8001 Oral Abstract Session

BEAT-SC: A randomized phase III study of bevacizumab or placebo in combination with atezolizumab and platinum-based chemotherapy in patients with extensive-stage small cell lung cancer (ES-SCLC).

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Background: Atezolizumab combined with carboplatin and etoposide is approved as first-line treatment for patients with ES-SCLC, based on results from the Phase I/III IMpower133 trial (NCT02763579). The VEGF inhibitor bevacizumab (bev) is approved for the treatment of many tumor types and has synergistic effects when combined with atezolizumab, as demonstrated by the Phase III IMpower150 study (NCT02366143) in non-small cell lung cancer. BEAT-SC (jRCT2080224946) is evaluating the efficacy and safety of bev combined with atezolizumab and platinum-based chemotherapy in patients with ES-SCLC from Japan and China. Here, we report the primary analysis for progression-free survival (PFS) and the first interim analysis for overall survival (OS) from BEAT-SC. **Methods:** Eligible patients had measurable ES-SCLC, were aged ≥20 y (≥18 y for patients from China), had an ECOG performance status of 0 or 1 and had no prior systemic treatment for ES-SCLC. Patients were randomized 1:1 to receive 4 cycles (21 days/cycle) of induction therapy with bev combined with atezolizumab + cisplatin or carboplatin + etoposide (ACE) or placebo combined with ACE, followed by maintenance therapy with bev + atezolizumab or placebo + atezolizumab, respectively. The primary endpoint was investigator-assessed PFS (INV-PFS). Key secondary endpoints included OS and safety. **Results:** The ITT population comprised 333 patients with a median age of 65.0 y; 82.6% of the patients were male, 57.7% were from China, 91.8% received carboplatin and 87.6% were current or former smokers. At data cutoff (June 30, 2023; median follow-up, 10.2 mo), median INV-PFS was 5.7 mo for bev + ACE vs 4.4 mo for placebo + ACE (HR, 0.70; 95% CI: 0.54, 0.90; P=0.0060; 2-sided α boundary=0.05). Median OS was 13.0 mo for bev + ACE vs 16.6 mo for placebo + ACE (HR, 1.22; 95% CI: 0.89, 1.67; P=0.2212; 2-sided α boundary=0.0079). Among the safety analysis population (n=330), bev + ACE was well-tolerated and treatment-related adverse events (TRAEs) were generally similar between treatment arms (Table). **Conclusions:** BEAT-SC met its primary endpoint, demonstrating that the addition of bev to ACE significantly increased PFS vs placebo + ACE. OS data were immature at the first interim OS analysis, and the numerical OS improvement of bev + ACE was not shown vs placebo + ACE; OS follow-up will continue. No new safety signals were observed. Clinical trial information: jRCT2080224946. Research Sponsor: Chugai Pharmaceutical Co, Ltd; F. Hoffmann-La Roche, Ltd.

n (%)	Bev + ACE (n=166)	Placebo + ACE (n=164)
All-grade AE	165 (99.4)	163 (99.4)
Any-grade TRAE[a]	165 (99.4)	162 (98.8)
Grade 3/4 TRAE[a]	142 (85.5)	141 (86.0)
Grade 5 TRAE[a]	5 (3.0)	8 (4.9)
Serious TRAE[a]	58 (34.9)	56 (34.1)
AE leading to study drug withdrawal	34 (20.5)	27 (16.5)
AE leading to study drug modification/interruption	127 (76.5)	119 (72.6)
TR-AESI[a]	65 (39.2)	52 (31.7)

AESI, AE of special interest.
[a]AEs related to any study drug.

LBA8002 **Oral Abstract Session**

BEAT-meso: A randomized phase III study of bevacizumab (B) and standard chemotherapy (C) with or without atezolizumab (A), as first-line treatment (TX) for advanced pleural mesothelioma (PM)—Results from the ETOP 13-18 trial.

Sanjay Popat, Enriqueta Felip, Urania Dafni, Anthony Pope, Susana Cedres Perez, Riyaz N.H. Shah, Filippo de Marinis, Laura Cove Smith, Reyes Bernabe Caro, Martin Früh, Kristiaan Nackaerts, Laurent Greillier, Amina Scherz, Bartomeu Massuti, Saemi Schaer, Spasenija Savic Prince, Heidi Roschitzki-Voser, Barbara Ruepp, Solange Peters, Rolf A. Stahel, for the ETOP 13-18 BEAT-meso Collaborators; Royal Marsden Hospital NHS Foundation Trust, London, United Kingdom; Medical Oncology Service, Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; National and Kapodistrian University of Athens and Frontier Science Foundation- Hellas, Athens, Greece; Clatterbridge Cancer Centre, Liverpool, United Kingdom; Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; Maidstone and Tunbridge Wells NHS Trust, Kent, United Kingdom; European Institute of Oncology, Milan, Italy; The Christie NHS Foundation Trust, Manchester University, Manchester, United Kingdom; Hospital Universitario Virgen del Rocio, Seville, Spain; Kantonsspital St. Gallen, St. Gallen, Switzerland; KU Leuven, University Hospitals Leuven, Leuven, Belgium; Assistance Publique-Hôpitaux de Marseille (AP-HM), Aix Marseille University (AMU), Marseille, France; Department of Medical Oncology, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland; Alicante University Hospital Isabial, Alicante, Spain; Swiss Group for Clinical Cancer Research (SAKK), Bern, Switzerland; Institute of Medical Genetics and Pathology, University Hospital Basel, University of Basel, Basel, Switzerland; ETOP IBCSG Partners Foundation, Bern, Switzerland; Lausanne University Hospital, Centre Hospitalier Universitaire Vaudois (CHUV), Lausanne, Switzerland

8003 Oral Abstract Session

Feasibility and safety of neoadjuvant nivolumab and chemotherapy for resectable diffuse pleural mesotheliomas: Results of a prospective pilot study.

Michael Offin, Yonit Lavin, Matthew Zatzman, Jennifer L. Sauter, Nicholas Ceglia, William D. Travis, Rania G. Aly, Andreas Rimner, Annemarie Shepherd, Charles B. Simone II, Mark G. Kris, Michelle S. Ginsberg, Andrew Chow, Alvaro Quintanal-Villalonga, Sohrab P Shah, Charles M. Rudin, Valerie W. Rusch, Prasad S. Adusumilli, Marjorie Glass Zauderer; Memorial Sloan Kettering Cancer Center, New York City, NY

Background: Diffuse pleural mesotheliomas (DPM) are an aggressive malignancy where even patients with potentially resectable disease have poor outcomes. With an evolving understanding of the role of pleurectomy/decortication (P/D) as the standard of care for resectable disease, the need to improve upfront therapies is more urgent. Here we report the results of our single institution prospective pilot study of nivolumab with platinum (cisplatin/carboplatin) and pemetrexed prior to P/D for patients with resectable DPM (NCT04162015). **Methods:** Patients deemed operable and resectable by a multidisciplinary team received 2 cycles of neoadjuvant nivolumab, pemetrexed, and platinum followed by P/D. Subsequent therapy was at the physician's discretion. Using a minimax Simon two-stage design, the primary objective was defined as attempted P/D within 30 days of the planned surgery date. Secondary objectives included evaluating safety, overall survival (OS) from diagnosis, and progression free survival (PFS). Tumor tissue and plasma were collected for exploratory analyses such as immune cell profiling and pathologic response. Using single cell RNA sequencing (scRNAseq), we explored DPM transcriptional heterogeneity and treatment-associated tumor microenvironment (TME) changes. **Results:** 22 patients received neoadjuvant chemo-immunotherapy and 19 underwent attempted P/D (2 progressed and 1 declined surgery). 68% were men (13/19), 89% were epithelioid (17/19; remaining 2 were biphasic), and the median age at diagnosis was 72 (range: 33-80). No patient experienced pre-operative toxicity precluding P/D. 95% (18/19) of patients underwent P/D within 30 days of the planned date; 1 patient had biopsy-proven tumor flare after cycle 2 and had surgery at day +37. As of January 2024, median OS for the 19 patients that went for attempted P/D was 41.0 mos (median follow up: 25.3mos). OS for those who underwent R1 resections (n = 12) was not reached and for R2 (n = 7) was 31.4 mos (p = 0.67; HR 1.43, 95% CI 0.28-7.30). 26% of specimens (5/19) had $\leq$ 10% viable tumor cells on the resection; there was no clear correlation with outcomes. scRNAseq was performed on 15 resection specimens with available material. Comparing patients with PFS greater than or less than 12mos (PFS12), we found significantly increased abundance of CD8 cytotoxic T cells, and ISG+ (interferon stimulated) T cells. **Conclusions:** Neoadjuvant platinum, pemetrexed, and nivolumab was reliably able to be given to patients with DPM without impacting their ability to undergo P/D. The encouraging OS of this cohort to date, and tolerance of the regimen, highlights the importance of patient selection and preoperative treatments when considering P/D. Ongoing exploratory analyses will profile the cellular and transcriptional landscape of DPM and identify correlates of response to neoadjuvant chemo-immunotherapy. Clinical trial information: NCT04162015. Research Sponsor: Bristol Myers Squibb; National Institutes of Health/National Cancer Institute [P30 CA008748, 2022].

8004 Oral Abstract Session

Adjuvant icotinib of 12 months or 6 months versus observation following adjuvant chemotherapy for resected EGFR-mutated stage II–IIIA non-small-cell lung cancer (ICTAN, GASTO1002): A randomized phase 3 trial.

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Background: The efficacy, safety and ideal treatment duration of adjuvant icotinib (first-generation EGFR tyrosine kinase inhibitor) for patients with completely resected EGFR-mutated non-small-cell lung cancer (NSCLC) after adjuvant chemotherapy were not known in 2014, when this study was initiated. This phase 3 trial investigated whether icotinib following adjuvant chemotherapy improves clinical outcomes compared with observation in stage II-IIIA NSCLC harboring EGFR mutation. **Methods:** This is a multicenter, randomized, open-label, phase 3 trial. From July 2014 to December 2021, patients with completely resected, EGFR-mutated, stage II-IIIA NSCLC after platinum-based adjuvant chemotherapy were enrolled. Patients were assigned in a 1:1:1 ratio to receive icotinib (125mg, three times daily) for 12 months, icotinib for 6 months or to observation. The primary endpoint was disease-free survival (DFS) in the intention-to-treat population. **Results:** This trial was terminated early due to slow accrual.A total of 251 patients were randomized, with 84 patients in the 12-month icotinib group, 84 patients in the 6-month icotinib group, and 83 patients in the observation group. Baseline characteristics were balanced between the groups. After a median follow-up of 61.4 months, 6 months of icotinib significantly improved DFS (HR: 0.41, 95% CI, 0.27-0.62; P = 0.000025) and overall survival (OS, HR: 0.56, 95% CI, 0.32-0.98; P = 0.041) compared with observation. Adjuvant icotinib of 12 months also significantly improved DFS (HR: 0.40, 95% CI, 0.27-0.61; P = 0.000014) and OS (HR: 0.55, 95% CI, 0.32-0.96; P = 0.035) compared with observation. Adjuvant icotinib of 12 months did not improve DFS (HR: 0.97; P = 0.89) and OS (HR: 1.00; P = 0.99) compared with 6 months of this drug. Median DFS was 61.8 months (95% CI, 43.3 to 80.3) for the 12-month icotinib group, 63.2 months (95% CI, 44.8 to 81.6) for the 6-month icotinib group compared with 23.7 months (95% CI, 16.5 to 30.9) for the observation group. The 5-year DFS and OS for the 12-month icotinib, 6-month icotinib and observation groups were 51.3%, 50.1% and 24.8%; and 74.5%, 74.0% and 65.1%; respectively. No differences in efficacy pertaining to icotinib duration were found in any of the subgroups. Rates of adverse events of grade 3 or higher were 8.3%, 5.9% and 2.4% for the 12-month icotinib, 6-month icotinib and observation groups, respectively. The safety profile remained similar to the previous reports for icotinib. **Conclusions:** Adjuvant icotinib for 12 months and 6 months provide a significant DFS and OS benefit compared with observation in patients with completely resected EGFR-mutated stage II-IIIA NSCLC with a manageable safety profile. Nevertheless, 12 months of icotinib had no additional benefit compared with 6 months. Clinical trial information: NCT01996098. Research Sponsor: None.

8005 Oral Abstract Session

Molecular residual disease (MRD) analysis from the ADAURA trial of adjuvant (adj) osimertinib in patients (pts) with resected EGFR-mutated (EGFRm) stage IB–IIIA non-small cell lung cancer (NSCLC).

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Background: Osimertinib (osi) is a third-generation, central nervous system-active EGFR-TKI, that potently and selectively inhibits EGFR-TKI sensitizing and EGFR T790M resistance mutations. Adj osi (3 years [yrs]) is recommended for resected EGFRm stage IB–IIIA NSCLC, based on significant improvements in disease-free survival (DFS) and overall survival (OS) in the Phase III ADAURA study (NCT02511106). A trend towards an increased DFS event rate beyond 3 yrs suggests some pts may benefit from longer adj osi treatment (tx). We explored if plasma ctDNA-based, tumor-informed MRD could predict disease recurrence. **Methods:** Eligible pts (≥18 yrs [≥20 in Japan/Taiwan], WHO PS 0/1 with completely resected EGFRm [Ex19del/L858R] stage IB, II or IIIA [AJCC 7th edition] NSCLC) were randomized 1:1 to osi 80 mg once daily or placebo (pbo) until disease recurrence, tx completion (up to 3 yrs), or a discontinuation criterion was met. Personalized MRD panels (RaDaR, NeoGenomics) were used, comprised of ≤50 tumor-specific variants, based on whole exome sequencing of resected tumor tissue (variants identified in germline DNA removed). Plasma sample collection: baseline (BL; at randomization surgery and adj Ctx, if received), on tx (every 12 weeks [wks]), tx discontinuation, and post-tx completion (wk 12, wk 24, then every 24 wks until 5 yrs). Plasma samples were analyzed for detection of ctDNA (MRD+). Molecular recurrence or DFS (MRD/DFS) was defined as time from randomization to post-BL MRD+, disease recurrence, or death and was compared across arms. DFS was investigator-assessed. **Results:** Of 682 pts randomized, 245 (36%) had samples required to produce MRD panels, which were evaluable for 220 (32%) pts across both arms. In the osi vs pbo arms, 5/112 (4%) vs 13/108 (12%) pts were MRD+ at BL; 4/5 pts became MRD− during osi tx vs 0/13 pts on pbo. On tx, MRD detection had clinical sensitivity of 65% (62 MRD+/96 DFS+), specificity of 95% (118 MRD−/124 DFS−) and preceded a DFS event by a median (95% CI) of 4.7 (2.2, 5.6) months (mos) across both arms. Median follow-up time from randomization was 44.2 (95% CI 42.4, 49.1) and 19.1 (95% CI 11.1, 28.3) mos for osi and pbo arms, respectively. Overall, 86% (95% CI 78, 92) vs 36% (95% CI 27, 45) pts in the osi vs pbo arms were MRD/DFS event free at 36 mos (HR: 0.23; 95% CI 0.15, 0.36). MRD/DFS events in the osi arm were detected at any time post-BL in 28 (25%) pts, of whom 19/28 (68%) had events post-adj osi. Most (11/19 [58%]) MRD/DFS events detected occurred within 12 mos of osi tx completion. **Conclusions:** MRD+ preceded DFS events in most pts with a median lead time of 4.7 mos across both arms. MRD− was maintained for most pts during adj osi tx with the majority of MRD/DFS events occurring after osi tx completion. MRD detection could potentially identify a subset of pts likely to benefit from longer adj osi. Clinical trial information: NCT02511106. Research Sponsor: AstraZeneca.

8006 Oral Abstract Session

Health-related quality of life (HRQoL) results for adjuvant alectinib vs chemotherapy in patients with resected *ALK*+ non-small cell lung cancer (NSCLC): Data from ALINA.

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Background: ALINA (NCT03456076) is a global, open-label, phase 3, randomized trial evaluating the efficacy and safety of adjuvant alectinib versus chemotherapy in patients with resected stage IB (≥4 cm)–IIIA, *ALK*+ NSCLC. A significant disease-free survival benefit was observed with alectinib vs chemotherapy (HR 0.24, 95% CI: 0.13–0.43, p<0.0001; N=257 patients in the ITT). In the adjuvant setting, where patients have received surgery with curative intent, the impact of treatment on HRQoL is an important clinical consideration. We report HRQoL results from ALINA. **Methods:** Patients ≥18 years old with ECOG PS 0/1 and completely resected, stage IB–IIIA, *ALK*+ NSCLC (UICC/AJCC 7th edition) were randomized 1:1 to receive oral 600 mg alectinib twice-daily for 2 years, or four 21-day cycles of platinum-based chemotherapy. HRQoL was an exploratory endpoint measured using the Short Form-36 version 2 (SF-36v2) health survey, which assesses functional health and well-being across 8 domains and 2 aggregated summary scores: the physical (PCS) and mental (MCS) component summary scores. Patients completed the SF-36v2 at baseline, every 3 weeks to Week 12, then every 12 weeks until disease recurrence, withdrawal of consent, death, or Week 96 (or equivalent post-chemotherapy follow-up visit). SF-36v2 was scored using norm-based scoring relative to the 2009 US general population (mean ± standard deviation: 50 ± 10), with higher scores indicating better health. Within-group minimal important differences (MIDs) were used as benchmarks for each domain, MCS and PCS. Data cut-off: 26 June 2023. **Results:** Completion rates were generally high (>90%) throughout the study. At baseline, most mean scores were low (<50) and were similar between study arms. With alectinib, mean scores were ≥50 for the Bodily Pain, Mental Health and Vitality domains by Week 96, suggesting that patients functioned as well as the general population on these aspects. The mean change from baseline met or exceeded MIDs for 5 domains and MCS by Week 12, and exceeded MIDs for 6 domains, MCS and PCS by Week 96. In the chemotherapy arm, mean scores were low during treatment; mean change from baseline for General Health and Vitality exceeded negative MIDs, indicating worsening in these domains. Mean scores improved in the post-chemotherapy period; in the final assessment, mean scores were ≥50 for the Bodily Pain, Mental Health and Vitality domains, and MIDs were met or exceeded for MCS, PCS and 5 domains. **Conclusions:** Alectinib demonstrated an improvement in most domains of HRQoL by Week 12, followed by maintenance of HRQoL on all 8 domains, MCS and PCS to Week 96. With chemotherapy, HRQoL was low during treatment, but improved in the post-chemotherapy period. Together with the DFS benefit seen in ALINA, these data support alectinib as an important new adjuvant treatment for patients with resected *ALK*+ NSCLC. Clinical trial information: NCT03456076. Research Sponsor: F. Hoffmann-La Roche Ltd.

LBA8007 **Oral Abstract Session**

Clinical outcomes with perioperative nivolumab (NIVO) by nodal status among patients (pts) with stage III resectable NSCLC: Results from the phase 3 CheckMate 77T study.

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8008 Oral Abstract Session

A phase II randomized trial evaluating consolidative nivolumab in locally advanced non-small cell lung cancer post neoadjuvant chemotherapy plus nivolumab and concurrent chemoradiotherapy (GASTO-1091).

