advanced-stage lung cancer typically have **complex conditions and historical records**, requiring significantly more time for individual patient care compared to early-stage patients.			
		For an **early-stage** case		For an **advanced-stage** case	
		Prep time	15mins	Prep time	In-hospital MDT – 30mins
					Inter-hospital MDT – 45min~1hr
		Discussion time	5~10 minutes	Discussion time	In-hospital MDT – 15mins
					Inter-hospital MDT –20~30mins
2	**High frequency of MDT consultation**	As patients progress rapidly, **MDT discussions need to be repeated and organized timely**, but fixed-cycle MDTs may not meet the timely needs of patient visits. Current MDTs for advanced-stage patients are organized **weekly for in-hospital** meetings and **monthly or bi-monthly for inter-hospital** meetings.			
3	**Substantial resource allocation of MDT experts (e.g., Stage III MDT composition)**	**Fixed members**		**Optional invited members**	
		Thoracic surgery, medical oncology, respiratory medicine, radiation oncology, and imaging		Pathology, cardiology, psychology etc. More **physiological burdens** such as anxiety and depression appeared at advanced stage	
4	**Limited treatment options**	Unlike early-stage patients, the **treatment goals** of patients with advanced-stage lung cancer may focus more on **symptom relief, prolonging survival, and improving quality of life**, rather than completely curing the disease.			
		Some severe patients may have **lost the opportunity for surgical treatment** and can only undergo control treatment through chemotherapy, radiotherapy, or targeted therapy. **MDT teams need to flexibly formulate plans based on comprehensive treatment effects and patient acceptance.**			

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EP.17F.05 The Impact of COVID-19 On Time Toxicity in Advanced Lung Cancer Patients

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Introduction: The COVID-19 pandemic prompted the rapid adoption of telemedicine in oncology, reducing the need for physical visits to hospitals or clinics, and altering the traditional landscape of healthcare utilization. Time toxicity is the burden of time spent on cancer treatment and it was initially characterized by Gupta et al. as any physical contact day with the healthcare system, excluding virtual and in-home care. This research project introduces the notion of comprehensive healthcare contact days, which includes those conducted virtually and at home to capture the shift in healthcare after the pandemic. The proposed study describes time toxicity within this new paradigm, focusing on advanced lung cancer patients' healthcare interactions before and after the global pandemic.

Methods: A retrospective cohort analysis was conducted including patients with advanced (stage 4) lung cancer who died within one year of diagnosis at Kaiser Permanente Northern California between January 1, 2018 and December 31, 2021. The study aimed to stratify comprehensive healthcare contact days before and after the pandemic (defined as starting March 1, 2020). Time toxicity was defined as comprehensive contact days, including outpatient days (imaging, labs, treatment, provider visits), institutional stays (emergency department, acute inpatient, and non-acute institutional stays), and in-home days (in-home care and virtual care).

Results: A total of 944 patients with advanced lung cancer (49.5% female, 73.3% White, median Elixhauser score of 4) were identified. 599 patients (63.5%) received care pre-pandemic, 68 (7.2%) partially during the pandemic, and 277 (29.3%) during the pandemic. Survival days were longer after the pandemic (median 135 days vs 100 days, p<0.001). The proportion of comprehensive contact days decreased during the pandemic (38.1% vs 50%, p<0.001). Institutional stay contact days were reduced during the pandemic (5.9% vs 19.8%, p<0.001). Conversely, in-home care contact days increased during the pandemic (11.2% vs 6.1%, p<0.001), with a significant rise in virtual care (5.6% vs 2.7%, p<0.001).

Conclusions: The COVID-19 pandemic has significantly influenced time toxicity for advanced lung cancer patients, leading to a decrease in comprehensive contact days with a shift towards telemedicine and in-home care. This evolution in care delivery not only reflects the healthcare system's adaptability in the face of a global health crisis but also underscores the critical importance of understanding the burden of time toxicity on patients with lung cancer. Future research on patient time-toxicity in the post-pandemic era should consider comprehensive contact days.

Table 1. Median healthcare contact days, presented as a proportion of the total survival period (percentage of contact) and number of days by pandemic (COVID).