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Background: Enhancing clinical outcomes in resectable non-small cell lung cancer (NSCLC) has been associated with neoadjuvant or perioperative administration of nivolumab. However, the efficacy and safety of consolidation nivolumab versus observation following neoadjuvant chemotherapy plus nivolumab, hypofractionated radiotherapy and concurrent chemotherapy (hypo-CCRT) in patients with unresectable stage III NSCLC remain underexplored. **Methods:** Conducted as a randomized, multi-center, phase 2 trial in patients with unresectable stage IIIA-C NSCLC, this study enrolled individuals aged 18 to 75 with an ECOG performance status of 0 or 1. Neoadjuvant therapy consisted of docetaxel, cisplatin, and nivolumab (360mg every 3 weeks for 2 cycles), followed by hypo-CCRT. Patients without disease progression or G2+ pneumonitis after hypo-CCRT were randomly assigned to receive nivolumab (360 mg every 3 weeks for up to 12 months) or undergo observation. Randomization factors included age, sex, smoking history, and EGFR mutation status. The primary endpoint was progression-free survival (PFS) from randomization, with preplanned analysis results reported herein. The trial is registered with ClinicalTrials.gov, NCT04085250. **Results:** Between Dec 3rd, 2019, and Aug 18th, 2023, 264 patients underwent neoadjuvant therapy, 242 received hypo-CCRT, and 172 were randomly assigned to nivolumab consolidation (n = 86) or observation (n = 86) post hypo-CCRT. At the January 31, 2024, data cutoff, the median follow-up for all randomized patients was 22.8 months. Nivolumab consolidation exhibited significantly longer PFS compared to observation (median not reached vs. 12.2 months [95% CI 6.2-18.1]; hazard ratio 0.49 [95% CI 0.31-0.79], p = 0.002). The 12-month and 18-month PFS rates were 72.6% and 64.8% in the consolidation group, contrasting with 52.5% and 42.3% in the observation group. Grade 3-4 nonhematological adverse events occurred in 14.0% (37/264) during neoadjuvant therapy and hypo-CCRT. Following randomization, grade 3-5 adverse events occurred in 7.0% (6/86) with consolidation (G3 pneumonitis, 2.3%; G5 pneumonitis, 1.2%; G3 proximal bronchial tree toxicity, 3.5%) and 4.6% (4/86) with observation (G3 pneumonitis, 2.3%; G3 proximal bronchial tree toxicity, 2.3%). **Conclusions:** Consolidation with nivolumab after neoadjuvant chemotherapy plus nivolumab and hypo-CCRT demonstrates effectiveness and tolerability for patients with unresectable stage III NSCLC. Extended follow-up is essential for confirming these findings. Clinical trial information: NCT04085250. Research Sponsor: None.

8009 Oral Abstract Session

Taiwan national lung cancer early detection program for heavy smokers and non-smokers with family history of lung cancer.

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Background: Lung cancer incidence in Taiwan has been rising with the epidemiological profiles distinct from Western country. Notably, nonsmoking lung cancers accounts for more than 60% and half of lung cancers were diagnosed in advanced stages. For early detection, a national program is therefore initiated to offer biennial low-dose computed tomography (LDCT) screening for heavy smokers and subjects with lung cancer family history (LCFH). Here, we report basic screening findings, analyze relevant effectiveness in reducing advanced lung cancer, and project the potential benefit of mortality reduction. **Methods:** Taiwan National Lung Cancer Early Detection Program was launched on July 1, 2022 to offer heavy smokers (30 pack-years) and nonsmokers (including light smokers) with a LCFH aged 45-74 years for female and aged 50-74 years for male. This is a continuous screening program using before and after study design for evaluation. We provided the overall first-year basic screening findings until Dec 31, 2023 and did per protocol analysis of stage II+ cancer reduction in comparison with tumor stage distribution in the year preceding the introduction of the national program. The corresponding findings were presented for subjects with LCFH and heavy smokers. The result for heavy smoker was compared with those per-protocol findings from previous randomized controlled trials. The potential mortality reduction was further projected. **Results:** A total of 78,000 individuals participated in this program, male 44,381 (56.9%) female 33,619 (43.1%); 31,111 participants (39.9%) were heavy smokers, 43,853 (56.2%) nonsmokers but with a LCFH, and 3,036 (3.9%) had both risk factors. Lung cancer confirmed in 956 subjects by surgery or biopsy, 85.0% were stage 0-1. The lung cancer detection rate was 1.2%. Subjects with a LCFH exhibited a higher detection rate (overall: 1.6%, nonsmokers: 1.7% and light smokers 0.9%) compared to heavy smokers (0.7%) and both (1.1%). Early detection of LDCT led to a statistically significant 77% (51%-89%) of reducing advanced stage of lung cancer, 53% (-3%-78%) reduction for heavy smokers, consistent with the corresponding 36%-64% reduction derived from the NLST trial and the Nelson trial, and 85% (67%-93%) reduction for nonsmokers with a LCFH. The benefit of reducing stage II or severe in conjunction with five-year stage-specific survival rate further projected 55% (10%-78%) of mortality reduction from lung cancer. **Conclusions:** This is the first large-scale LC screening service enrolling 40% heavy smokers and 60% non-smoker with a LCFH. The potential effectiveness of early detection was demonstrated for both targets. As the results based on per-protocol analysis for heavy smoker were consistent with those of previous evidence-based studies the similar and significant intention-to-treat results as before while waiting for the subsequent follow-up would be expected. Research Sponsor: None.

LBA8010 **Rapid Oral Abstract Session**

Neoadjuvant nivolumab (NIVO) + chemotherapy (chemo) vs chemo in patients (pts) with resectable NSCLC: 4-year update from CheckMate 816.

Jonathan Spicer, Nicolas Girard, Mariano Provencio, Changli Wang, Tetsuya Mitsudomi, Mark M. Awad, Everett E. Vokes, Janis M. Taube, Lorena Lupinacci, Gene B. Saylors, Fumihiro Tanaka, Moishe Liberman, Sung Yong Lee, Aurelia Alexandru, Manolo D'Arcangelo, Phuong Tran, Javed Mahmood, Vishwanath Suresh Gharpure, Apurva Bhingare, Patrick M. Forde; McGill University Health Centre, Montreal, QC, Canada; Institut du Thorax Curie-Montsouris, Institut Curie, Paris, France; Hospital Universitario Puerta de Hierro, Madrid, Spain; Tianjin Lung Cancer Center, Tianjin Medical University Cancer Institute & Hospital, Tianjin, China; Kindai University Faculty of Medicine, Ohno-Higashi, Osaka, Japan; Dana-Farber Cancer Institute, Boston, MA; University of Chicago Medicine, Chicago, IL; The Bloomberg–Kimmel Institute for Cancer Immunotherapy, Johns Hopkins Medicine, The Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD; Hospital Italiano de Buenos Aires, Buenos Aires, Argentina; Charleston Oncology, Charleston, SC; University of Occupational and Environmental Health, Kitakyushu, Japan; Centre Hospitalier de l'Universite de Montreal, Montreal, QC, Canada; Korea University Guro Hospital, Korea University College of Medicine, Seoul, South Korea; Institutul Oncologic Bucure□ti Prof. Dr. Alexandru Trestioreanu, Bucharest, Romania; Azienda Unita Sanitaria Locale della Romagna, Ravenna, Italy; Bristol Myers Squibb, Princeton, NJ

8011 Rapid Oral Abstract Session

Outcomes with perioperative durvalumab (D) in pts with resectable NSCLC and baseline N2 lymph node involvement (N2 R-NSCLC): An exploratory subgroup analysis of AEGEAN.

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Background: In the phase 3 AEGEAN study (NCT03800134), perioperative D + neoadj chemotherapy (CT) vs neoadj CT alone significantly improved the primary EPs of event-free survival (EFS) and pathological complete response (pCR; absence of residual viable tumor [RVT] in resection specimen, incl. primary tumor and sampled lymph nodes) with manageable safety in pts with R-NSCLC (modified ITT [mITT] population). Here, we report exploratory analyses of pts in AEGEAN with baseline N2 nodal status. **Methods:** Pts with Tx-naïve R-NSCLC (stage II–IIIB[N2]; AJCC 8th ed) were randomized (1:1) to 4 cycles of platinum-based CT plus D 1500 mg IV or placebo (PBO) Q3W before surgery (Sx), followed by D or PBO (Q4W, 12 cycles) after Sx. The mITT population excluded pts with known *EGFR*/*ALK* alterations. Efficacy was assessed in an mITT subpopulation with baseline N2 nodal status (per investigator). Safety was assessed in all N2 R-NSCLC pts who had ≥1 Tx dose. **Results:** Of 740 pts in the mITT population, 366 (49.5%) had baseline N2 nodal status (D, n = 181; PBO, n = 185). In the N2 subgroup, 83.4% in the D arm and 84.9% in the PBO arm completed 4 cycles of platinum-doublet CT; 77.9% and 77.8%, respectively, had Sx; and 73.5% and 71.9% completed Sx. In the N2 subgroup, similar to the overall mITT population, EFS was prolonged in the D vs PBO arm (HR, 0.63 [95% CI: 0.43–0.90]); rates of pCR (16.6% vs 4.9%; difference, 11.7% [95% CI: 5.6–18.4]) and major pathological response (MPR, ≤10% RVT in primary tumor; 32.6% vs 15.1%; difference, 17.5% [95% CI: 8.8–26.0]) were higher in the D vs PBO arm. While EFS benefit in the D vs PBO arm was similar among pts with single- (HR, 0.61 [95% CI: 0.39–0.94]) or multi-station N2 (HR, 0.69 [95% CI: 0.33–1.38]), pCR benefit was less pronounced in multi-station pts (difference in pCR rate, 13.9% [95% CI: 6.6–21.7] for single-station N2 vs 3.8% [95% CI: −9.2–18.8] for multi-station N2). Among pts in the N2 subgroup who had Sx, similar proportions in the D and PBO arms had open (47.5% vs 50.0%) and minimally invasive procedures (50.4% vs 46.5%); 9.2% vs 11.1% had pneumonectomy (9.2% vs 9.6% in the overall mITT population). Of pts in the N2 subgroup who completed Sx, the proportion with R0 resection in the D vs PBO arm (94.7% vs 91.7%) was similar to that in the overall mITT population. Sx was delayed in a similar proportion who had Sx in the D vs PBO arm (19.9% vs 23.6%, respectively), most commonly for logistical reasons (e.g., scheduling issues). Among 394 pts who received Tx (N2 safety analysis subset; D, n = 200; PBO, n = 194), max grade 3/4 any-cause AEs occurred in 38.5% vs 41.8% in the D and PBO arm, respectively, similar to rates in the overall safety analysis set. **Conclusions:** With clinically meaningful improvement in efficacy, no adverse impact on Sx outcomes and a manageable safety profile, the addition of perioperative D to neoadj CT remains a potential new Tx option for pts with N2 R-NSCLC. Clinical trial information: NCT03800134. Research Sponsor: AstraZeneca.

8012 Rapid Oral Abstract Session

Health-related quality of life (HRQoL) outcomes from the randomized, double-blind phase 3 KEYNOTE-671 study of perioperative pembrolizumab for early-stage non-small-cell lung cancer (NSCLC).

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Background: Neoadjuvant pembrolizumab + cisplatin-based chemotherapy (neoadj pembro + chemo), resection, and adjuvant (adj) pembro (pembro arm; n=397) significantly improved EFS, OS, pCR, and mPR and had an expected safety profile versus neoadj placebo (pbo) + chemo, resection, and adj pbo (pbo arm; n=400) in patients (pts) with resectable stage II, IIIA, or IIIB (N2) NSCLC. We present prespecified pt-reported outcome (PRO) endpoints from KEYNOTE-671. **Methods:** Pts completed EORTC QLQ-C30 and QLQ-LC13 questionnaires at baseline (BL), the last scheduled presurgery visit, adj cycles 1–4, 7, 10, and 13, and each post treatment visit. A constrained longitudinal data analysis model was used to estimate least squares mean (LSM) score changes from BL to neoadj wk 11 and adj wk 10 (latest time of ≥60% completion and ≥80% compliance) in QLQ-C30 global health status (GHS)/QoL, physical functioning (PF), role functioning (RF), and dyspnea and QLC-LC13 cough and chest pain in all treated pts who completed ≥1 PRO assessment. Data are from interim analysis 2 (10 Jul 2023 cutoff). **Results:** Across arms, questionnaire completion was ≥87% at neoadj wk 11 and ≥62% at adj wk 10; compliance was ≥87% and ≥92%, respectively. There were no differences in LSM change from BL in the neoadj or adj phase for any PRO score (Table). **Conclusions:** Adding perioperative pembro maintained HRQoL in both the neoadj and adj settings versus neoadj chemo and surgery alone in pts with resectable early-stage NSCLC. Together with the significant efficacy improvements and absence of new safety signals, HRQoL data support the perioperative pembro regimen as a new standard of care. Clinical trial information: NCT03425643. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

	LSM (95% CI) Change from BL to Neoadj wk 11, Pembro Arm	LSM (95% CI) Change from BL to Neoadj wk 11, Pbo Arm	Difference (95% CI), Neoadj Phase	LSM (95% CI) Change from BL to Adj wk 10, Pembro Arm	LSM (95% CI) Change from BL to Adj wk 10, Pbo Arm	Difference (95% CI), Adj Phase
QLQ-C30	N=390	N=395		N=395	N=397	
GHS/QoL	-9.31 (-11.67, -6.94)	-10.73 (-13.07, -8.40)	1.43 (-1.64, 4.49)	-1.52 (-3.67, 0.63)	-3.74 (-5.96, -1.52)	2.22 (-0.58, 5.02)
PF	-6.30 (-8.00, -4.60)	-6.65 (-8.32, -4.97)	0.35 (-1.99, 2.68)	-5.06 (-6.77, -3.35)	-5.81 (-7.58, -4.04)	0.75 (-1.63, 3.13)
RF	-9.43 (-12.00, -6.87)	-10.47 (-13.00, -7.94)	1.04 (-2.41, 4.49)	-4.86 (-7.39, -2.34)	-7.00 (-9.62, -4.39)	2.14 (-1.33, 5.61)
Dyspnea	2.16 (-0.35, 4.67)	3.94 (1.46, 6.42)	-1.77 (-5.10, 1.55)	5.78 (2.96, 8.59)	9.64(6.73, 12.55)	-3.86 (-7.63, -0.09)
QLQ-LC13	N=390	N=394		N=395	N=397	
Cough	-11.40 (-13.92, -8.88)	-9.57 (-12.07, -7.08)	-1.82 (-5.01, 1.36)	-6.78 (-9.73, -3.84)	-4.63 (-7.67, -1.59)	-2.15 (-5.95, 1.65)
Chest pain	1.13 (-1.02, 3.28)	0.41 (-1.72, 2.54)	0.72 (-2.03, 3.47)	2.99 (0.38, 5.59)	6.03 (3.33, 8.73)	-3.04 (-6.53, 0.45)

Increases in GHS/QoL and functioning scores indicate improvement. Decreases in symptom scores indicate improvement.

8013 Rapid Oral Abstract Session

Global retrospective study comparing consolidation ALK tyrosine kinase inhibitors (TKI) to durvalumab (durva) or observation (obs) after chemoradiation (CRT) in unresectable locally-advanced ALK+ non-small cell lung cancer (NSCLC).

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Background: For patients (pts) with unresectable locally-advanced NSCLC, standard of care involves durva consolidation after concurrent CRT, although its benefit in ALK+ tumors is unclear. The ALINA trial demonstrated adjuvant efficacy of alectinib in resected ALK+ NSCLC, but the optimal consolidation strategy for unresectable locally-advanced ALK+ NSCLC remains elusive. **Methods:** This multi-institutional international retrospective analysis included pts with stage III unresectable ALK+ NSCLC who received an ALK TKI, durva, or obs alone after concurrent CRT between 2015-2022. Baseline characteristics of age, sex, smoking history, and PD-L1 status were collected. Clinical outcomes including real-world progression-free survival (rw-PFS), overall survival (OS), and treatment-related adverse events (trAE) as defined using CTCAE 5.0 were assessed, and multivariate cox regression models were performed. **Results:** Sixty-four pts across 16 institutions were included. The median age was 57 (IQR 49-66) and 61% were females. The majority had adenocarcinoma (97%) and had never smoked (58%). 15 received ALK TKI (10 alectinib, 3 crizotinib, 1 brigatinib, 1 lorlatinib), 30 received durva, and 19 received obs alone. There was no significant difference in stage of cancer (IIIA, B, or C) or PD-L1 status among groups. After adjusting for stage and age at CRT initiation, median rw-PFS was significantly longer for ALK TKI (rw-PFS not reached [NR], 95% CI 22.7-NR) vs durva (11.3 months (mo), 95% CI 9.2-18.5, p= 0.005, HR = 0.12) or obs (7.4 mo, 95% CI 3.4-12.5, $p < 0.0001$). Two (13%) pts progressed on ALK TKI. 25 pts (83%) progressed on durva leading to treatment with ALK TKI in 23, and 18 (95%) progressed while under obs leading to treatment with ALK TKI in 15. 3-year OS was 100% for ALK TKI vs 90.5% for durva vs 63.5% for obs. Median OS was NR (95% CI NR-NR) for both ALK TKI and durva vs 70.6 mo (24.9-NR) in the obs group (p= 0.03 for both ALK TKI and durva compared to obs). Median duration of therapy was 24.7 mo with ALK TKI and 6.5 mo with durva. Grade ≥3 trAE occurred in 27%, 7%, 6% of pts treated with ALK TKI (1 fatigue, 1 diarrhea, 1 hyperbilirubinemia, 1 pneumonitis), durva (1 fatigue, 1 neutropenia), and obs (1 neutropenia) respectively. Treatment discontinuation due to toxicity occurred in 4 (27%) with ALK TKI and in 3 (10%) with durva. **Conclusions:** In this retrospective study of stage III ALK+ NSCLC, consolidation ALK TKI demonstrated clinically meaningful improvement in PFS and OS over durva and obs, while showing a slightly higher rate of trAE over dura and obs. Furthermore, we show a high rate of progression following CRT alone in ALK+ NSCLC. These findings underscore the need for prospective molecularly driven trials to determine the optimal consolidation therapy for unresectable ALK+ NSCLC. Research Sponsor: None.

8014 Rapid Oral Abstract Session

Overall survival of adebrelimab plus chemotherapy and sequential thoracic radiotherapy as first-line treatment for extensive-stage small cell lung cancer.

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Background: The phase 3 trial (CAPSTONE-1) showed that adebrelimab (PD-L1 antibody) combined with first-line chemotherapy could prolong overall survival (OS) in patients (pts) with extensive-stage small cell lung cancer (ES-SCLC). Previous studies have shown that radiotherapy can enhance the immunogenicity of tumors, indicating the great potential of combining radiotherapy with immunotherapy. The purpose of this study was to explore the efficacy and safety of adebrelimab combined with chemotherapy and sequential thoracic radiotherapy (TRT) as first-line therapy for ES-SCLC. **Methods:** Key inclusion factors were 18-75 years old, histologically or cytologically confirmed ES-SCLC, ECOG performance status 0-1, no previous systematic treatment. Pts received 4~6 cycles of adebrelimab (20mg/kg, D1, q3w) combined with EP/EC (etoposide, 100mg/m^2, D1-3, q3w and cisplatin, 75mg/m^2, D1, q3w or carboplatin, AUC = 5, D1, q3w). Pts with response sequentially received adebrelimab combined with consolidate TRT (≥30 Gy in 10 fractions or ≥50 Gy in 25 fractions, involved-field irradiation). Pts then entered the maintenance treatment stage with adebrelimab until disease progression or intolerable side effects. The primary endpoint was OS. The secondary endpoints included objective response rate (ORR), disease control rate (DCR), progression-free survival (PFS) and safety. **Results:** From October 2020 to April 2023, 67 pts with ES-SCLC were enrolled. Most patients were male (83.6%), current or former smokers (65.7%) with an ECOG performance status of 1 (95.5%). 22 (32.8%) patients were diagnosed with brain metastasis and 21 (31.3%) patients had liver metastasis at baseline. 45 patients received sequential TRT as planned. All patients were included in the safety and efficacy analysis population. At data cutoff (December 22, 2023), the median follow-up duration was 17.7 months. The median OS was 21.4 months (95% CI: 17.2—not reached months). 1-year and 2-year OS rate were 74.1% (95% CI: 63.6-86.4%) and 39.7% (95% CI: 25.5-61.9%). The median PFS was 10.1 months (95% CI: 6.9—15.5 months). The confirmed ORR was 71.6% (95% CI: 59.3-82.0%) and DCR was 89.6% (95% CI: 79.7-95.7%). The most common grade 3 or higher treatment-related adverse events included neutrophil count decreased (41.8%), white blood cell count decreased (19.4%) and lymphocyte count decreased (13.4%). No unexpected adverse events were observed. **Conclusions:** Adebrelimab plus chemotherapy and sequential TRT as first-line therapy for ES-SCLC showed promising efficacy and acceptable safety. Clinical trial information: NCT04562337. Research Sponsor: Jiangsu Hengrui Pharmaceuticals Co., Ltd.

8015 Rapid Oral Abstract Session

DeLLphi-301: Tarlatamab phase 2 trial in small cell lung cancer (SCLC)—Efficacy and safety analyzed by presence of brain metastasis.

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Background: Brain metastases affect 40%–70% of patients with SCLC. Tarlatamab, a BiTE (bispecific T-cell engager) immunotherapy targeting delta-like ligand 3, demonstrated durable responses and promising survival outcomes in patients with previously treated SCLC (10 mg Q2W) (DeLLphi-301; NCT05060016; Ahn M-J, *N Engl J Med* 2023). Here, tarlatamab efficacy and safety in patients with baseline brain metastases from DeLLphi-301 are reported. **Methods:** The DeLLphi-301 study design has been published. Patients with treated, stable, asymptomatic brain metastases were included. Subgroup analyses for efficacy (blinded independent central review [BICR] assessments) and safety by presence or absence of baseline brain metastases were performed. Intracranial activity was assessed. Post enrollment, brain imaging was performed if clinically indicated. **Results:** As of 27 June 2023, 186 patients had received tarlatamab (ECOG PS: 0–1; median prior lines of therapy: 2; median follow-up: 13.6 months). 29% of patients (54/186) had treated and stable brain metastases at baseline. Most patients (91%) with brain metastases had received prior local radiotherapy; 6% each had received surgery only or both radiotherapy and surgery. Overall systemic objective response rate (ORR; RECIST 1.1) was 45.3% in patients with brain metastases and 32.6% in patients without brain metastases (Table). Any grade immune effector cell associated neurotoxicity syndrome and associated neurological events occurred in 24.1% of patients with brain metastases and in 13.6% of patients without brain metastases; grade ≥ 3 events occurred in the 100 mg group only: 9.4% and 1.8%, respectively, and did not lead to tarlatamab discontinuation in any patient with brain metastases. Analysis of intracranial activity will be presented. **Conclusions:** Tarlatamab showed promising efficacy and a favorable benefit-risk profile in patients with previously treated SCLC and stable brain metastases. Clinical trial information: NCT05060016. Research Sponsor: Amgen Inc.

	10 mg (N = 99)		100 mg (N = 87)		Overall (N = 186)	
Baseline brain metastases	Yes (n=22)	No (n=77)	Yes (n=31)	No (n = 55)	Yes (n=53)	No (n=132)
ORR* (95% CI)	54.5 (32.2, 75.6)	36.4 (25.7, 48.1)	38.7 (21.8, 57.8)	27.3 (16.1, 41.0)	45.3 (31.6, 59.6)	32.6 (24.7, 41.3)
Responders with sustained response at 12 months, KM estimate, % (95% CI)	54.7 (22.2, 78.5)	51.8 (30.3, 69.6)	61.4 (26.6, 83.5)	41.3 (15.8, 65.4)	57.6 (34.0, 75.5)	48.0 (31.1, 63.0)
Progression-free survival*, median, months (95% CI)	7.1 (3.9, NE)	4.0 (2.8, 5.6)	4.1 (2.6, 8.1)	2.9 (1.5, 4.3)	5.6 (3.9, 8.2)	3.9 (2.7, 4.4)
Overall survival†, median, months (95% CI)	14.3 (14.3, NE)	NE (9.3, NE)	NE (NE, NE)	NE (8.9, NE)	NE (14.3, NE)	NE (10.1, NE)

*N = 185; 1 enrolled pt in the 100 mg group did not have a measurable target lesion at baseline as assessed by BICR using RECIST 1.1 criteria.

†OS data yet to mature.

CI, confidence interval; KM, Kaplan-Meier; NE, not estimable.

Smoking history requirement and lung cancer (LC) screening (LCS) eligibility disparities.

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Background: LCS eligibility criteria are not optimal. US Preventive Services Task Force 2021 criteria (USPSTF21) expanded eligibility, but race and sex disparities persist. We evaluated how 4 modified criteria impact LCS eligibility. **Methods:** We analyzed data from all persons enrolled into LCS and a non-screening detected Lung Nodule Program (LNP) in a prospective community-based cohort. The LNP used Fleischner Society guidelines. We compared sex, race, and Area Deprivation Index (ADI) of LCS-eligible persons and LC patients diagnosed based on USPSTF21 (Age 50-80, 20 pack-years [PY], 15 year quit duration [QD]) versus 4 more-relaxed smoking history criteria in LNP including the new American Cancer Society (ACS) criteria (Group 4, Table). **Results:** Of 38,740 individuals from 2015-2023, 11,886 had LCS and 26,854 were from LNP. Expanded criteria increased the total eligible over USPSTF21 from 3939, to 4572, 4611, 4950, 5747 in Groups 2-5, respectively. LC was detected in 3.7% of LDCT (17.4% of those with Lung-RADS 3/4), and in 21%, 20%, 19%, 19%, and 18% of LNP Groups 1-5; number needed to treat (NNT) was 26.8 (LDCT), 5.8 (LDCT Lung-RADS 3/4), and 4.9, 4.9, 5.2, 5.2, 5.5 in Groups 1-5. LC was most frequently adenocarcinoma (41-51%) or squamous (21-30%); with similar stage across groups (47-48% stage I/II). LC was diagnosed in 17%, 11%, 14%, and 13% of additional eligible persons vs. 21% in USPSTF21 (Table). The additional eligible individuals with LC were 42%, 58%, 40%, and 46% female in Groups 2-5. We compared % female in Group 3 with LNP (58 v 51%, p=.25) and LCS (58 v 52%, p=.22). In terms of race, additional eligible individuals were 11%, 47%, 10%, and 24% Black in Groups 2-5; with significant differences between Group 3 and both LNP (47 v 25%, p<.001) and LCS (47 v 16%, p<.001) cohorts. These groups (2-5) were 26%, 38%, 29%, and 33% in the highest (poorest) ADI quintile, with no differences between Group 3 and LNP (38 v 36%, p=.66) or LCS (38 v 42%, p=.56). Group 3 / 5 criteria yielded a 17% / 46% increase in persons screened, and a 9.5% / 28% increase in LC identified over USPSTF21. **Conclusions:** Relaxed smoking history requirements provided better access to LCS while maintaining diagnostic efficiency in terms of NNT. The shift from 20 PY to 20 years reduced race- and sex- based disparities in LCS eligibility and LC diagnosis, while still reaching the most socially disadvantaged groups. Research Sponsor: None.

			Additional Eligible with Expanded Criteria			
	Full LNP	Group 1	Group 2	Group 3	Group 4	Group 5
Criteria		USPSTF21	Age >50, 20 PY, other risk factor (NCCN)	Age 50-80, 20 Y, QD <15	Age 50-80, 20 PY, No QD (ACS)	Age 50-80, 20 PY or 20Y, No QD
#With lung cancer / #screened (%)	1702 / 26854	810 / 3939	221 / 1312	79 / 707	144 / 1011	231 / 1843
	(6.3)	(20.6)	(17)	(11)	(14)	(13)
Persons screened,%						
Female	56	49	42	56	40	48
Black	29	21	13	40	14	26
Highest quintile ADI	36	37	30	40	30	34
Persons screened with lung cancer,%						
Female	52	51	42	58	40	46
Black	25	21	11	47	10	24
Highest quintile ADI	36	39	26	38	29	33

8017 Rapid Oral Abstract Session

Niraparib and dostarlimab efficacy in patients with platinum-sensitive relapsed mesothelioma: MIST5, a phase IIa clinical trial.

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Background: Prognosis for patients with relapsed malignant mesothelioma remains dismal. Mesotheliomas exhibit multiple somatic alterations in DNA damage response (DDR) genes which may in part, account for platinum sensitivity. Inhibition of poly ADP ribose polymerase or the immune checkpoint PD1 have demonstrated meaningful clinical activity in this setting [1,2]. We hypothesized that in patients exhibiting platinum-sensitive mesothelioma, a combination of PARP and PD1 inhibition would be synergistic. Niraparib (N) and dostarlimab (D) was therefore evaluated in a multi-centre single arm phase IIa clinical trial. Mesothelioma Stratified Therapy 5 (MIST5) trials.gov identifier NCT03654833. **Methods:** Patients with any histological subtype or site of malignant mesothelioma (MM - pleural or peritoneal) were enrolled. Key inclusion factors: histological confirmation of MM with an available archival tissue block, ECOG performance status 0-1, prior platinum-doublet 1st line chemotherapy (any line allowed) with >6 months disease control, evidence of disease progression with measurable disease by CT (mRECIST), and adequate haematological/organ function. Patients received niraparib (N) in combination with dostarlimab (D). The primary endpoint was disease control rate at 12 weeks (DCR12w). The null hypothesis was rejected if ≥ 11 patients had disease control (A'Hern design). Secondary endpoints: DCR at 24 weeks (DCR24w), best objective response rate and toxicity (NCI CTCAE 5.0). Patients could undergo an optional re-biopsy upon disease progression. Tissue was collected at baseline (n=24) to enable multiplex immunofluorescence microscopy, whole exome and RNA transcriptome sequencing. Gut microbiome 16s RNA sequencing also was undertaken at baseline (n=26). **Results:** Between September 2021 and November 2022, 26 patients with MM started treatment and received at least one dose of N + D. Median age: 69.5 (range, 33-85) years; Gender: 80.8% male, 19.2% female. Histology: 80.8% epithelioid, 3.8% Biphasic, 7.7% Sarcomatoid, 7.7% NOS. Performance status: ECOG =0, 7.7%, ECOG=1, 92.3%. Line of therapy: 2nd line 76.9%, 3rd line 23.1%. The median cycles received was 5 (IQR, 3-8) and D was 5 (IQR, 3-8). DCR12w: 65.4% (90% confidence limit (CI, 47.4% –80.6%; 17 of 26 patients), DCR24w: 30.8% (95%CI, 14.3% – 51.8%; 8 of 26 patients). Best responses (within 24w): partial – 15.4% (95%CI, 4.4- 34.9%); stable disease – 65.4% (44.3 – 82.8%); progression – 15.4% (4.4 – 34.9%). Adverse events (any cause): ≥ grade 3 toxicities affected 19.2% of pts. **Conclusions:** MiST5 met its primary endpoint with an overall disease control rate of 80.8%. Analysis of the cellular and molecular correlates of response are ongoing and will be presented.[1] Fennell et al, Lancet Respiratory Medicine 2019 9(6) p593-600; [2] Fennell et al, Lancet Oncology, 2021 22(11) p1530-1540. Clinical trial information: NCT03654833. Research Sponsor: GSK; Asthma and Lung UK.

8018 Rapid Oral Abstract Session

ctDNA-Lung-DETECT: ctDNA outcomes for resected early stage non-small cell lung cancers at 12 months.

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Background: ctDNA Lung DETECT is a multicentre investigator initiated prospective study at 3 thoracic surgery centres in the Greater Toronto Area assessing ctDNA detection and association with recurrence free survival (RFS) in patients with early stage non-small cell lung cancer (NSCLC) (NCT05254782). Patients who have ctDNA detected perioperatively are offered ctDNA Lung RCT, a randomized trial investigating the benefit of adjuvant chemo-immunotherapy in patients where the standard of care is observation alone after surgery (NCT04966663). Herein, we report on ctDNA outcomes at 12 months for patients with resected early stage NSCLC. **Methods:** Patients with stage I (T1-2N0) or multifocal T3-4 < 4cm N0 NSCLC planned for resection at University Health Network consented to plasma ctDNA assessment before and after surgery, and at 12 months post-operatively or relapse using the tumor-informed RaDaR® assay, which detects up to 48 tumor-specific variants in plasma with a Limit of Detection (LoD_{95}) of 0.0011% variant allele fraction. **Results:** From July 2021 to January 2024, 178 patients were enrolled; 115 had sufficient tissue for assessment. Of these, 68/72 patients have 12 month post-resection ctDNA results available (3 withdrew, 1 sample failed). ctDNA was detected pre-operatively in 18 patients; 99% (71/72) had ctDNA clearance post-operatively, and 93% (62/67) remained ctDNA negative at 12 months. Median follow up time was 18.7 months (range 12.0–28.3); 8/72 (11%) patients (5 stage I, 3 stage II) experienced lung cancer recurrence. Median time to recurrence was 13.9 months (range 6.2- 24.9). Of these, 3 had ctDNA detected on their preoperative and 12-month or recurrence sample, 1 had ctDNA detected at 12 months prior to relapse, 1 had ctDNA detected at 12 months and recurred around the same time, 2 had negative ctDNA samples and 1 missed sample collection preoperatively. The recurrence rate was 16.7% (3/18, 95% exact CI 3.6-41.4%) in patients with ctDNA detected pre-operatively vs. 7.5% (4/53, CI 2.1-18.2%) in those without. New lung cancers were diagnosed in 5/72 (median time to new primary 15.3 months, range 4.9-14.2) and 2/72 patients had new cancers diagnosed (ovarian/liposarcoma). For those with new lung primaries, 1 had ctDNA detected preoperatively but none had ctDNA detected at time of new primary diagnosis. Of 4 patients who have died, 2 were from recurrent lung cancer and 2 from new primaries (lung/sarcoma). **Conclusions:** This study represents one of the largest prospective cohorts of ctDNA kinetics in patients with resected lung cancer. Of patients with at least 12 months follow up, 8/72 experienced a lung cancer recurrence with a higher rate in those with pre-operative ctDNA detected (16.7% vs 7.5%). Pre-operative ctDNA detection may help identify patients with resected stage I NSCLC that could benefit from treatment intensification, currently under study in ctDNA Lung RCT (NCT04966663). Clinical trial information: NCT05254782. Research Sponsor: Ontario Institute for Cancer Research; Princess Margaret Cancer Foundation Grand Challenge.

Real-world data based on PD-L1 expression in early-stage NSCLC in an east-Asian patient population: A 10-year follow-up study.

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Background: Recent studies on the perioperative treatment of Non-Small Cell Lung Cancer (NSCLC) have often excluded patients with stage IA. To address this issue and bridge the knowledge gap, we aim to investigate the impact of PD-L1 and EGFR status on survival in stage IA NSCLC. **Methods:** Our study aimed to determine the impact of PD-L1 expression on overall survival (OS) in patients with resectable stage IA-IIIB NSCLC who underwent curative resection between May 2010 and April 2020. We analyzed survival and clinicopathological data and categorized patients based on PD-L1 tumor proportion score (TPS). PD-L1 TPS $\geq$ 50% were categorized as PD-L1 high and $<$ 50% as PD-L1 negative/low. Our primary objective was to assess the association between PD-L1 expression status and OS in resectable NSCLC patients. We also investigated the relationships between OS, PD-L1 expression, EGFR status, and tumor stage. **Results:** Among the 386 patients recruited, those with PD-L1 negative/low and high had a 5-year OS of 82% and 63%, respectively (p = 0.00011). Among patients with stage IA NSCLC, those with PD-L1 negative/low demonstrated the most favorable 5-year OS (96%) compared to the other subgroups (stage IA PD-L1 high 63%, stage IB-IIIB PD-L1 negative/low 67% and stage IB-IIIB PD-L1 high 62%, $p < 0.0001$). Stage IA EGFR mutant NSCLC showed a significantly better 5-year OS compared to EGFR wildtype (97% versus 84%, p= 0.0028). In comparison, survival in stage IB-IIIB NSCLC was similar regardless of EGFR status (stage IB-IIIB/EGFR mutant 66% vs EGFR wildtype 65%, p= 0.13). Next, we addressed the impact of the co-occurrence of an EGFR mutation and PD-L1 expression on survival in stage IA. In stage IA, the PD-L1 high EGFR mutant and wildtype subgroups demonstrated a 5-year OS of 83% and 56%, respectively, while in the PD-L1 negative/low subgroup, the EGFR mutant and wildtype had a 98% and 93% OS ($p<$ 0.0001), respectively. **Conclusions:** Stage IA NSCLC patients with PD-L1 high and *EGFR* wildtype, surprisingly, were associated with poorer survival outcomes. These findings highlight the urgent need for clinical trials investigating perioperative management strategies in this population. Research Sponsor: None.

Surgical outcomes in patients with non-small cell lung cancer receiving neoadjuvant chemoimmunotherapy versus chemotherapy alone: A systematic review and meta-analysis.

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Background: Neoadjuvant immune checkpoint blockade (ICB) including programmed cell death protein 1 (PD-1) and programmed death-ligand 1 (PD-L1) blockade in combination with chemotherapy has been shown to improve survival outcomes in patients with early-stage non-small cell lung cancer (NSCLC). However, its impact on surgery has not been fully elucidated yet. We aimed to compare surgical outcomes between neoadjuvant chemoimmunotherapy with PD-1/PD-L1 blockade and chemotherapy alone in patients with resectable NSCLC. **Methods:** We performed a systematic search of PubMed and Embase for randomized-controlled trials (RCTs) that compared neoadjuvant chemoimmunotherapy to chemotherapy alone in patients with resectable NSCLC and reported surgical outcomes including surgical resection rates, R0 resection rates, postoperative complications, any-grade treatment-related adverse events (TRAEs), grade 3-5 TRAEs, serious AEs (SAEs), and AEs leading to cancellation of surgery. Meta-analysis was performed using the random-effects model to pool odds ratios (ORs) of these surgical and safety outcomes. Heterogeneity among the included studies for each outcome was assessed using I^2 statistics and high heterogeneity was defined as I^2 higher than 50%. **Results:** A systematic review identified 5 RCTs with 2,069 patients for a meta-analysis. All identified RCTs evaluated combination of neoadjuvant PD-1/ PD-L1 blockade with chemotherapy versus chemotherapy alone. Chemoimmunotherapy was associated with an improvement in R0 resection rates (OR 1.72, 95% CI 1.22 - 2.42; p = 0.002), whereas surgical resection rates were comparable between two groups (OR 1.51, 95% CI 0.90 - 2.51; p = 0.12). No significant difference was observed for complication rates, any-grade TRAEs, grade 3-5 TRAEs, SAEs, or AEs leading to cancellation of surgery. (Table). **Conclusions:** Although the surgical resection rate itself was not significantly different between neoadjuvant chemoimmunotherapy and chemotherapy alone, neoadjuvant chemoimmunotherapy was associated with increased R0 resection rates without an increase in the incidence of complications, TRAEs, and cancellation of surgery. This indicates that neoadjuvant chemoimmunotherapy can be safely administered with an increase in R0 resection rate, which potentially leads to improvement of survival outcomes in patients with resectable NSCLC. Research Sponsor: None.

Pooled OR (95% CI) and number of studies (N) for surgical and safety outcomes.

	OR	N	p-value	Heterogeneity	
				I^2 (%)	p-value
Surgical Resection Rate	1.28 (0.90 - 1.83)	5	0.17	46	0.11
R0 Resection Rate	1.53 (1.15 - 2.04)	5	0.004	42	0.14
Complication Rate	1.06 (0.84 - 1.33)	3	0.63	0	0.83
Any Grade TRAEs	1.03 (0.57 - 1.86)	4	0.92	42	0.16
Grade 3-5 TRAEs	1.43 (0.64 - 3.22)	3	0.39	55	0.11
SAEs	1.12 (0.79 - 1.59)	2	0.51	0	0.84
AEs leading to Cancellation of Surgery	1.52 (0.89 - 2.61)	4	0.12	0	0.87

8021 Poster Session

Cost-effectiveness in perioperative therapy in the era of immune checkpoint inhibitors.

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Background: The use of immune checkpoint inhibitors (ICIs) in lung cancer treatment, particularly in perioperative therapy, has significantly expanded. In Japan, atezolizumab was approved in 2022 for adjuvant therapy and nivolumab in 2023 for neoadjuvant therapy. Despite the long-term prognosis improvements associated with ICIs, their high costs have escalated healthcare expenses. This study evaluates the cost-effectiveness of perioperative therapies incorporating ICIs in Japan. **Methods:** A network meta-analysis (NMA) was conducted to derive hazard ratios (HRs) for disease-free survival (DFS) and overall survival (OS) from pivotal phase 3 clinical trials. Additionally, a partitioned survival model was developed to calculate quality-adjusted life years (QALYs) and life years (LYs). Cost data included drug and administration costs based on standard regimens. **Results:** ICIs with available DFS and OS data included atezolizumab, nivolumab, and pembrolizumab for adjuvant, neoadjuvant, and sandwich therapy, respectively. HRs (DFS/OS) compared to no perioperative therapy were as follows: adjuvant chemotherapy (0.81/0.86), neoadjuvant chemotherapy (0.87/0.80), adjuvant ICI (0.66/0.86), neoadjuvant ICI (0.55/0.49), and sandwich therapy (0.51/0.58). Cost/QALY/LY for each treatment were: no perioperative therapy (¥831,379/2.55/3.57), adjuvant chemotherapy (¥969,600/2.67/3.73), neoadjuvant chemotherapy (¥903,046/2.71/3.82), adjuvant ICI (¥9,209,863/2.70/3.74), neoadjuvant ICI (¥2,760,383/3.02/4.22), and sandwich therapy (¥8,235,047/2.95/4.10). Incremental cost-effectiveness ratios (ICERs) per QALY/LY were ¥425,189/¥295,036 for neoadjuvant chemotherapy and ¥6,152,576/¥4,592,090 for neoadjuvant ICI ($1 = \145). ICERs were not calculated for adjuvant chemotherapy, adjuvant ICI, and sandwich therapy due to extended dominance. **Conclusions:** In Japan, the general ICER threshold is ¥5,000,000, and ¥7,500,000 for treatments requiring special consideration, such as cancer therapies. The ICER for neoadjuvant chemotherapy was below the general threshold, and neoadjuvant ICIs below the special consideration threshold, making them cost-effective options for NSCLC patients in Japan. Other therapies were dominated, primarily due to 1) adjuvant chemotherapy being marginally more expensive and less effective than neoadjuvant chemotherapy, and 2) the high costs of long-term post operative ICI treatment for adjuvant ICI, and sandwich therapy. Research Sponsor: None.