	Total	Pre-COVID	Partial/During-COVID[1]	P-value
	Median (IQR)	Median (IQR)	Median (IQR)	
Survival in Days	110.0 (61.0-199.5)	100.0 (59.0-173.0)	135.0 (68.0-241.0)	<.0001
Percentage of Contact				
Comprehensive Contact Days	44.7 (31.7-64.7)	50.0 (35.3-71.1)	38.1 (26.6-54.6)	<.0001
Institutional Stays	12.8 (3.9-32.4)	19.8 (6.7-43.2)	5.9 (2.0-14.0)	<.0001
ED/Acute IP	5.2 (1.4-12.5)	5.6 (1.4-14.3)	4.5 (1.4-9.9)	0.07
Non-acute institutional stay	0.0 (0.0-17.2)	5.2 (0.0-30.0)	0.0 (0.0-0.0)	<.0001
Outpatient	13.0 (7.1-18.9)	13.0 (6.8-20.2)	13.0 (7.4-18.0)	0.21
Outpatient visit	8.6 (3.7-12.8)	9.0 (4.1-14.0)	7.6 (3.0-11.5)	<.001
Outpatient service[2]	4.0 (1.8-6.0)	3.7 (1.4-5.7)	4.7 (2.6-6.6)	<.0001
In-home	8.0 (3.5-17.0)	6.1 (2.7-13.6)	11.2 (6.5-22.6)	<.0001
In-home care	0.9 (0.0-12.5)	0.0 (0.0-9.8)	3.0 (0.0-15.5)	<.0001
In-home virtual care	3.6 (1.6-6.2)	2.7 (1.3-5.0)	5.6 (3.1-8.5)	<.0001
Days of Contact				N/A[3]
Comprehensive Contact Days	49.0 (30.0-78.0)	49.0 (31.0-80.0)	48.0 (27.0-77.0)	
Institutional Stays	14.0 (6.0-31.0)	18.0 (8.0-38.0)	7.0 (3.0-16.0)	
ED/Acute IP	6.0 (2.0-12.0)	6.0 (2.0-13.0)	6.0 (2.0-12.0)	
Non-acute institutional stays	0.0 (0.0-16.0)	6.0 (0.0-28.0)	0.0 (0.0-0.0)	
Outpatient	13.0 (5.0-28.0)	12.0 (5.0-25.0)	16.0 (6.0-31.0)	
Outpatient visits	9.0 (3.0-19.0)	8.0 (3.0-18.0)	9.0 (3.0-20.0)	
Outpatient service	4.0 (2.0-9.0)	3.0 (1.0-7.0)	5.0 (2.0-11.0)	
In-home	9.0 (4.0-21.0)	6.0 (3.0-15.0)	15.0 (7.0-29.0)	
In-home care	1.0 (0.0-13.0)	0.0 (0.0-11.0)	5.0 (0.0-18.0)	
In-home virtual care	4.0 (2.0-8.0)	3.0 (1.0-5.0)	7.0 (3.0-12.0)	

Differences in median survival days and percentage of contact between pre-and partial/during-COVID are evaluated using Wilcoxon signed-rank test.
[1]Parital-COVID is defined as patients diagnosed with cancer pre-pandemic but received at least part of their care during-pandemic. During-COVID is defined as patients diagnosed and received care after pandemic started (i.e., March 1, 2020).
[2]Outpatient service is defined as visits related to imaging and labs.
[3]Due to different survival periods, comparing days of contact between two groups is not meaningful.

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EP.17F.06 Enhancing Lung Cancer Care and Patient Access at Regional Level - The Impact of Inter-Hospital Remote Multidisciplinary Team Consultations

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Introduction: Given China's vast population, wide geographic span, and diverse cultures and socioeconomic groups, cancer treatments vary greatly. Regional primary hospitals face challenges in lung cancer diagnosis and treatment due to limited medical resources and expertise, adversely affecting patient outcomes. Inter-hospital remote multidisciplinary team (MDT) consultations offer a promising approach to share medical resources effectively, enhance the level of lung cancer diagnosis and treatment, and benefit more lung cancer patients from rural areas. This study aims to assess the effectiveness of inter-hospital MDT consultations, evaluate their educational value, and extract replicable experiences to share and guide other MDT teams, so as to benefit more patients from rural areas.

Methods: Utilizing the iMDT digital platform (an AI-facilitated MDT management tool for physicians), 35 inter-hospital remote MDT sessions were organized, involving MDT teams from various regions across China. Relevant data from MDT management as well as physicians' and patients' feedback, were collected and analyzed.

Results: Analysis revealed that after MDT consultations, the comprehensiveness and individualization of treatment plans were enhanced, with a significant improvement in guideline adherence. Analytical assessment results on educational coverage, feedback from HCPs and patients are shown in Figure 1. Additionally, the use of the iMDT digital platform significantly reduced MDT preparation time from 2 hours to 10 minutes per session and improved online materials reading efficiency, facilitating the integration of multiple information sources. The data statistics function after MDT consultations enabled visual analysis and tracking, facilitating the timely optimization of inter-hospital remote MDT management.

Conclusions: The inter-hospital remote MDT model is an effective approach to break geographical barriers, alleviate regional disparities in medical resource allocation, offer innovative treatments opportunities via good clinical practice, and provide a compensatory solution for patient care unbalance caused by the limited access to tertiary hospitals, especially in central and western China. To facilitate this model, it is strongly recommended to utilize effective communication channels to enhance information dissemination. For instance, leading hospitals 1) share access links of MDT meetings or live surgical broadcasts by top-tier physicians promptly via WeChat groups, allowing HCPs learn at their convenience, 2) provide in-hospital training opportunities for doctors from regional hospitals, in turn, facilitating the delivery of standardized, timely, and personalized care to the patients from rural areas, and ultimately improving their survival rates and quality of life. Additionally, the integration of digital tools can effectively save HCPs' time and enhance the allocation of healthcare resources.

Keywords: Inter-Hospital Multidisciplinary Team, Patient Access, Digital Health

Figure 1. Key analytical results of the assessment of inter-hospital remote MDT study

Educational coverage with 35 inter-hospital MDT sessions	Feedback collected from **regional hospital HCPs**	Feedback collected from **MDT discussed 105 patients** with lung cancer at advanced stage
• 143 lung cancer treatment hospitals of different sizes and expertise levels • 21 provinces and cities nationwide • ~500 HCPs/MDT session	• 98% with high satisfaction • 95.2% with agreement on the experience accumulation • 91.2% with a notable desire for continued engagement	• 98.1% with satisfaction to the MDT recommendations • 91.4% with positive feedback on their treatment outcomes and quality of life improvement
Geographically, hospitals and patients in the Central and Western regions exhibited greater demand and participation rates to inter-hospital remote MDT consultations.		

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