8022 Poster Session

Multiplex analysis of the immune environment before and after neoadjuvant durvalumab as a prognostic factor in resectable non-small cell lung cancer (NSCLC) in the IFCT-1601 IONESCO phase 2 trial.

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Background: Immune checkpoint inhibitors (ICI) are currently included in the peri-operative standard of care for NSCLC with the objective of a curative strategy. In early stages of NSCLC, biomarkers predicting ICI efficacy should be more stringent than PD-L1 tumoral expression in order to improve the benefit-toxicity ratio. We deeply analyzed the tumor microenvironment of patients included in the IONESCO multicenter phase 2 trial (stage IB > 4cm–IIIA, non N2 resectable NSCLC). Diagnostic biopsies and surgical resection specimen after 3 cycles of Durvalumab were available. We previously showed that the % of residual viable tumor cells (RVT) was associated with disease free survival (DFS) and overall survival (OS). PD-L1 tumor positive score was not correlated to RVT nor survival. **Methods:** 46 patients were included in the IONESCO trial. Among them, diagnostic biopsy (n = 32), surgical resection specimen post durvalumab (n = 39) and paired tumor samples (n = 31) were analyzed. Immune environment was assessed using 7 quantitative 7-plex immunofluorescence panels generating 349 different cellular phenotypes in 3 different compartments (whole tumor, intra cytokeratin and stroma), focusing on T and B lymphocytes, macrophages, immune checkpoint, NK cells, apoptosis, innate and adaptive immunity, dendritic cells. Densities of cells were quantified using Fluorescent Multiplex immunohistochemistry performed on Leica Bond RX, using OpalTM technology. A fisher's exact test or chi2 test was used for demographics variables and RVT. HRs and 95% CIs were estimated using a Cox model. NCT number: NCT03030131. **Results:** With median follow-up of 4.5 years, 16/31 patients had a disease recurrence. Histology, sex, stage and survival were significantly associated with intra-tumor densities of CD3, CD8, PD1, TIM3, and CD163 cells in the diagnostic biopsy, and with the delta of CD3, FoxP3, CD4, CD163PD1, TIM3, PDL1 on immune cells and TIM3PDL1 cells, between biopsy and surgical specimen. DFS was significantly associated with high density of CD8+TIM3+ in biopsies (HR = 0.25 [0.09-0.71], p = 0.0092) and with the high density of CD20+ cells in surgical specimen (HR = 0.36 [0.13-0.97], p = 0.04). The RVT was significantly associated with CK+Caspase3- cells and CK+PDL1+ cells in the surgical specimen. No biomarker was associated with OS. **Conclusions:** Multiparameter analysis of the immune NSCLC environment of patients treated with neoadjuvant anti-PDL1 allows identification of markers associated with clinical, pathological parameters and DFS. Our findings highlight the substantial impact of high CD8+TIM3+ cell density pre-durvalumab and of high CD20+ cell density post-durvalumab on DFS. These findings deserve to be assessed in patients treated with neoadjuvant combined immunotherapy chemotherapy. Clinical trial information: NCT03030131. Research Sponsor: AstraZeneca; Intergroupe Francophone de Cancerologie Thoracique.

8023 Poster Session

Impact of *EGFR* mutation and types of treatment on the longitudinal recurrence risk in patients with completely resected non-small cell lung cancer: A combined analysis of two phase III studies (JIPANG and IMPACT).

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Background: In completely resected non-small cell lung cancer patients who received adjuvant treatment, the impact of *EGFR* mutation and types of treatment on the longitudinal recurrence risk has not been elucidated. **Methods:** The individual data was obtained from two adjuvant phase III trials conducted almost the same period in Japan (JIPANG [CDDP + PEM versus CDDP + VNR] and IMPACT [gefitinib versus CDDP+VNR]). According to *EGFR* mutation status and types of adjuvant treatment, 626 patients were categorized into three groups (arm A [*EGFR* wild-type, chemo: n = 299], arm B [*EGFR* mutant, chemo: n = 211], and arm C [*EGFR* mutant, gefitinib: n = 116]). Disease-free survival (DFS) and overall survival (OS) were analyzed using the Kaplan-Meier method, and sites of recurrence were compared. Additionally, the longitudinal recurrence risk was analyzed by estimating hazard function among the arms. The impact of *EGFR* mutation and the types of adjuvant treatment on the recurrence site (central nervous system vs others) and death was also analyzed using the multi-state model. **Results:** Median follow-up time was 69.3 months (range, 0.0 to 113.4 months). DFS was not different between the arms (median DFS: 42.2 months in arm A, 30.3 months in arm B, and 35.9 months in arm C, respectively), however, the DFS rate at 8 years was numerically different (arm A: 40.4%, arm B: 33.9%, and arm C: 22.3%, respectively: Table). Median OS was not reached in each arm, and OS rates at 8 years were 61.3%, 67.7%, and 59.8%, respectively. In the longitudinal recurrence risk analysis, arms A and B had a higher hazard function level than arm C for the first two years and the curves crossed thereafter. Risks in arms A and B gradually decreased and reached a plateau at a lower level, whereas arm C sustained a recurrence risk and finally it was higher than arms A and B. Regarding sites of recurrence, arm C showed a slightly higher distant relapse (51.7%) than arm A (47.2%) or arm B (45.5%), of those, CNS was the most frequent site (33.8%). Among *EGFR* mutant cases, gefitinib likely to have higher risk of CNS relapse (HR 1.46, 95% confidence interval: 0.62-3.45) than chemotherapy. When treated with chemotherapy, *EGFR* mutation status did not affect any types of recurrence. **Conclusions:** In patients with completely resected NSCLC, chemotherapy led to cure regardless of *EGFR*mutation status, whereas gefitinib showed a sustained recurrence risk even after completion. Clinical trial information: UMIN000006252 and UMIN000006737. Research Sponsor: None.

DFS rate at each month.

	12 mo	24 mo	36 mo	48 mo	60 mo	72 mo	84 mo	96 mo	108 mo
Arm A	0.78	0.61	0.52	0.49	0.44	0.42	0.40	0.40	0.40
Arm B	0.80	0.57	0.48	0.41	0.38	0.37	0.34	0.34	0.34
Arm C	0.87	0.64	0.48	0.40	0.32	0.31	0.27	0.22	-

A phase II study of tislelizumab (TIS) and chemotherapy as neoadjuvant therapy for potentially resectable stage IIIA/IIIB non-small cell lung cancer (NSCLC).

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Background: Neoadjuvant immunotherapy and chemotherapy provide more surgical opportunities and survival benefits to potentially resectable locally advanced NSCLC remains unclear. Herein, we initiated a phase II study to evaluate the feasibility of neoadjuvant immunotherapy and chemotherapy in stage IIIA/IIIB NSCLC. We report the the updated analysis of the study. **Methods:** Patients (pts) with stage IIIA/IIIB EGFR/ALK/ROS wild-type NSCLC received 2 cycles of neoadjuvantchemoimmunotherapy (PD-1 inhibitor TIS, *nab*-paclitaxel, and cisplatin/carboplatin) and were reassessed for surgery.Thereafter, pts underwent surgery within 6 weeks and continued 2 cycles of TIS plus chemotherapy, followed by up to 15 cycles of TIS monotherapy. The primary endpoint was R0 resection rate, and secondary endpoints included major pathologic response (MPR), pathologic complete response (pCR), 1/2-year EFS rate, and overall survival, etc. **Results:** From Jan 2021 to Sep 2023, 33 pts were enrolled; 19 (58%) pts with IIIA and 14 (42%) pts with IIIB disease, As of 14 Sep 2023, 27 pts completed neoadjuvant and 25 pts underwent resection. and 6 pts were on neoadjuvant. 2 pts downstaging had obvious downstaging after neoadjuvant treatment and were unwilling to surgery. 24 of 25 pts (96%) underwent successful R0 resection (Table). Of 25 pts who underwent resection,8 (32%) pts achieved pCR, 15 (60%) pts achieved pathologic response rate.Of the 7 pts who achieved MPR, 5 had only about 1% viable tumor cells in the resection specimen. The overall response rate (ORR) and disease control rate (DCR) were 88% (22/25) and 100 % (25/25), respectively. The clinical downstaging occurred in 22 of 25 pts (88%).The pathological downstaging occurred in 23 of 25 pts (92%).And The 1-year EFS rate 82.3% (95%CI 58.3-93.2), 2-year EFS rate 76.4% (95%CI 51.1-89.8). **Conclusions:** Neoadjuvant TIS plus chemotherapy increased surgical opportunities and survival benefits in potentially resectable locally advanced stage IIIA/IIIB NSCLC. Research Sponsor: None.

Outcomes (n = 25)	Results, n (%, 95%CI)
Radiological response	
PR	22 (88, 68.78-97.45)
SD	3 (12, 2.55-31.22)
ORR	22 (88, 68.78-97.45)
DCR	25 (100, 86.3-100.0)
Surgical resection	
R0	24 (96, 79.65-99.90)
R1	1 (4, 0.10-20.35)
Downstaging rate	
clinical	22 (88, 68.78-97.45)
pathologic	23 (92, 73.97-99.02)
Pathologic response	
MPR	15 (60, 38.66-78.88)
pCR	8 (32, 14.95-53.5)
	%, (95%CI)
1-year EFS rate	82.3% (58.3-93.2)
2-year EFS rate	76.4% (51.1-89.8)

Efficacy and safety of perioperative, neoadjuvant or adjuvant immunotherapy alone or in combination chemotherapy in early-stage non-small cell lung cancer: A systematic review and meta-analysis of randomized clinical trials.

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Background: Adjuvant (AD), neoadjuvant(NE), or perioperative(PE) immunotherapy in early-stage non-small cell lung cancer (eNSCLC) has been validated in multiple clinical trials in recent years. However, the comparations of efficacy and safety among three treatment modalities remain unclear. **Methods:** The PubMed, Embase, and Cochrane databases were searched for randomized controlled trials (RCTs) of immune checkpoint inhibitors (ICI) plus chemotherapy (CT) for eNSCLC. We calculated hazard ratios (HRs) or advantage ratios (ORs) for binary endpoints with 95% confidence intervals (CIs). Network meta-analysis was performed using a Bayesian framework to indirectly compare the three treatment modalities. **Results:** A total of 11 RCTs (2 NE, 6 PE, and 3 AD) including 6951 NSCLC patients were included. Among the three treatment modalities, indirect comparisons revealed that efficacy differed between PE and AD immunotherapy was only observed in the EFS/DFS (HR=0.68, 95%CI: 0.49-0.89). Compared with the control group, NE/PE immunotherapies significantly improved pathologic complete response (pCR) (OR=7.56, 95%CI: 5.24-10.92), major pathologic response(MPR) (OR=5.46, 95%CI: 3.97-7.51), EFS(HR=0.58, 95% CI: 0.50-0.67), and AD immunotherapy significantly improved DFS (HR=0.83, 95% CI: 0.73-0.94). No significant OS difference was observed in NE and AD setting (HR=0.62, 95% CI: 0.36-1.05; HR=0.90, 95% CI: 0.76-1.06, respectively), and only PE immunotherapy showed OS benefits(HR=0.67, 95%CI: 0.54-0.84). In addition, EFS was significantly improved in the PE treatment subgroup regardless of stage, pathologic response, histology, PD-L1 expression, and gender (Table), but no significant benefit in the EGFRm NSCLC subgroup(HR=0.54, 95% CI: 0.21-1.43). AD (OR 1.52, 95% CI: 1.01-2.30) and PE (OR 1.29, 95% CI: 1.08-1.54) immunotherapies were significantly associated with higher grade ≥3 adverse events (AEs) compared with controls. Rash was the most common grade ≥3 irAEs. **Conclusions:** PE immunotherapy seems to be more effective than NE and AD immunotherapy in three treatment modes. NE and PE immunotherapy significantly improved pCR, MPR, EFS, and AD immunotherapy significantly improved DFS in eNSCLC patients in comparison with the control group, but only PE immunotherapy significantly improved OS. Research Sponsor: None.

	EFS HR (95% CI)
Sex	
Male	0.54 (0.44, 0.66)
Female	0.67 (0.48-0.94)
Stage	
II	0.64 (0.46, 0.89)
IIIA	0.54 (0.45, 0.65)
IIIB	0.54 (0.31, 0.94)
Pathological response	
pCR	0.33 (0.13, 0.86)
Non-pCR	0.68 (0.56, 0.83)
Histology	
Squamous	0.50 (0.39, 0.65)
Non-squamous	0.65 (0.54, 0.78)
PD-L1 expression	
< 1%	0.75 (0.61, 0.92)
≥1-49%	0.58 (0.44, 0.78)
≥50%	0.43 (0.31, 0.59)
EGFR mutation	
Positive	0.54 (0.21, 1.43)
Negative	0.50 (0.41, 0.60)

Efficacy and safety of immunotherapy plus chemotherapy for lung cancer neoadjuvant treatment: A network meta-analysis based on randomized controlled trials.

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Background: With immunotherapy's swift progress in lung cancer treatment, combining immunotherapy with chemotherapy (CT) for neoadjuvant use has attracted significant interest, though direct comparisons of its efficacy and safety are still scarce. This study aims to comprehensively evaluate the efficacy and safety of immunotherapy combined with chemotherapy versus chemotherapy alone in the neoadjuvant treatment of lung cancer. **Methods:** We searched databases, including PubMed and EMBASE, for phase II and III randomized global trials that assessed neoadjuvant lung cancer treatment with immunotherapy combined with chemotherapy. We performed a Bayesian random-effects network meta-analysis to evaluate efficacy, presenting Hazard Ratios (HRs) and 95% Confidence Intervals (95%CI). Bias risk was determined using the Cochrane risk of bias tool, and evidence quality was appraised via the CINeMA framework. **Results:** Our analysis included eight randomized controlled trials, comprising a total of 3,316 patients. The results indicated that, compared to neoadjuvant chemotherapy alone, the Event-Free Survival (EFS) was highest for the durvalumab+CT group, ranking first with an HR of 2 (95% CI: 1.0 to 3.7). The pembrolizumab+CT group ranked second with an HR of 1.8 (95% CI: 0.76 to 4.2), followed by the nivolumab+CT group in third place with an HR of 1.7 (95% CI: 0.95 to 3.1). Both the nivolumab and ipilimumab+CT and toripalimab+CT groups tied for fourth place with HRs of 1.4 (95% CI: 0.58 to 3.5) and 1.5 (95% CI: 0.70 to 3.2), respectively. The camrelizumab+CT group had the lowest EFS ranking, with an HR of 1.7 (95% CI: 0.74 to 3.8). The combination of nivolumab+ipilimumab+CT showed the most favorable outcomes in terms of Pathologic Complete Response (PCR) and R0 resection rates among the six treatments, with lnOR values of 3.17 and 1.48, respectively. This combination also had the lowest occurrence of treatment-related adverse events greater than grade 3, with an lnOR value of -1.38. **Conclusions:** This network meta-analysis indicates that durvalumab, when combined with chemotherapy, offers the best EFS among the immunotherapy options evaluated, demonstrating good safety and efficacy. Concurrent use of nivolumab and ipilimumab resulted in the highest pCR and R0 resection rates. Moreover, for patients with lung cancer, the preliminary evidence supports the value of combining immunotherapy with chemotherapy as a neoadjuvant treatment strategy over chemotherapy alone. Research Sponsor: None.

	EFS		PCR		R0 resection		TRAEs(Grade≥3)	
Drug	HR	Rank	lnOR	Rank	lnOR	Rank	lnOR	Rank
Durvalumab+CT	2	1	1.6	3	0.39	3	-0.18	3
Pembrolizumab+CT	1.8	2	1.67	3	0.62	2	0.2	2
Nivolumab+CT	1.7	3	2.44	2	0.54	2	-0.18	3
Nivolumab + Ipilimumab+CT	1.4	4	3.17	1	1.48	1	-1.38	6
Toripalimab+CT	1.5	4	1.14	6	/	/	/	/
Camrelizumab+CT	1.7	6	1.72	3	0.88	2	0.98	1
Neoadjuvant chemotherapy	1	7	1	7	1	6	1	3

8027 Poster Session

Investigation of the role of personalized molecular residual disease in the assessment of high-risk non-small cell lung cancer (NSCLC) post-operation.

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Background: Radical surgical resection is preferred treatment for early-stage Non-Small Cell Lung Cancer (NSCLC) patients. Despite this, recurrence and metastasis significantly impact patient survival. High-risk factors like Tumor Thrombus (TT) and Spread Through Air Spaces (STAS) are known to exacerbnate the recurrence and metastasis rates, yet there is lacking research exploring the association between these riskes and treatment outcomes. The study aims to evaluate the utility of circulating tumor DNA (ctDNA)-based molecular residual disease (MRD) in assessing and monitoring high-risk NSCLC post-operatively. **Methods:** NSCLC patients underwent curative surgery (R0) were recruited in this study and their tissue samples were collected after surgical resection. Whole exome sequencing (WES) was performed to identify somatic mutation information across individual, from which bespke molecular residual disease (MRD) detection panel was designed and used in later detection. Plasma samples were collected 3-4 weeks post-surgery and analyzed for MRD status through using next-generation sequencing (NGS) at 100,000x sequencing depths. **Results:** The study enrolled 124 NSCLC patients with a median age of 60 years (ranged 29-86)., The cohort comprised 63 male (77.3%) and 61 females (22.7%). Pathologically, 92 patients were classified in stage I, 5 as stage II, 17 as stage III, and 10 as stage IV. A total of 10,260 somatic mutationwere identified across 6,315 genes, including 639 insertions/deletions (InDels), 9613 single nucleotide variants (SNVs), and 8 gene fusions. The most prevalent mutations were EGFR (58.87%), followed by TTN (45.97%), TP53 (40.32%), CEP192 (20.97%), XIRP2 (19.35%), ZFHX4 (19.35%), and TOPAZ1 (16.94%). The MRD positivity was observed in 29.0% (36/124) of patients, with a higher incidence in males (34.9%, 22/63) than females (22.9%, 14/61). By stage, MRD positivity was 16.3% (16/92) in stage I, 40.0% (2/5) in stage II, 47.0% (8/17) in stage III, and 100% (10/10) in stage IV patients. Among patients with risk factors, 31.6% (12/38) with STAS, , 60.0% (6/10) with TT, and 53.8% (7/13) with pleural invasion were MRD positive, which indicating a higher postoperative MRD positivity in high-risk groups. **Conclusions:** NSCLC patients with high-risk factors, such as STAS and TT, , exhibit a high rate postoperative MRD positivity, even after R0 resection. Current research reports indicate that the MRD post-operation is an indicator of recurrence, metastasis, and poor prognosis. The findings imply that NSCLC patients harboring these high-risk factors are more susceptible to recurrence and metastasis, possibly necessitating postoperative adjuvant therapy for effective management. Research Sponsor: None.

Implications of EGFR expression in MAPK dependency and adaptive immunity status of *EGFR*-mutated lung adenocarcinoma.

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Background: EGFR expression (EGFR-exp) varies among patients (pts) with *EGFR*-mutated (m*EGFR*) NSCLC. It remains unknown how EGFR-exp status influences tumor and clinical characteristics in m*EGFR* NSCLC. **Methods:** Whole-exome and RNA sequencing were performed of pts with resectable early-stage (ES) and advanced-stage (AS) lung adenocarcinoma (LUAD) and *EGFR*mutations. EGFR-exp was classified into low or high groups based on median transcripts per million. We retrospectively examined the association between EGFR-exp, mutation status, copy number variations, *EGFR* clonality, and clinical outcomes. Additionally, we assessed EGFR signaling by evaluating the MAPK activation score, derived from the transcript levels of 10 MAPK target genes. Gene set enrichment analysis was used to compare transcriptional profiles, and immune cell (IC) infiltration was estimated through RNA deconvolution. **Results:** This study involved 450 and 45 pts in the ES and AS cohorts, respectively. In the AS cohort, all pts received osimertinib (Osi) as first-line treatment. The EGFR-exp low group exhibited a lower incidence of *TP53* co-mutation and *EGFR* amplification, more subclonal *EGFR*mutations, and lower MAPK activation scores than the EGFR-exp high group (Table). Additionally, the EGFR-exp low group had significantly up-regulated adaptive immune responses pathway ($q < 0.0001$) and increased IC infiltration in the tumor microenvironment (TME) in both cohorts. The EGFR-exp low group in the ES cohort exhibited significantly longer relapse-free survival than the EGFR-exp high group (median, 105.9 vs. 37.1 months; hazard ratio, 0.6; $p < 0.0001$), and low EGFR-exp was a significant favorable factor for postoperative relapse (odds ratio [OR], 0.6; $p = 0.04$) in multivariate analysis. In the AS cohort, the EGFR-exp low group had a higher proportion of Osi non-responders than the EGFR-exp high group (34.8% vs 4.5%, respectively; $p = 0.02$), and low EGFR-exp was a significant risk factor for primary Osi resistance (OR, 29.1; $p = 0.04$) on multivariate analysis. **Conclusions:** Pts with low EGFR-exp in m*EGFR* LUAD demonstrated less activation of MAPK signaling, along with enhanced adaptive immunity and increased IC infiltration in the TME. These pts are less likely to experience postoperative relapse; however, they showed suboptimal benefit with Osi in AS setting. The EGFR-exp status can be valuable in decision making for adjuvant Osi and perioperative immunotherapy in pts with resectable m*EGFR* LUAD. Research Sponsor: None.

Differences in features of *EGFR*-mutated LUAD by EGFR expression status.

	ES Cohort			AS Cohort		
EGFR Expression	**Low (n = 225)**	**High (n = 225)**	**p**	**Low (n = 23)**	**High (n = 22)**	**p**
***TP53* co-mutation, n (%)**	73 (32)	119 (53)	< 0.0001	7 (30)	11 (50)	0.3
***EGFR* amplification, n (%)**	17 (8)	69 (31)	< 0.0001	2 (9)	11 (50)	0.003
Subclonal *EGFR* mutation, n (%)	33 (15)	17 (8)	0.02	3 (13)	0 (0)	0.23
MAPK activation score, median	-0.7	0.3	< 0.0001	-1.1	1.1	0.0004

Deep-learning model for real-time prediction of recurrence in early-stage non-small cell lung cancer: A multi-modal approach.

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Background: The surveillance protocol for early-stage non-small cell lung cancer (NSCLC) is not contingent upon individualized risk factors for recurrence. Longitudinal risk calculation for the prediction of recurrence was based on circulating tumor DNA. This study aimed to develop a deep-learning model using comprehensive data from clinical practice for practical longitudinal monitoring. **Methods:** A multi-modal deep-learning model employing transformers was developed for real-time recurrence prediction using clinical, pathological, and molecular data at baseline, alongside longitudinal laboratory, and radiologic data during surveillance. Patients with histologically confirmed NSCLC (stage I-III) undergoing curative intent surgery between January 2020 and September 2022 were included. The collected data was divided into training, validation, and test sets in a 6:2:2 ratio. The primary outcome focused on predicting likelihood of recurrence within one year from the monitoring point. This study demonstrated the timely provision of risk scores (RADAR score), determined thresholds, and the corresponding Area Under the Curve (AUC). **Results:** A total of 14,345 patients were enrolled (10,262 with stage I, 2,380 with stage II, and 1,703 with stage III). The training, validation, and test sets comprised 8,578, 2,866, and 2,901 patients, respectively. The model incorporated 64 clinical-pathological-molecular factors at baseline, alongside longitudinal laboratory, and radiologic text data. Radiologic data of 177,246 was used (mean 12.4 chest CT scan per patient) during surveillance. Baseline RADAR score was 0.20 (standard deviation [Std] 0.17) in stage I, 0.51 (Std 0.20) in stage II, and 0.64 (Std 0.19) in stage III. The AUC for predicting relapse within one year from that monitoring point was 0.847 across all stages with the sensitivity of 80.6% and specificity of 74.4% (Table) (AUC=0.851 in stage I, AUC=0.763 in stage II, and AUC=0.721 in stage III). **Conclusions:** This pilot study introduces a deep-learning model utilizing multi-modal data from routine clinical practice for predicting relapse in early-stage NSCLC. It demonstrates the timely provision of risk score, RADAR score, to clinicians for recurrence prediction, potentially guiding risk- adapted surveillance strategies and aggressive adjuvant systemic treatment. Notably, the RADAR score exhibited a high prediction ability for relapse in stage I disease. Research Sponsor: None.

Baseline RADAR score and optimal threshold of predicting relapse within one year from that monitoring point predicting relapse within one year from that monitoring point.

Stage	Baseline RADAR Score (Mean ± Std)	AUC	Threshold	Specificity	Sensitivity	F1-score
Total	0.32 ± 0.28	0.847	0.455	74.4%	80.6%	0.34
Stage I	0.20 ± 0.17	0.851	0.353	80.9%	74.4%	0.27
Stage II	0.51 ± 0.20	0.763	0.593	64.5%	77.1%	0.36
Stage III	0.64 ± 0.19	0.721	0.747	64.7%	67.5%	0.48

Unlocking therapeutic potential: IL-1β as a target in non-small cell lung cancer with oncogenic mutations—Prognostic and predictive insights.

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Background: Preclinical studies have demonstrated heterogeneity in interleukin-1β (IL-1β) expression and its potential implications in non-small cell lung cancer(NSCLC). The phase II CANTOS trial incidentally showed reduced lung cancer incidence and mortality with the IL-1β inhibitor canakinumab. However, the phase III CANOPY-1/2 trials failed to demonstrate survival benefit when combining canakinumab with chemo/immunotherapy. The impact of IL-1β inhibition in NSCLC with actionable mutations remains unknown. This study aims to evaluate the prognostic and predictive role of IL-1β in NSCLC and its potential as a target for combination therapy. **Methods:** 34,960 NSCLC tumors underwent next-gen sequencing of DNA (592-gene or whole exome) and RNA (whole transcriptome) at Caris Life Sciences (Phoenix, AZ). Tumors were stratified by IL-1β transcriptional expression quartiles (Q1: low expression and Q4: high expression). Quartiles were established within each subpopulation. Significance was calculated using chi-square, Fisher's exact, or Mann-Whitney U test, with p-values adjusted for multiple comparisons ($p < 0.05$). Overall survival (OS) from either time of tissue collection to last contact or time on treatment (TOT) was estimated from insurance claims data using the Cox proportional hazards model to calculate hazard ratio (HR) and log-rank tests to calculate p-values. **Results:** In the entire cohort, low IL-1β expressors showed improved OS compared to high expressors (20.0 months (m) vs 17.3 m, HR 0.88, 95%CI 0.88-0.95, $p < 0.0001$). For NSCLC without driver mutations, IL-1β expression did not correlate with OS difference. IL-1β expression was positively associated with TP-53 mutations (Q4 76% vs Q1 57%), high TMB (Q4 44% vs Q1 37%) and PD-L1+ expression by IHC (Q4 67% vs Q1 44%), while negatively associated with mutations in *KRAS*(Q4 24%vs Q1 31%), *EGFR*(Q4 8% vs Q1 14%), *ERBB2* (Q4 1% vs Q1 2%), *BRAF* (Q4 4% vs Q1 5%),and *STK11* (Q4 10% vs Q1 18%) ($p < 0.05$). In EGFR-mutant NSCLC, Q1 showed superior OS than Q4 (34.6 m vs 25.1 m, HR 0.79, 95% CI 0.68-0.92, p = 0.002). This survival benefit was amplified in adenocarcinoma (Q1 41.2 m vs Q4 27.1 m, HR 0.74, 95% CI 0.63-0.87, $p < 0.001$). For *ALK* fusion-positive NSCLC, low expressors demonstrated improved OS (Q1 63.4 m vs Q4 27.0 m, HR 0.53, 95% CI 0.37-0.76, $p < 0.001$). In *KRAS*-mutant adenocarcinoma, high expressors showed improved immune-checkpoint inhibitor (ICI) TOT (Q4 6.4 m vs Q1 5.4 m, HR 0.85, 95% CI 0.74-0.98, p = 0.026); however, this did not correlate with improved OS. **Conclusions:** Our study shows promising prognostic value of IL-1β expression in NSCLC, associating low expression with improved OS across NSCLC subtypes. IL-1β expression is closely linked to key driver mutations in NSCLC and may have predictive value for ICIs. The findings suggest the potential benefit of targeting IL-1β in high IL-1β expressing NSCLC with driver mutations. Research Sponsor: None.

The association between osimertinib and nutritional deficiency among patients with non-small cell lung cancer.

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Background: Osimertinib, a third-generation epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI), is the standard-of-care in EGFR mutation-positive non-small-cell lung cancer (NSCLC) in various settings. Osimertinib commonly causes gastrointestinal adverse effects thereby potentially leading to nutritional deficiencies. Therefore, we aim to evaluate the association between the use of osimertinib and nutritional deficiencies among patients with NSCLC. **Methods:** We performed a retrospective, propensity score matched study using the TriNetX database, a network comprising deidentified data across more than 120 participating healthcare institutions. We included patients with NSCLC who received either osimertinib or other EGFR-TKIs (afatinib, dacomitinib, erlotinib, gefitinib). The outcomes of interest included vitamin B deficiency, vitamin D deficiency, iron deficiency as well as associated anemia including vitamin B12 deficiency anemia, folate deficiency anemia, and iron deficiency anemia within 5 years of EGFR-TKI initiation. **Results:** We matched 4264 patients who received osimertinib to patients who received other EGFR-TKIs. In Cox proportional hazard analysis, osimertinib was associated with a 50% higher risk of vitamin B deficiency (Hazard ratio, 1.52 [95% CI: 1.07-2.16]) compared to other EGFR-TKIs. Consistent with this observation, osimertinib was associated with an increased risk of vitamin B12 deficiency anemia and a tendency towards folate deficiency anemia. We also noted a 2-fold higher risk of vitamin D and 5-fold higher risk of iron deficiency in the osimertinib cohort. Consistent with this observation, osimertinib was associated with an increased risk of iron deficiency anemia compared to other EGFR-TKIs. **Conclusions:** The use of osimertinib is associated with a higher risk of nutritional deficiencies and associated anemias compared to other EGFR-TKIs. One potential explanation is the extended duration of osimertinib therapy, driven by its potent anti-cancer effects. Therefore, it is advisable to consider screening for specific nutritional deficiencies in individuals receiving osimertinib therapy. Research Sponsor: None.

	Osimertinib		Other EGFR-TKIs		Hazard Ratio [a]	
Outcomes	Patients at risk	Cases	Patients at risk	Cases	(95% CI)	P-value (Log-rank)
Vitamin B deficiency	4149	76	4162	56	1.52 (1.07-2.16)	0.018
Vitamin D deficiency	3996	146	4027	68	2.58 (1.93-3.47)	<0.001
Iron deficiency	4245	35	4246	10	5.42 (2.60-11.32)	<0.001
Vitamin B12 deficiency anemia	4247	26	4228	16	2.02 (1.08-3.81)	0.026
Folate deficiency anemia	4261	10	4263	10	2.40 (0.81-7.09)	0.103
Iron deficiency anemia	4021	224	4047	164	1.56 (1.27-1.91)	<0.001

[a]After propensity score matching by incorporating variables: age, sex, metastatic disease, cancer therapy, underlying comorbidities, and use of medications.

Retrospective analysis of change in frequency of STK11 mutation in lung adenocarcinomas over a 10-year period.

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Background: Previous studies have linked the presence of inactivating mutations in the tumor suppressor gene STK11 with reduced efficacy of immune checkpoint inhibitor (ICI) treatments in lung adenocarcinoma (LA). We queried whether there has been a change in the STK11 mutation frequency over the last 10-year period that could potentially reflect the emergence of additional acquired resistance mutations. **Methods:** Over a 10-year period from 2013 through 2022, 109,763 clinically advanced LA underwent hybrid capture based comprehensive genomic profiling (CGP) to assess all classes of genomic alterations (GA) at a single reference laboratory (Foundation Medicine). MSI-high status and tumor mutational burden (TMB) were determined from the sequencing data. PD-L1 status was measured by immunohistochemistry (IHC) using the Dako 22C3 kit with TPS scoring. Statistical comparisons utilized the 2-tailed Chi Square method with the Yates' correction. **Results:** The frequency of STK11 inactivating GA in all cases of LA significantly increased during the study period from 2013 to 2022 (16.1% vs 20.1%; p=0.0005). This increase appeared to be predominantly in KRAS wild type LA (10.1% vs 15.5%; p<0.0001). The STK11 GA frequency slightly declined in the KRAS mutated LA over the 10-year period (29.9% vs 0 27.0%, P=0.25). During the same time period, the KEAP1 GA frequency increased from 12.6% to 14.9% (p= 0.076) and the frequency of combined STK11 and KEAP1 GA increased from 4.8% to 8.0% (p=.0006). The frequencies of MSI-high status, TMB and PD-L1 expression did not significantly change over the observation period. **Conclusions:** The continuously increasing approved indications for ICI-based treatments for both early stage and clinically advanced LA appears to be accompanied by a significant increase in the frequency of inactivating STK11 GA predominantly in the KRAS mutation negative LA population. This inactivation is associated with an attenuated response rate and progression-free survival in this population. Given the development of novel therapies focused on potential restoration of STK11 function by HDAC/CoREST inhibition, further study of the STK11 GA distribution in LA appears warranted. Research Sponsor: None.

	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2014 vs 2022 (P value)
Total Number of Cases (Cumulative, n)	934	3,303	6,184	8,637	10,933	13,730	16,046	16,268	16,758	16,970	
All *STK11* GA (%)	16.1%	17.4%	17.9%	18.4%	19.4%	20.2%	20.3%	20.2%	20.2%	20.1%	0.005
***STK11* GA in *KRAS*Mut- only (%)**	10.1%	12.4%	12.8%	13.3%	14.4%	15.6%	15.8%	15.1%	14.9%	15.5%	<0.0001
***STK11* GA in *KRAS*Mut+ only (%)**	29.9%	28.4%	27.2%	26.8%	27.7%	28.3%	27.8%	28.0%	28.0%	27.0%	NS
MSI High Status (%)	0%	0%	0.2%	0.2%	0.2%	0.2%	0.2%	0.3%	0.3%	0.2%	NS
TMB > 10 mut/Mb (%)	NA	NA	30.8%	32.3%	31.9%	31.2%	30.9%	31.1%	31.7%	29.4%	NS
PD-L1 Low (1-49% TPS) (%)	NA	NA	11.1%	22.3%	31.6%	26.2%	28.4%	30.2%	33.8%	31.9%	NS
PD-L1 High (≥50% TPS) (%)	NA	NA	11.1%	13.7%	31.7%	27.8%	30.7%	32.7%	32.6%	30.5%	NS

Sex and racial disparities in incidence and survival outcomes in adolescents and young adults (AYA) with lung cancer in the United States.

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Background: Limited data exists on the impact of race on the incidence and survival of lung cancer among adolescents and young adults (15 – 39 years). We examined the Surveillance, Epidemiology, and End Results Plus Data (SEER) to determine the association of race, sex and other demographic/clinicopathologic factors with incidence trends and survival in AYA. **Methods:** Lung cancer cases in AYA diagnosed between 2000 and 2020 were extracted from the SEER database. Age-standardized incidence rates per 100,000 persons were obtained, and the annual percentage change (APC) was used to compare incidence trends stratified by various demographics. Relative survival was calculated with the SEER Stat software. Multivariate regression analyses were performed to determine association with mortality. **Results:** We identified 5129 cases of lung cancer among AYA of which 50.9% (n=2610) were female, 56.6% (n=2904) were Non-Hispanic Whites (NHW), 17% (n=872) were Hispanics, 13.3% (n=684) were Non-Hispanic Blacks (NHBs), 12.5% (n=643) were Non-Hispanic Asian or Pacific Islander (NHAPI) and 0.5% (n=26) were Non-Hispanic American Indian/Alaska Native (NHAIA). Overall age-adjusted incidence rates (AAIR) of lung cancer among AYA decreased (APC, -2.01 [- 2.72 to -1.34)], slightly more in females (APC -2.05 [-2.93 to -1.26)] compared to males (APC, -2.01 [-2.74 to -1.34)]. The greatest decrease was seen in NHWs -2.4 [-3.1 to -1.8)]. There was no significant change in the AAIR among NHBs and Hispanics. NHBs showed the lowest 5-year survival rate (RSR-5: 58.8 [57.3-60.1]) with NHWs showing the highest survival (RSR-5: 77.8 [77.4-78.3]). On multivariable analysis, race was an independent predictor of mortality: Hispanics (HR: 0.78: 95% CI = 0.69 - 0.88) and NHAPI (HR: 0.79: 95% CI = 0.68 - 0.87) compared to NHW, had reduced odds of mortality. There was no association between sex and mortality. **Conclusions:** There is an overall decline in age-adjusted incidence rates of lung cancer, with more pronounced decline in females and specific racial groups. NHBs exhibited the lowest 5-year survival rate. Additionally, various socioeconomic and histologic factors demonstrated varying impacts on mortality. Research Sponsor: None.

Incidence trends of lung cancer in AYA by race and sex.

	Male APC [95% CI, P Value]	Female APC [95% CI, P-Value]
All	-2.01 [-2.74 - (-1.34) p <0.05]	-2.05 [-2.93 - (-1.26) p <0.05]
Non-Hispanic White	-2.1 [-2.9 - (-1.3) p <0.05]	-2.7 [-3.6 - (-1.9) p <0.05]
Non-Hispanic Black	-0.6 [-1.8 - 0.6 p >0.05]	-1.3 [-3.4 - 0.9 p >0.05]
Hispanic (All races)	-0.8 [-2.6 - 1.0 p >0.05]	0.9 [-0.6 - 2.4 p >0.05]
Non-Hispanic Asian or Pacific Islander	-3.1 [-4.3 - (-1.8) p <0.05]	-1.2 [-3.3 - 0.9 p >0.05]
Non-Hispanic American Indian*	-	-

APC = annual percentage change; *could not be calculated.

8034 Poster Session

Artificial intelligence-based prediction model of malignant lung nodules for pre-operative planning.

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Background: The histopathological prediction of malignant lung nodules is crucial for pre-operative planning, but it always remains not precise until the detailed pathological evaluation is performed after the surgery. Thus, to define the histology types (in situ adenocarcinoma (AIS), microinvasive adenocarcinoma (MIA), and invasive adenocarcinoma (IA)) of pulmonary adenocarcinoma appearing as lung nodules before the operation and reduce unnecessary invasive diagnosis and treatment operations, we developed a classification model of based on CT images. **Methods:** Patients who were diagnosed with pulmonary adenocarcinoma (tumor diameter ≤ 3cm) at Nanfang Hospital, Southern Medical University, China, were retrospectively enrolled, including detailed pathology results, computed tomography (CT) images, and basic information. Through training the model proposed in our previous study, we proposed a new model for defining histopathological types. Then, we used this data to train and compare the diagnostic efficacy of our model with another previously reported deep learning (DL) model (that was a segmentation - classification model with the 3D Unet++ - ResNet-50 combined model) and machine learning (ML) model (that was a traditional model Grey Level Co-occurrence Matrices (GLCM) as the feature extractor and the support vector machine (SVM) as the classifier) in the same method. **Results:** A total of 2061 patients (with 395 of AIS, 334 of MIA and 1332 of IA) were retrospectively enrolled from January 2019 to April 2022. The data from 2/3 of the patients were randomly selected for training and another 1/3 for verifying. Through training and verifying, our model shows much better diagnostic efficacy, with areas under receiver operating characteristic (ROC) curves with 95% confidence interval (CI) of 0.97(0.96, 0.98), comparing with those of the ML model of 0.77(0.73, 0.81) and the DL model of (0.90(0.88, 0.92). The heatmap visualization of the proposed model shows the classification ability with prediction probabilities of our model clearly and understandably. **Conclusions:** In this study, we developed a novel artificial intelligence multi-task learning model to precisely predict the pathology type of malignant lung nodules with satisfying diagnostic efficacy, which might provide a new and reliable way for preoperative planning of lung nodules. Further external verifying should be done in the future. In addition, prediction of the growth patterns of pulmonary adenocarcinoma could be more helpful in addition to predicting histopathological types. Research Sponsor: None.

LBA8035 **Poster Session**

IMpower010: Final disease-free survival (DFS) and second overall survival (OS) interim results after ≥5 years of follow up of a phase III study of adjuvant atezolizumab vs best supportive care in resected stage IB-IIIA non-small cell lung cancer (NSCLC).

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Prospective "common arm" comparison of US SWOG S0424 and Japanese JME studies in early-stage non-small cell lung cancer (NSCLC): Survival differences in the context of race, gender and smoking.

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Background: In NSCLC, overall frequencies and subtype distribution of EGFR and KRAS mutations differ significantly between Japanese and US patients. In many NSCLC clinical trials, Japanese patient outcomes appear superior to those in western populations. Since 2009, SWOG and Japanese investigators have used the "Common Arm" analytic method to interpret globally-conducted lung cancer clinical trials, providing a mechanism for direct patient-level comparisons in matching trials performed in the US and Japan. S0424 and the Japanese Molecular Epidemiology Study (JME) are large prospective molecular epidemiology studies conducted by SWOG and Japanese investigators and prospectively planned for "Common Arm" analysis. We investigated the effects of mutation distribution on overall survival in early stage NSCLC using data from JME and S0424. **Methods:** Both studies were designed to accrue representative proportions of ever-smokers (ES) versus never-smokers (NS) in male and female cohorts. Accrual to S0424 was completed in 2011 with 981 pts enrolled (Cheng et al JNCI 2018); JME was completed in 2012 with 957 pts (Kawaguchi et al JCO 2016). A comprehensive questionnaire was used to capture lifestyle, carcinogenic exposures, demographic and clinical data. Five years of follow-up was completed for each study. The association between baseline characteristics and mutation types were analyzed using multivariate logistic regression. The product-limit method was used to estimate overall survival and Cox regression models were fit to estimate hazard ratios. p-values were two-sided and p-values < 0.05 were considered significant. **Results:** Evaluable pts: 876 for JME; 957 for S0424. Demographic distribution: S0424: 87% Caucasian, 5% Asian, 4% Black; JME: 100% Japanese. As expected, multivariate logistic models adjusting for age, smoking status, gender and BMI showed JME were more likely to have EGFR mutations ($p < 0.0001$) and less likely to have KRAS mutations ($p = 0.02$). EGFR mutations were associated with never-smoking ($p < 0.0001$) and female sex ($p < 0.0001$); KRAS was associated with smoking ($p < 0.0001$). Adjusting for age, smoking status and gender, overall survival was greater in JME patients ($p < 0.0001$,HR = 0.49 (95% CI: 0.40-0.60)). In the subset of pts without an EGFR mutation, survival still favored the JME cohort ($p < 0.001$, HR = 0.68 (0.53-0.86). **Conclusions:** Patient level comparison of US (SWOG) and Japanese (JME) patients with early stage NSCLC demonstrated longer survival in Japanese patients even after adjusting for EGFR mutation frequency. Identification of factors that contribute to this finding are under investigation. Female sex remained a risk factor for EGFR mutation-driven disease in both populations. This analysis forms the basis for applying this population-related model in other clinical settings. Research Sponsor: National Cancer Institute/U.S. National Institutes of Health; U10CA180888, U10CA180819, UG1CA189974.

Clinicopathologic and molecular landscape of invasive mucinous adenocarcinoma of the lung.

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Background: Invasive mucinous adenocarcinoma (IMA), accounting for 2–10% of lung adenocarcinomas, often mimics pneumonia with multicentric opacities in multiple lobes and both lungs. Notable for its microscopic skip lesions leading to tumor spread through air spaces (STAS), IMA is still under-researched in terms of its comprehensive clinical and genetic characteristics in large, multicenter studies. **Methods:** Primary lung cancer cases were obtained from the Tempus database, categorized into either IMA or non-IMA, and compared by patient, clinical, biopsy, and molecular characteristics. The normalization of RNA-seq data involved computing transcripts per million (TPM), performing log2 transformations, and adjusting for assay and batch effects. Significantly up- and down-regulated genes were defined as false discovery rate q-values < 0.05 and $|\log2(\text{fold change})| > 0.5$. **Results:** The study analyzed 18,857 cases, with 655 (3.5%) in the IMA group and 18,202 (96.5%) in the non-IMA group. The IMA group predominantly consisted of older individuals (median age 70 vs. 68; $p<0.001$), had fewer smokers (63% vs. 73%; $p<0.001$), and included more individuals of Hispanic or Latino ethnicity (4.3% vs. 2.7%; $p=0.007$). This group was more likely to be diagnosed with early-stage cancer and less likely to have stage 4 cancer at diagnosis (stage 1: 23% vs. 14%, stage 2: 18% vs. 7.3%, stage 3: 23% vs. 17%, stage 4: 36% vs. 62%; $p<0.001$). They exhibited significantly lower tumor mutational and neoantigen burdens (median 3.1 vs. 4.6 mutations/Mb and 6 vs. 9 neoantigens/Mb, respectively; both $p<0.001$), fewer positive PD-L1 statuses (27% vs. 58%; $p<0.001$), and different immune cell infiltration patterns (Table). Gene expression analysis revealed 416 upregulated and 258 downregulated genes in the IMA group compared to the non-IMA group. **Conclusions:** This analysis underscores the unique clinicopathologic and molecular characteristics of IMAs. An improved understanding of IMA's biological behavior could lead to the development of more effective, personalized treatment strategies. Research Sponsor: None.

Immune cell Type,Median (Q1, Q3)	IMA (*n* = 655)	Non-IMA (*n* = 18,202)	*p*-value
All	24 (18, 29)	25 (17, 34)	<0.001
B cell	22 (12, 33)	18 (8, 30)	<0.001
CD4 T cell	26 (20, 33)	24 (17, 32)	<0.001
CD8 T cell	7.9 (3.9, 11.1)	6.7 (1.4, 10.3)	<0.001
NK cell	11 (7, 17)	11 (6, 17)	0.30
Macrophage	27 (19, 37)	33 (22, 47)	<0.001

Predicting response of patients with NSCLC to immunotherapy using innate immune fitness (IIF) profiling.

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Background: Aberrant activity of AID/APOBEC deaminase enzymes can cause 'off-target' somatic mutations in cancerous cells. Mutations associated with deaminases and other mechanisms can be quantified using metrics relating to motif usage, strand bias, transitions/transversions, codon context, and amino acid changes. Collectively, these metrics form an Innate Immune Fitness (IIF) profile (US Patent 20200370124). The aim of this project was to conduct IIF profiling on a cohort of Non-Small Cell Lung Cancer (NSCLC) patients treated with immune checkpoint inhibitors (ICI), and use the IIF profiles to build and evaluate a predictive model. **Methods:** Whole exome and progression-free survival (PFS) data was obtained from Rizvi et al. 2015, Hellmann et al. 2018, Miao et al. 2018, Fang et al. 2019, Frigola et al. 2021, and Ravi et al. 2023 (n = 515). IIF profiles were generated using CRIS (v5.0.0; GMDx Genomics Ltd). Patients were classified as a 'Responder' (PFS $>$ 12 months or Complete Response; n = 148) or 'Non-Responder' (PFS $\leq$ 12 months; n = 367). Machine learning models were generated using the H2O.ai AutoML platform and evaluated using multiple rounds of cross-validation. Patient response predictions were collated for each patient and a consensus 'IIF Score' was calculated. Multivariable analysis of IIF Score, TMB (10mut/Mb) and PD-L1 TPS ($<$1%, 1% - 50%, $>$ 50%) was conducted using a Cox proportional-hazards model. **Results:** The predictive accuracy of IIF Scores was 76% (Sensitivity = 58%; Specificity = 83% , NPV = 83% , PPV = 58%) with a Hazard Ratio (HR) of 0.39 (0.29-0.53; $p < 0.001$; corrected for TMB and PD-L1). In comparison, the predictive accuracy of TMB was 67% (Sensitivity = 53%; Specificity = 79% , NPV = 79% , PPV = 44%), HR = 0.77 (0.59-1.00; p = 0.049; corrected for IIF Score and PD-L1). 'PD-L1 $>$ 50%' accuracy was 53% and HR = 0.64 (0.44-0.94; p = 0.023; corrected for IIF Score and TMB). The Area Under the Curve (AUC) for IIF Score was significantly higher than TMB (0.77 vs 0.70; DeLong test: $p < 0.001$). **Conclusions:** IIF Score was the strongest predictor of patient response to ICI. Despite the inherent limitations of combining data from multiple cohorts, IIF Score outperformed TMB and PD-L1 in predictive accuracy, HR and AUC. With a Negative Predictive Value of 83%, these results support the use of IIF Score as a biomarker for identifying ICI Non-Responders in NSCLC patients. Research Sponsor: GMDx Genomics Ltd. Research Sponsor: None.

8039 Poster Session

The genomic, transcriptomic, and immunological profile of patients with recurrent/refractory NSCLC.

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Background: Lung cancer is the leading cause of cancer-related deaths worldwide, and often presents at advanced stages, with > 50% of patients presenting as stage III or IV. Patients with recurrent stage III NSCLC (R/R) previously treated with definitive chemoradiation and immunotherapy consolidation may have a difference in overall survival compared to *de novo* stage IV (DN). In this study, we aim to compare the molecular and immune landscapes of these two patient populations to identify potential genomic patterns and biomarkers of resistance. **Methods:** 3728 NSCLC specimens underwent sequencing of DNA (592-gene panel or whole exome) or RNA (whole transcriptome) or immunohistochemistry at Caris Life Sciences (Phoenix, AZ). Patients were classified as R/R (n = 26) if they received Durvalumab and chemoradiation within 12 months (m) before tissue collection and treated with Pembrolizumab within 6 m after tissue collection. Patients treated with Pembrolizumab within 6 months after tissue collection and had no prior (or post) treatment with Durvalumab and chemoradiation at any point in time were classified as DN (n = 3702). Tumor microenvironment (TME) cell fractions were estimated from bulk RNA sequencing using QuanTIseq. Significance was determined using chi-square, Mann Whitney U and adjusted for multiple comparisons where applicable ($q < 0.05$). **Results:** *TP53* (91 vs 68%) and *KEAP1* (30 vs. 14%, both $p < 0.05$, $q > 0.05$) mutation prevalence was higher in R/R, whereas a decreased prevalence of *KRAS* mutations was noted in this group (13 vs. 33%) as compared to the DN group. Compared to DN patients, R/R patients were associated with an increased prevalence of mutations in *BCL2* (4.3 vs. 0%, $q < 0.05$), *BCL9* (4.3 vs. 0.2%, $q < 0.05$), *HNF1A* (4.3 vs. 0.2%), *TNFAIP3* (4.3 vs. 0.2%), *AKT1* (4.3 vs. 0.4%), *MAP3K1* (4.3 vs. 0.5%), and *SPEN* (4.3 vs. 0.6%; all $p < 0.05$, $q > 0.05$). Further, copy number amplification of *NUTM1* (4.5 vs. 0%), *SMO* (4.3 vs. 0.5%), *CHIC2* (4.5 vs. 0.2%; all $q < 0.05$), *PIK3CA* (9 vs. 1.2%) and *FLCN* (4.5 vs. 0.3%; both $p < 0.05$, $q > 0.05$) was more common in R/R compared to DN. R/R TME was associated with decreased B cell (2.9 vs 4.4%, $q < 0.05$) and regulatory T cell fractions (1.3 vs. 2.6%, $p < 0.05$, $q > 0.05$). **Conclusions:** R/R patient tumors had distinct molecular alterations and immune landscapes, including an increased prevalence of biomarkers associated with immunotherapy resistance (*TP53* and *KEAP1* mutations) and lower tumor B- and T reg- cell fractions, which may suggest decreased likelihood of response to immunotherapy compared to patients with DN NSCLC. The RR population had a lower-than-expected percentage of *KRAS*mutations. These distinct molecular differences highlight the need for NGS testing in the recurrent setting, despite initial NGS testing at diagnosis. Molecularly targeted interventions may be options in the future for patients with R/R Stage III NSCLC. Research Sponsor: None.

8040 Poster Session

Smoking and pathogenic germline variants in patients with lung cancer.

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Background: Few studies have investigated the correlation of smoking history with pathogenic germline variants (PGVs) in patients diagnosed with lung cancer. With emerging opportunities for PGVs in DNA damage-repair (DDR) genes to inform precision therapies, we investigated the prevalence of PGVs in patients with lung cancer, stratified by smoking status. **Methods:** Germline genetic testing (GGT) (Invitae Corp.) and insurance claims (Komodo Healthcare MapTM) data were reviewed for 14,317 patients with an ICD code for lung cancer from 2015-2023 and hereditary cancer GGT of $\geq$ 10 genes. PGV rates were assessed overall, in DDR genes and in lung cancer related genes. Smoking history was defined by ICD codes. Number of genes tested varied per ordering clinician preference. Clinically actionable PGVs were defined as those associated with clinical management recommendations or trial eligibility per current standard of care guidelines. Chi-square tests were used with significance set to $p < 0.05$. **Results:** The cohort was predominantly female (70.9%), white (65.7%), and over half had a history of smoking (57.1%). PGVs in 73 known cancer-risk genes were identified in 1,804/14,317 (12.6%) patients. Frequencies of PGV were 12.6% (1,026/8,175) in patients with smoking history compared to 12.7% (778/6,142) in those with no reported smoking history. There was no statistically significant difference in DDR gene, *TP53*, or *EGFR* PGV rates for patients with or without smoking history ($p > 0.05$). Mean (SD) age of lung cancer diagnosis was significantly younger for patients with a history of smoking and DDR PGVs (61 (11)) compared to those with negative results (62 (12), $p = 0.005$). There was no significant difference in age of diagnosis between patients with no smoking history and DDR PGVs (60 (12)) and those with negative results (59 (13), $p = 0.888$). PGV rates by clinician-reported ancestry: Black/African-American, 9%; Asian or Pacific Islander, 11%; Hispanic, 12%; White, 13%. Among genes with $>$ 1,000 patients tested, PGVs were most common in *BRCA2* (2.2%), *CHEK2* (2.0%), *ATM* (1.6%), *SPINK1* (1.6%), and *BRCA1* (1.2%). **Conclusions:** In 14,317 patients with lung cancer, 12.6% had PGVs. There was no significant difference in enrichment of PGVs in DDR genes when patients were stratified by reported smoking history, suggesting the enrichment of these genes is independently associated with lung cancer. The age of onset for patients with DDR gene PGVs varied with smoking history, suggesting that risk conferred by these PGVs could be additive to smoking risk. These data reinforce prior studies supporting consideration of GGT for all patients with lung cancer, independent of age or reported smoking history. Research Sponsor: None.

8041 Poster Session

Differentially expressed microRNAs in prediagnostic serum linked to lung cancer up to eight years before diagnosis in prospective, population-based cohorts: A HUNT study.

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Background: With lung cancer incidence and mortality on the rise, blood biomarkers are increasingly in demand for early detection. The aim of this study is to discover and validate novel biomarkers based on next-generation sequencing performed on blood samples from non-cancer, ever-smokers up to eight years prior to diagnosis. **Methods:** Initial consideration was given to serum samples from the population-based prospective HUNT2 and HUNT3 cohorts, age $>$ 18 (n = 98,737). Inclusion criteria for cases were ever-smokers, no prior cancer at study entry, and 0–8 years between blood sampling and lung cancer diagnosis in the discovery and 0-4 years in the validation cohort. Among future cases, equal numbers of adenocarcinoma, squamous cell carcinoma and small-cell lung carcinoma were included. Every subsequent case of lung cancer had a matched control, ratio 1:1. The controls were matched for sex, age at study entry, pack-years, smoking cessation duration, comparable HUNT Lung Cancer Model risk score and no cancer diagnosis until the end of the study. The total number of serum samples included in the discovery and validation dataset were 240 (from HUNT2) and 72 (from HUNT3), respectively. The samples were analyzed by genome-wide small RNA seq (Illumina). **Results:** When we contrasted all cases against all controls, nine differentially expressed microRNAs with AUC $>$ 0.60 (FDR $<$ 0.25) and total raw count of $>$ 0.5 appeared in common in the discovery and validation datasets. Among these, three microRNAs were associated with non-small cell metastatic with mean AUC of 0.65 and 0.76 in the discovery and validation datasets, respectively. Furthermore, the signature of these three microRNAs in combination reached an AUC of 0.75 (discovery) and 0.90 (validation). **Conclusions:** Up to eight years before diagnosis, a small number of substantially differentially expressed microRNAs were found in serum. These intriguing microRNAs can potentially function as early diagnostic indicators for lung cancer, either alone or in combination. Further investigation and validation of these results in a larger prospective serum dataset are required. Research Sponsor: Liaison Committee between the Central Norway Regional Health Authority and the Norwegian University of Science and Technology.

8042 Poster Session

Signatures of early plasticity in the histological transformation of lung cancer.

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Background: Tumor plasticity, especially histological transformation, is an emergent mechanism of therapeutic resistance. Lung adenocarcinoma (LUAD) can transform to small cell lung cancer (SCLC), a more aggressive tumor type of neuroendocrine (NE) histology, leading to EGFR inhibitor resistance and a more aggressive disease phenotype. TP53 and RB1 loss are enriched but insufficient for NE transformation, and it remains unknown what additional molecular changes underlie plasticity. We use single-cell RNA sequencing (scRNA-seq) to profile the intratumoral transcriptional heterogeneity of NE transformation across multiple time points. **Methods:** We performed 10X scRNA-seq in patient samples to create an atlas of NE plasticity (47 transformed and admixed LUAD-SCLC, 10 EGFR/RB1/TP53 mut LUAD, 17 de novo SCLC, 4 normal lung). Our pipeline performed ambient RNA removal, outlier filtering, normalization, and batch correction. Tumor cells from transformed and admixed LUAD-SCLC tumors were divided into the LUAD compartment prior to transformation (pre-transformed LUAD) and the transformed SCLC compartment based on acquisition of NE marker expression. We performed copy-number inference, pseudotime analysis, and estimation of differentiation potential to establish dynamic changes in phenotypic and subclonal architecture across longitudinal timepoints. **Results:** We captured 12,105 (9%) pre-transformed LUAD cells from transformed and admixed LUAD-SCLC tumors. Canonical squamous cell carcinoma genes (KRT5, KRT6A, TP63, SERPINB4) were found to be enriched in this pre-transformed LUAD compartment. By projecting a force-directed layout of cells from these samples, we modeled the transition between LUAD, LUSC, and SCLC cell types. Genetic pathways promoting angiogenesis, inflammatory signaling, epithelial-to-mesenchymal transition, and RAS/RAF signaling were highly overexpressed during LUAD-LUSC transformation. Furthermore, we show that macrophages from transforming LUAD-LUSC tumors exhibit a pro-fibrotic phenotype. CNV inference revealed distinct subclonal populations in pre-transformed LUAD tumors. Subclones with high CNV burden and high differentiation potential represented early plastic cells whose lineage could be traced to matched longitudinal post-transformation samples. **Conclusions:** There is remarkable intratumoral heterogeneity within transforming LUAD. Squamous transformation, mediated by early RAS/RAF signaling, may represent a precursor to SCLC transformation. Identifying early hallmarks of plasticity can help stratify patients at high risk for transformation and reveal therapeutic vulnerabilities. Research Sponsor: American Lung Association; Druckenmiller Center for Lung Cancer Research; U.S. National Institutes of Health; National Cancer Institute.

8043 Poster Session

Comprehensive analysis of predictive factors for efficacy in concurrent chemoradiotherapy for locally advanced non-small cell lung cancer, utilizing individual patient data from the Japan lung cancer society integrated clinical trial database: Is there room for further improvement?

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Background: The standard treatment for unresectable, locally advanced NSCLC is concurrent chemoradiotherapy followed by durvalumab. While the effectiveness of chemoradiotherapy is pivotal, the exploration into predictive factors of the efficacy is notably limited. **Methods:** The Japanese Lung Cancer Society (JLCS) integrated eight randomized Phase II/III trials (JCOG9812, JCOG0301, NJLCG0601, OLCSG0007, SPECTRA, TORG1018, WJOG5008L, WJTOG0105) concerning chemoradiotherapy for locally advanced NSCLC, constructing the JLCS Integrated Clinical Trial Database (JIDB), with individual data of 1288 patients. This study analyzed 1162 patients who underwent concurrent chemoradiotherapy, focusing on factors impacting PFS. A logistic regression with the least absolute shrinkage and selection operator (LASSO) analyses for 3-yr PFS were performed, and the five most related factors were further evaluated using the Kaplan-Meier method and log-rank tests. The impact of pneumonitis and esophagitis on PFS was also explored. **Results:** Age [median (Q1;Q3)]; 64 (57;71), male/female; 961/201, Ad/Sq/Oth; 580/446/134, PS 0/1/2; 562/578/5, stage IIIA/IIIB; 468/694, T factor 4/3/2/1/0; 436/158/341/156/3, N factor 3/2/1/0; 300/692/44/62, PS 0/1/2; 562/578/5, primary site; upper, middle/lower lobe; 599/161, BMI; 21.8 (19.7;24.0), weight loss (≥5% within 6m) yes/no; 135/644, LDH (IU/l); 203 (175;276), CRP (mg/dl); 0.70 (0.20;2.60), irradiated dose (Gy); 60 (60;60), combined regimen; platinum/taxane 303, CDDP/mitomycin/vindesine; 254, CDDP/5-FU-based; 196, CDDP/vinorelbine 87, CDDP/pemetrexed 50, others 272. The median PFS in all patients was 9.72m (95% CI; 9.33 – 10.38), with 3-yr, 5-yr, and 10-yr PFS rates of 19.7, 14.3, 10.1%. LASSO logistic regression identified Sq, lower lobe primary, age, pack-years, and weight loss as the top negative influencers. The PFS curve was significantly shorter in patients with lower lobe primary (median of 8.15 *vs.* 9.46m, $p = 0.023$) and weight loss (median of 7.29 *vs.* 9.72m, $p < 0.0001$). Pneumonitis occurred in 50.9% (grade≥3 in 6.7%) and esophagitis in 41.9% (grade≥3 in 3.9%). Grade≥2 pneumonitis shortened PFS (8.2 *vs.* 10.2m, $p = 0.00015$), while, unexpectedly, grade≥1 esophagitis was associated with longer PFS (12.9 *vs.* 8.6m, $p < 0.0001$). **Conclusions:** The efficacy of concurrent chemoradiotherapy varies significantly based on the primary site. Weight loss is a significant predictor of efficacy, as is in metastatic disease. The impact of pneumonitis and esophagitis suggest that modifying lung and esophageal irradiation might enhance treatment efficacy. Further research in this area is still certainly warranted. Research Sponsor: None.

8044 Poster Session

Induction therapy with PD-1 antibody combined with platinum-based doublet chemotherapy for locally-advanced non-small cell lung cancer: A randomised controlled, open-label, phase 2 trial.

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Background: Chemoradiotherpay plus immunotherapy is recommended for unresectable locally-advanced non-small cell lung cancer (NSCLC) based on PACIFIC trial. However, it is unclear whether surgery can provide survival benefit for patients with tumors initially unresectable transformed into resectable ones after chemoimmunotherapy. This trial aims to investigate the efficacy and safety of the therapeutic regimen of chemoimmunotherapy plus surgery or radiotherapy. **Methods:** Patients with unresectable stage IIIB-IIIC NSCLC were enrolled to receive 4 cycles (q21d) of PD-1 antibody (Serplulimab, 4.5mg/kg) and platinum-based doublet chemotherapy. After the induction therapy, those with disease downstaged to IIIA or lower stage and resectable were randomized to receive radical surgery or radiotherapy with a ratio of 1:1, and those with stage IIIB or higher stage or unresectable disease after induction therapy were then treated by oncologists. Primary endpoint was event-free survival (EFS). Secondary endpoints included objective response rate (ORR), major pathologic response (MPR), pathologic complete response (pCR), progression-free survival (PFS), disease-free survival (DFS), overall survival (OS), R0 rate of resection, severe adverse event (SAE) rate, and health related quality of life (HRQol). Preliminary short-term results were collected. **Results:** One hundred patients will be enrolled as planned, and a total of 82 patients were enrolled by the data cutoff date (January 6, 2024). Fifty-four and 28 patients were diagnosed with stage IIIB and IIIC disease, respectively. The percentage of squamous carcinomas, adenocarcinomas, and NSCLCs not otherwise specified were 68.3% (56/82), 15.9% (13/82), and 15.9% (13/82), respectively. ORR in 73 evaluable patients was 74.0% (54/73). Twenty-six of them are still in induction therapy phase, and the other 47 and 9 patients received 4 cycles and 1-3 cycles of induction therapy, respectively. Thirty-one patients had downstaged and resectable disease after 4 cycles of induction therapy, and 26 of them were randomized to arm A (n = 13) and arm B (n = 13), and 5 refused randomization (3 received surgery). One patient received surgery after 2 cycles of induction therapy. In 56 patients finished 1-4 cycles of induction therapy, the rate of conversion to resectability was 57.1% (32/56). In total, 17 patients received surgery, and the MPR and pCR rate in 16 evaluable patients were 62.5% (10/16) and 31.3% (5/16), respectively. The grade 3-5 adverse event rate in 56 patients finished induction therapy was 50.0% (28/56). One patient died of immune-related pneumonia. **Conclusions:** Induction therapy with PD-1 antibody (Serplulimab) and chemotherapy could transform half of unresectable stage IIIB-IIIC NSCLC into resectable, and the efficacy and safety were satisfactory. Clinical trial information: NCT05766800. Research Sponsor: None.

Neoadjuvant and perioperative immunotherapy in resectable non-small cell lung cancer (NSCLC): A systematic review and extracted individual patient data meta-analysis.

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Background: Neoadjuvant and perioperative immunotherapy are emerging approaches for resectable NSCLC. However, survival outcomes are still immature and subgroup analyses are underpowered. We report extracted individual patient (pt) data (eIPD) and trial-level (TL) meta-analyses of phase II and III randomized controlled trials (RCTs) in this setting. **Methods:** The systematic review included Cochrane, Embase, and major oncology conferences (ASCO annual meetings, ESMO meetings, WCLC meetings). Primary objectives were eIPD event-free survival (EFS) and overall survival (OS). Secondary objectives included eIPD and TL meta-analysis of subgroups. Kaplan-Meier plots of time-to-event outcomes were reconstructed with WebPlotDigitizer (v4.6, 2022), and eIPD was estimated with IPDfromKM (v0.1.10, 2020) stratified by study. Comparisons between arms were made in a 1-stage model with a Cox Proportional Hazards model stratified by study. The difference of restricted mean survival time (D-RMST), a quantification of the postponement of an event during a specified interval, was used to compare survival when the proportional hazard assumption (PHA) was violated, tau being the shortest follow-up time of the available trials. TL meta-analysis was performed with a random effects model. This meta-analysis was registered in the PROSPERO database under CRD42024502150. **Results:** Seven RCTs (AEGEAN, CM816, CM77T, KN671, NADIM II, NeoTorch, and Lei et al. [ESMO IOTECH 2022, #560]) were identified, comprising 2995 pts. EFS analysis included all pts, with HR of 0.58 (0.52-0.65; $p<0.01$). OS analysis (1645 evaluable pts from 4 trials) showed a D-RMST of 5.17 mo. ($p<0.01$) due to PHA violation. Full eIPD analysis in the table. TL meta-analysis showed benefit in all subgroups, including PD-L1 expression, histology, stage, smoking status, sex, and age. TL EFS and OS results were comparable to results obtained from eIPD analysis, with low heterogeneity measures. **Conclusions:** This meta-analysis provides robust and nuanced insights into the positive impact of immunotherapy in resectable NSCLC. While evidence supports its efficacy, uncertainty surrounding the benefit in stage < III disease highlights the need for additional research and more mature results to guide clinical decision-making effectively. Research Sponsor: None.

eIPD analysis of survival outcomes.

Outcome	N Patients	N Studies	HR (95% CI)	p value	D-RMST p value
EFS	2995	7	0.58 (0.52-0.65)	<0.01	-
OS*	1645	4	0.66 (0.55-0.80)	<0.01	<0.01
EFS PD-L1 ≥1%	1192	4	0.50 (0.41-0.61)	<0.01	-
EFS PD-L1 <1%	727	4	0.75 (0.60-0.95)	0.01	-
EFS Non-SCC	551	2	0.61 (0.46-0.81)	<0.01	-
EFS SCC	542	2	0.73 (0.54-0.97)	0.03	-
EFS stage < III	503	3	0.81 (0.58-1.13)	0.2	-
EFS stage III*	1081	6	0.55 (0.44-0.68)	<0.01	<0.01

HR = Hazard ratio, 95% CI = 95% Confidence interval, N = Number of, D-RMST = Difference of restricted mean survival time, * = PHA violation.

Updated results from COAST, a phase 2 study of durvalumab (D) ± oleclumab (O) or monalizumab (M) in patients (pts) with stage III unresectable non-small cell lung cancer (uNSCLC).

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Background: D consolidation after concurrent chemoradiotherapy (cCRT) improves survival in pts with uNSCLC. Rational immunotherapy combinations may further improve outcomes. As radiotherapy can induce expression of CD73, HLA-E (NKG2A ligand), and PD-L1 in tumor cells, all of which suppress antitumor immunity, there is a rationale for blockade of these immune checkpoints after cCRT. Interim results from COAST (NCT03822351), a global, open-label, Phase 2 study of D ± M (anti-NKG2A) or O (anti-CD73) as consolidation therapy in pts with Stage III uNSCLC, suggested improved progression free survival (PFS) with D+O and D+M vs D alone. We present updated efficacy and safety. **Methods:** Pts with histologically / cytologically documented Stage III uNSCLC and ECOG PS 0 / 1 with no progression after cCRT were randomized (1:1:1; stratified by histology) within 42 days post cCRT to receive D 1500 mg IV every 4 weeks (Q4W) for 12 months ± O 3000 mg IV Q2W for two cycles then Q4W or M 750 mg IV Q2W. Primary endpoint: objective response rate (ORR). Key secondary endpoints: safety, PFS, and overall survival (OS). **Results:** From Jan 2019 to Jul 2020, 186 of 189 randomized pts received treatment. Baseline characteristics were generally balanced across arms. As of Jul 18, 2023, median follow-up was 30.1 mo (range, 0.4–48.9). Of pts receiving D, D+O, and D+M, 69.7%, 44.1%, and 41.0% discontinued treatment (Tx), primarily due to progressive disease (42.4%, 18.7%, and 19.6%) or adverse events (AEs; 15.2%, 15.3%, and 14.8%). Median exposure was 7 cycles (range, 1–13) for D, and 13 (1–13) for D+O and D+M. ORR, PFS, and OS (39.6% maturity) are summarized in the Table. Tx-emergent AEs occurred in 98.5%, 96.6%, and 100% (Grade [G] 3/4: 34.8%, 33.9%, and 32.8%) of pts receiving D, D+O, or D+M, respectively; immune-mediated AEs (imAEs) occurred in 34.8%, 25.4%, and 34.4% (G 3/4: 3.0%, 0%, and 3.3%); and the AE of special interest pneumonitis occurred in 16.7%, 20.3%, and 18.0% (G 3/4: 0%, 0%, and 1.6%). Subgroup analyses and biomarker data will be presented. **Conclusions:** D+O and D+M increased ORR and prolonged PFS and OS vs D alone. Safety was similar across arms, with no new safety signals. Further investigation of D, D+O, and D+M in this population is ongoing in the Phase 3 PACIFIC-9 study (NCT05221840). Clinical trial information: NCT03822351. Research Sponsor: AstraZeneca.

	D (n=67)	D+O (n=60)	D+M (n=62)
Confirmed ORR (95% CI), %	23.9 (14.3, 35.9)	35.0 (23.1, 48.4)	40.3 (28.1, 53.6)
Complete / partial response, n (%)	2 (3.0) / 14 (20.9)	0 / 21 (35.0)	3 (4.8) / 22 (35.5)
Median duration of response (95% CI), mo	NR (14.1, NR)	29.9 (17.1, NR)	23.0 (10.2, NR)
Median PFS (95% CI), mo	7.3 (4.0, 13.8)	21.1 (10.4, 30.9)	19.8 (13.6, 31.3)
PFS HR (95% CI)	-	0.59 (0.37, 0.93)	0.63 (0.40, 0.99)
Median OS (95% CI), mo	40.9 (22.6, NR)	NR (31.9, NR)	NR (31.3, NR)
OS HR (95% CI)	-	0.69 (0.40, 1.20)	0.77 (0.44, 1.33)
2-year OS rate (95% CI), %	61.5 (47.4, 72.9)	76.8 (63.3, 85.8)	72.1 (58.6, 81.9)

NR, not reached.

8047 Poster Session

Biomarker testing in early-stage NSCLC: Results from the MYLUNG Consortium.

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Background: The Molecularly Informed Lung Cancer Treatment in a Community Cancer Network: A Pragmatic Consortium (MYLUNG) program seeks to identify and resolve barriers to biomarker testing in patients (pts) with non-small-cell lung cancer (NSCLC). We previously reported prospectively collected molecular testing data in pts with Stage IB-IV NSCLC (Evangelist et al. 2023). Herein we report additional data on molecular testing rates and patterns in the cohort of pts with early-stage (ES) NSCLC. **Methods:** Pts were enrolled from 12/20-9/22 at 18 community practices (76 sites) across the US Oncology Network. Analyses performed in the ES cohort include rates of molecular testing for targets with approved (PD-L1, *EGFR*)or emerging (*ALK*) therapies for ES NSCLC and next-generation sequencing (NGS); reasons for not testing; and treatment (Tx) received, including targeted therapy and immunotherapy (IO). Analyses are preliminary as data collection continues over 5-year follow-up. **Results:** Included in this analysis were 284 pts with newly diagnosed Stage IB-IIIA NSCLC: median age 68y (range 32, 92); 50% female; 54% ECOG 0-1; 61% adenocarcinoma, 36% squamous cell carcinoma. In total, 76% of pts (82% of pts with adenocarcinoma vs 67% with squamous cell carcinoma) had molecular testing ordered prior to or within 12 weeks of initiating first systemic therapy. Rates of testing (either alone or inclusive of other tests) were PD-L1,74%; *EGFR*,71%; *ALK*, 62%; *EGFR* + PD-L1, 61%. In total, 52% of pts had NGS testing; overall, 16% received no molecular testing. The most common reasons for not testing were patient and/or provider attitude/perception (34%) and insufficient tumor tissue (25%). **Conclusions:** New therapeutic options provide a catalyst to increase molecular testing in ES NSCLC. EGFR and PD-L1 testing are now standard for the management of these pts, with other biomarkers emerging. In this study, 54% of pts received testing for PD-L1, EGFR, and ALK, with additional therapy being offered in pts with biomarker-positive tumors; however, 16% still received no molecular testing at all. For pts with EGFRwt/PD-L1+ tumors, prescription of IO increased 1.8-fold post-adjuvant FDA approval. Data from this and future analyses will be used to implement interventions to improve molecular testing rates in NSCLC. Research Sponsor: Amgen; AstraZeneca; Eli Lilly and Company; Genentech; Johnson & Johnson Innovative Medicine; Mirati Therapeutics, Inc.

First systemic therapy for pts with *EGFR*-mutated (*EGFR*mt) and *EGFR*-wild-type (*EGFR*wt)/PD-L1+ tumors.

Tx Received, %	*EGFR*mt/ PD-L1- or Unknown* (N=21)	*EGFR*mt/ PD-L1+* (N=13)	*EGFR*wt/PD-L1+ Pre-Adjuvant IO Approval, 1/20-10/21† (N=18)	*EGFR*wt/PD-L1+ Post-Adjuvant IO Approval, 11/21-12/22† (N=62)
***EGFR*inhibitor alone**	47.6	0	-	-
***EGFR*inhibitor + chemotherapy**	23.8	23.0	-	-
IO alone	0	0	0	11.3
IO + chemotherapy	4.8	38.5	38.9	59.6
Chemotherapy alone	23.8	30.8	44.4	27.4
Clinical trial	0	7.7	5.6	0
None	0	0	11.1	4.8

**EGFR*mt rate of 20% in 172 pts with *EGFR* testing †Pts tested for PD-L1, *EGFR*, and *ALK*; analysis excluded 4 pts receiving IO in neoadjuvant setting only

8048 Poster Session

Final survival outcomes and exploratory biomarker analysis from the randomized, phase 2 neoSCORE trial: Two versus three cycles of neoadjuvant sintilimab plus chemotherapy for resectable non-small cell lung cancer.

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Background: In the neoSCORE trial (NCT04459611), three cycles of neoadjuvant sintilimab plus chemotherapy achieved a numerically higher major pathological response (MPR) rate compared to two cycles. However, the relationship between MPR and survival in resectable non-small cell lung cancer (NSCLC) patients receiving neoadjuvant immunotherapy is not currently fully elucidated. Furthermore, reliable predictive biomarkers are still lacking. Here, we report the survival and biomarker results of the study. **Methods:** Eligible patients with stage IB-IIIA resectable NSCLC were randomized 1:1 to receive either two or three cycles of neoadjuvant treatment with sintilimab (200mg) plus platinum-doublet chemotherapy (Q3W). After surgery, patients received totally four doses of perioperative immuno-chemotherapy. The primary endpoint was the MPR rate. Secondary endpoints included the complete pathological response (pCR) rate, objective response rate (ORR), 2-year disease-free survival (DFS) rate, 2-year overall survival (OS) rate, and safety. Tumor samples (n = 19) were obtained for immune biomarker analysis via mass cytometry time of flight (CyTOF). Multiplexed immunofluorescence (mIF) was performed on FFPE tumor samples (n = 42). **Results:** At the data cutoff (15/1/2024), 55 patients received neoadjuvant immuno-chemotherapy and underwent surgical resection, with a median follow-up of 36.1 months. DFS (HR = 1.25, P= 0.595) and OS (HR = 0.88, P= 0.830) were similar between the two-cycle and three-cycle groups. The median DFS and OS were not reached in both groups. The 2-year DFS rate in the two-cycle and three-cycle groups were 76.9% and 65.5%, and the 2-year OS rates were 84.6% and 86.2%, respectively. In a multivariable Cox analysis including clinical characteristics, therapy, and pathological response, only MPR was significantly associated with longer DFS (HR = 0.32, P= 0.044). The AUC for the percentage of residual viable tumor in predicting DFS was 0.649 (P= 0.061). CyTOF analysis demonstrated that increased infiltration of CD8+CD38+CD103- T cells after neoadjuvant immuno-chemotherapy was significantly associated with MPR (P= 0.035). The mIF confirmed that patients achieving MPR showed higher frequencies of CD8+CD38+CD103- T cells than those without MPR (P= 0.005). Additionally, patients with higher proportions of CD8+CD38+CD103- T cells had a trend towards improved DFS (HR = 0.39, P= 0.061) and OS (HR = 0.45, P= 0.259). **Conclusions:** Neoadjuvant sintilimab plus chemotherapy was feasible and demonstrated a robust and persistent survival benefit in resectable NSCLC. MPR was associated with improved DFS. Increased CD8+CD38+CD103- T cells were associated with MPR, with a trend towards a better survival benefit, suggesting that it could be a promising predictive biomarker. Clinical trial information: NCT04459611. Research Sponsor: None.

8049 Poster Session

Multi-institution real world analysis of patients with non-small cell lung cancer (NSCLC) treated with standard of care (SOC) neoadjuvant chemo-immunotherapy (chemoIO).

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Background: The approval of neoadjuvant chemoIO transformed the treatment paradigm for patients (pts) with early-stage, resectable NSCLC. Here we present a multi-institution, real world analysis of pts treated with neoadjuvant chemoIO as SOC. **Methods:** This was a retrospective analysis performed across 3 academic institutions. Pts were eligible if they received neoadjuvant chemoIO as SOC therapy for NSCLC with intent to proceed to surgery. **Results:** 107 pts were included. Median age was 69 (range, 45-84); 47% were male and 83% were white. 84% were former/current smokers with median 35 pack year history. ECOG scores of 0/1/2 at treatment start were 55%/44%/1%, respectively. Histologies were 65% adenocarcinoma, 27% squamous, and 7% other. PD-L1 scores (in 93% of pts) were $\geq$ 50% in 30%, and median TMB (in 73% of pts) was 8.2 (range, 0-56). Of tumors with next generation sequencing (81%), 45% had *KRAS* mutation and 18% had other oncogenic driver present. Pts were clinical stage IB (0.9%), IIA (6%), IIB (24%), IIIA (60%), or IIIB (8%); 47% had N2 disease and 3% had N3. 78% of pts underwent $\geq$ 3 cycles of chemoIO, with most pts receiving carboplatin (70%). 11 pts (10%) experienced grade $\geq$ 3 immune-related adverse events, 72% of which were pre-op. 82 pts (77%) proceeded to surgical resection. Of those who did not undergo surgery, 68% were stage III. The most common reason for no surgery was progression (PD)/unresectability (52%), followed by operability (36%) and pt decision (8%). 2 pts (2%) proceeded to surgery but had unresectable tumors. Median interval between last cycle of induction and surgery was 43 days (d) (range, 17-210); median length of stay was 4d (range, 1-21). 5 of 79 (6%) were readmitted within 30d. For pts without resection (27), 48% underwent chemoradiation (CRT), 26% RT alone, and 15% systemic therapy. 29 tumors (36%) demonstrated major pathologic response (MPR); of these, 16 (20%) had pathologic complete response (pCR). 2 pts had no decrement in viable tumor. Of 79 pts with adjuvant treatment data, 11% underwent RT alone, in combination with chemo, or in sequence with systemic therapy; 8% were recommended for RT but declined. 24% had systemic treatment including 14% IO, 6% targeted therapy, and 4% chemo. 18/107 pts (17%) had PD; 14/18 had stage III disease. PD occurred in 10/25 pts (40%) who did not have surgery; 6 of those had undergone definitive CRT or RT. PD occurred in 8/82 pts (10%) after surgery; of these, 5 had undergone adjuvant treatment at median 58d (range, 33-103). **Conclusions:** Real world analysis demonstrated older, frailer pts with more advanced disease than those enrolled on trial; lower chemoIO completion rates but comparable pCR and resection rates were seen. Further analyses will focus on outcomes of pts who did not undergo surgery.
Research Sponsor: None.

LBA8050 **Poster Session**

Radiation therapy (RT)-free pembrolizumab plus chemotherapy (P+C) for PD-L1 TPS ≥50% locally advanced non-small cell lung cancer (LA-NSCLC): Primary analysis from multicenter single arm phase II study (Evolution trial; WJOG11819L).

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Cost analysis of targeted and immunotherapies in operable esophageal and non-small cell lung cancers.

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Background: The National Comprehensive Cancer Network (NCCN) currently recommends the use of Atezolizumab, Nivolumab, Osimertinib, and Pembrolizumab in the perioperative management of non-small cell lung cancers (NSCLC) and esophageal cancers (EC). As the therapeutic landscape evolves, we aim to evaluate the cost implications of these guidelines for eligible patients in the United States. **Methods:** The Medicare Part B payment allowance limits of each medication were ascertained except Osimertinib for which an approximate wholesale acquisition cost (WAC) was reported due to privately administered Medicare Part D coverage. Using national data and published literature, we estimated the annual incidence of patients with newly diagnosed EC and NSCLC who would be eligible for surgery combined with neoadjuvant and/or adjuvant immune and targeted therapy. We applied the estimated cost of the medication based on dosing and duration of treatment, which spanned 1 year for all but adjuvant Osimertinib, which spanned 3 years. Using these data, the cost per patient and the total cost for an incident cohort were estimated. **Results:** We estimated that 8,602 patients with newly diagnosed EC would be eligible for adjuvant Nivolumab; the cost to treat one patient was $248,529, and the cost to treat one incident cohort was approximately $2 billion (Table). We estimated that 50,409 patients with NSCLC will meet the criteria for neoadjuvant Nivolumab with a total cost of three cycles of $32,894 per patient and $1.7 billion per cohort. Among NSCLC patients who may undergo resection and qualify for adjuvant therapy (Stage IB – IIA with high-risk features or IIB-IIIA), 85,063 patients are anticipated to be EGFR-negative and treated with adjuvant Atezolizumab or Pembrolizumab. Treatment costs range from $178,584 – $197,320 per patient with up to $16 billion cost per cohort. The cost to treat one patient with adjuvant Osimertinib was $556,720, and the cost to treat one incident cohort was close to $10 billion. In total, the cost to treat an incident cohort of eligible operable thoracic malignancies could exceed $30 billion. **Conclusions:** Neoadjuvant and adjuvant immune and targeted therapy in operable thoracic patients is associated with a significant cost burden. Prospective large-scale studies are needed to assess cost-effectiveness, particularly given the paucity of superior overall survival data with these agents. Research Sponsor: None.

Cost of targeted and immunotherapies in operable NSCLC and EC.

Cancer	Therapy	Cost per Person	N of Incident Cases	Cost to Medicare to Treat Incident Cohort
Esophagus	Adjuvant Nivolumab	$ 248,529	8,602	$ 2,137,847,490
NSCLC	Neoadjuvant Nivolumab	$ 32,894	50,409	$1,658,131,466
NSCLC (non-EGFR)	Adjuvant Atezolizumab or Pembrolizumab	$ 178,584 – $ 197,320	85,063	$ 15,190,890,792 – $ 16,784,631,160
NSCLC (EGFR +)	Adjuvant Osimertinib	$ 556,720	17,423	$ 9,699,728,624
Total Cost		$ 28,686,598,372 – $ 30,280,338,740		

Analysis of outcomes in resected early-stage non-small cell lung cancer (NSCLC) with rare targetable driver mutations.

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Background: As postoperative adjuvant NSCLC treatment has evolved with *EGFR* and *ALK* targeted therapies, consideration may be given to treating other NSCLC with targetable mutations. Thus, having baseline outcomes for early-stage NSCLC with these targetable mutations is crucial, given their rarity. This study reports on recurrence-free survival (RFS) and overall survival (OS) in patients with resected NSCLC with *treatable* rare driver mutations. **Methods:** A retrospective single centre study identified stage I-III NSCLC patients with rare targetable mutations who underwent curative surgery. Tissue based next-generation sequencing identified mutations in *KRAS* G12C, *EGFR* Exon20, *ERBB2*, *ALK*, *ROS1*, *BRAF*V600E, *MET* exon14 skipping, *RET*. Baseline characteristics, adjuvant chemotherapy, mutation subtype, and *TP53* co-mutation were correlated with RFS and OS using Cox regression. The *KRAS* G12C cohort was used as the reference for survival comparisons. **Results:** Among 201 patients (mean age: 66.4, 63% female) 61% had stage I, 19% stage II, 20% stage III. Predominant histology was adenocarcinoma (95%) and lobectomy (77%) was the most common surgery. Adjuvant chemotherapy was given to 37% (median 4 cycles). Mutations identified included: *KRAS* G12C (87, 43%), *EGFR* Exon 20 (27, 13%), *ERBB2* (23, 11%), *MET* (20, 10%), *ALK* (14, 7%), *ROS1* (13, 6%), *BRAF* (10, 5%) and *RET* (5, 2%). For all patients, 5-year survival probabilities were 75% stage I, 56% stage II (Hazard ratio [HR]: 2.17, p=0.038), 55% for stage III (HR: 2.38, p=0.015). Stage was also a significant predictor of RFS: stage II (HR: 1.90, p=0.04), stage III (HR: 2.26, p=0.006) vs stage I. *TP53* co-mutation was associated with poorer OS (stage-adjusted HR (aHR): 2.50, p=0.004) and RFS (aHR: 1.70, p=0.037). All patients with rare mutations had shorter RFS compared to those with *KRAS* G12C mutation (Table). The difference for *ERBB2* was significant (aHR 2.26, p=0.014), with only 37% of patients relapse free at 5 years. In contrast, except for *ERBB2*, other mutations were associated with *better* OS, with fusion mutations having the greatest difference (aHR 0.24, p=0.021). *ERBB2* mutation had the highest cumulative incidence of brain metastasis, 29% at 5 years. **Conclusions:** Despite consistently poorer RFS, our study shows that, with the exception of ERBB2, OS of all other rare mutations was superior to KRAS G12C mutated NSCLC. TP53 co-mutation was demonstrated to be prognostic of poorer outcome. These dichotomous results may be explained by the use of targeted treatments at relapse, and suggest a potential role of targeted agents in the adjuvant setting. Research Sponsor: None.

Mutation	RFS			OS			Brain Metastases at 5 years (%)
	aHR	p	5-yr RFS	aHR	p	5-yr OS	
***KRAS* G12C N=87**	Ref		61%	Ref		64%	1.9%
***EGFR* Exon 20 N=27**	1.13	0.73	49%	0.86	0.71	56%	18%
***ERBB2* N=23**	2.26	**0.014**	37%	1.09	0.84	53%	29%
***MET* Exon 14 N=20**	1.22	0.72	77%	0.60	0.51	84%	0
***Other* N=30**	1.40	0.30	78%	0.18	0.02	93%	20%
All fusions	1.54	0.18	52%	0.24	**0.021**	90%	21%

Prediction of recurrence in stage I EGFR mutation-positive NSCLC: Combination of CT appearance and selected co-occurring gene alterations by machine learning.

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Background: Predicting the risk of postoperative recurrence is becoming increasingly important in patients (pts) with resectable *EGFR* mutation positive (*EGFR*m) non-small cell lung cancer (NSCLC) after the ADAURA trial. The presence of non-solid ground-grass opacity (GGO) component on computed tomography (CT) images is known to affect the prognosis of stage I lung cancer. Only a few reports investigating the relationship between gene alterations and CT images in stage I *EGFR*m NSCLC. **Methods:** We have developed a machine learning-based model to predict recurrence within five years in TNM stage I (UICC 8th) *EGFR*m NSCLC pts who underwent surgery between 1985 and 2019 using whole exome sequencing in the PRISM project. We evaluated the pts' characteristics, recurrence-free survival (RFS), the CT appearance (pure GGO and part solid [GGO]), without GGO [pure solid]), and consolidation tumor ratio (CTraio). Then, we analyzed the correlation between the image findings and gene alterations predicting a high risk of recurrence. **Results:** Among 1351 pts, stage I, *EGFR*m were 308 (22.8%). The median RFS for stage I *EGFR*-m pts was 123.2 months (m). In the prediction model, *TP53* and *RBM10* genes were among the gene alterations that had a high impact on the high-risk recurrence within five years. Among the 302 stage I, *EGFR*m pts for whom CT images were available, 166 (55.6%) pts had GGO, and 137 (45.4%) pts had pure solid appearance. The median CTratio was 0.87. The median RFS was not reached (NR) for GGO, 86.5m for pure solid (hazard ratio [HR] 2.42 [1.58-3.73], $p<0.0001$). There was a negative correlation indicating that the larger the CTratio, the shorter the RFS ($p<0.0047$). The proportion of *TP53* mutation (TP53m) was lower in GGO and higher in pure solid ($p<0.0001$, Table). The median RFS was NR for GGO plus TP53m-negative pts, was 119.7m for GGO plus TP53m-positive pts, 84.8m for pure solid plus TP53m-negative pts, and 98.8m for pure solid plus TP53m-positive pts, respectively. Among pts with $0 \leqq \text{CTratio} < 0.5$ 46 (15.2%), with $0.5 \leqq \text{CTratio} < 1$ 119 (39.4%), and with CTratio=1 137 (45.4%), the proportion of TP53m increased as the CTratio increased. **Conclusions:** We found a linear relationship between CTratio and proportion of co-occurring TP53m with *EGFR*m. Combination of CT appearance (GGO or pure solid) and co-occurring TP53m can predict recurrence in stage I, *EGFR*m NSCLC. Research Sponsor: None.

	GGO		Pure Solid (without GGO)	
n (%)	165 (54.6)		137 (45.4)	
median RFS (m), 95%CI	NR (119.7-NR)		86.5 (71.0-107.4)	
5year RFS rate (%)	82.9		64.2	
HR (95%CI), p-value	1		2.42 (1.58-3.73), p<0.0001	
Co-occurring TP53-mutation	negative	positive	negative	positive
n (%)	135 (81.8)	30 (18.2)	81 (59.1)	56 (40.9)
median RFS (m), 95%CI	NR (123.2-NR)	119.7 (53.1-NR)	84.8 (70.8-NR)	98.8 (57.1-NR)
5year RFS rate (%)	83.8	58.7	61.1	60.0
HR (95%CI)	1	2.24 (1.07-4.70)	2.87 (1.68-4.91)	2.94 (1.65-5.21)

8054 Poster Session

Neoadjuvant hypofractionated radiotherapy combined with pembrolizumab plus chemotherapy for potentially resectable non-small cell lung cancer: A phase Ib study.

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Background: Neoadjuvant PD-1 inhibitor plus chemotherapy in resectable non-small cell lung cancer (NSCLC) has become a standard of care. hypofractioned radiotherapy (HFRT) served as an immunomodulator and enhanced the effect of preoperative immunotherapy. In this phase Ib study, we evaluated the safety and feasibility of neoadjuvant HFRT with pembrolizumab plus chemotherapy in patients with potentially resectable stage III NSCLC. **Methods:** Patients with potentially resectable stage III NSCLC with EGFR/ALK wild-type were recruited to receive HFRT to the primary tumor followed by two cycles of pembrolizumab (100 mg/body) plus platinum-based doublet chemotherapy (Q3W). HFRT was delivered using 3 daily fractions, with a dose of 24 Gy for peripheral lesions and 12 Gy for central lesions. Central lesion is defined as a 2 cm area around the pulmonary artery and main bronchus. The decision for surgery was made through multidisciplinary team (MDT) discussion within a 4–6-week period after the completion of neoadjuvant treatment. Patients underwent surgery followed by adjuvant pembrolizumab for 2 years. Primary endpoint was safety. Secondary endpoints were efficacy, such as pathological complete response (pCR), progression-free survival (PFS), and overall survival (OS). **Results:** Between April 2021 and November 2023, 17 patients were enrolled with a median age of 66 years (range 54-74) and 15 (88.2%) having squamous cell lung cancer. 12 (70.6%) patients had stage IIIB disease, and 10 (58.8%) had central primary lesion. PD-L1 was ≥1% in 9 patients (52.9%). All patients received HFRT and at least one cycle of immunochemotherapy. No grade 3 or high adverse events were observed during neoadjuvant therapy. Only one patient had grade 1 nephrotoxicity, and another patient had grade 2 pneumonitis. A partial response was achieved in 16 out of 17 patients (94.1%), while one patient had stable disease after neoadjuvant therapy. Following MDT discussion, 11 patients (64.7%) met the surgical standards, while the remaining 6 patients were transitioned to definitive chemoradiotherapy. Among the 11 patients who underwent surgery, 8 (72.7%) achieved R0 resection, and 6 patients (54.5%) attained pCR. Only one patient died from intraoperative bleeding, and the remaining patients were followed up. The median PFS was 21.7 months, median OS were not reached, and the 2-year OS rate was 85.6%. The study was terminated early due to slow recruitment. **Conclusions:** Neoadjuvant HFRT with immunotherapy for potentially resectable stage III NSCLC is a tolerable treatment with an improved surgical conversion rate and pCR rate. Clinical trial information: ChiCTR2100045361. Research Sponsor: None.

8055 Poster Session

Operability changes in patients with NSCLC after neoadjuvant chemotherapy and anti-PD-1/PD-L1.

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Background: The neoadjuvant (NA) treatment for non-small cell lung cancer (NSCLC) has evolved with the emergence of chemotherapy (CT) and immunotherapy (IO) combinations as the standard of care. However, limited data exist on the impact of these treatments on functional parameters. This is a multicenter retrospective study, focuses on respiratory function in NSCLC patients (pts) undergoing NA therapy. **Methods:** We conducted a multicenter study of NSCLC pts undergone NA from January 2021 to December 2023 with pre- and post-NA respiratory tests. They were treated with CT or CT-IO. Clinical, pathological and surgical variables were collected. Comparative analysis between DLCO (Diffusing Capacity for Carbon Monoxide), FEV1 (Forced Espiratory Volume in first second) and FVC (Forced Vital Capacity) pre- and post-NA in CT/CT-IO subgroups were studied. We performed a regression univariate analysis with variables influencing DLCO, FEV1 and FVC variations. **Results:** We included 159 patients from 13 hospitals. Median age was 70, with 67% men, 72% ECOG 0, and 93% smokers or ex-smokers. Squamous histology was present in 50.3%, and PD-L1 expression was balanced. Non-G12C KRAS mutation was the most common molecular finding (15%). Pre-NA treatment stages included IB (0.6%), IIA (0.6%), IIB (1.8%), IIIA (89%), and IIIB (6.9%). NA treatment comprised CT in 25% and CT-IO in 75%. Surgery was performed in 88.5% pts, with lobectomy as the most common procedure (82%). After surgery, ypTNM: cPR (35%); mPR (28.7%); ypN1 (10 %); ypN2 (7.9%). 20 pts did not surgery: persistent N2 (25%), M1 (10%), complications (15%) and functional inoperability (50%). No significant differences were found in median pre-NA DLCO, FEV1, and FVC between CT and CT-IO subgroups. However, post-NA DLCO showed a reduction in CTIO (69.7% vs. CT 77%, p=0.003), while post-NA FEV1 and FVC increased in CT-IO (FEV1: 88% vs. CT 81.8%, p=0.029; FVC: 100.6% vs. CT 91%, p=0.003). Variation rates from pre- to post-NA values indicated a trend towards DLCO reduction in CT-IO (13% vs. CT 8%, p=0.08), and an increase in FEV1 (5% vs. CT 0%, p=0.002) and FVC (4% vs. CT -1.2%, p=0.001). Complications during NA treatment showed no significant differences. 10 patients were ineligible for surgery, with functional deterioration more prominent in the CT-IO subgroup, though without statistical significance (p=0.091). Conversions to thoracotomy were more common in CT-IO (66.6% vs. CT 33.3%, p=0.49). Univariate regression analysis revealed trends towards significance between FVC and liver disease, renal disease, and type of NA, as well as between FEV1 and liver disease, BMI, type of NA, and patient outcomes. **Conclusions:** Significant differences in post-NA functional variables were observed between CT-IO and CT subgroups, including lower DLCO and higher FEV1/FVC in the CT-IO group. Prospective validation is essential to confirm these findings. Research Sponsor: None.

8057 Poster Session

Four-year outcomes and circulating tumor DNA (ctDNA) analysis of pembrolizumab (pembro) plus concurrent chemoradiation therapy (cCRT) in unresectable, locally advanced, stage III non–small-cell lung cancer (NSCLC): From KEYNOTE-799.

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Background: The nonrandomized phase 2 KEYNOTE-799 study (NCT03631784) of pembro + cCRT in previously untreated unresectable, locally advanced, stage III NSCLC demonstrated an ORR of 70.5% in cohort A (squamous and nonsquamous) and 70.6% in cohort B (nonsquamous only) after median follow-up of 18.5 mo and 13.7 mo, respectively. We present outcomes with ☐4 y of follow-up and analysis of ctDNA. **Methods:** Eligible patients (pts) were aged ≥18 y with unresectable confirmed stage IIIA–C NSCLC (per AJCC v8), measurable disease per RECIST v1.1, and ECOG PS 0 or 1. Pts in cohort A (squamous and nonsquamous) received carboplatin + paclitaxel and pembro 200 mg for one 3-wk cycle, followed by carboplatin + paclitaxel QW for 6 wks + 2 cycles of pembro 200 mg Q3W + standard thoracic radiotherapy (TRT). Pts in cohort B (nonsquamous only) received 3 cycles of cisplatin, pemetrexed, and pembro 200 mg Q3W + standard TRT in cycles 2 and 3. All pts received 14 additional cycles of pembro. Primary endpoints were ORR per RECIST v1.1 by BICR and incidence of grade ≥3 pneumonitis (per NCI CTCAE v4.0). As an exploratory endpoint, tumor ctDNA was assessed in available plasma samples collected at baseline and cycle 7 using the Signatera ctDNA assay. **Results:** Of 214 pts enrolled, including 112 in cohort A and 102 in cohort B. Median (range) time from first dose to database cutoff (Oct 16, 2023) was 54.1 (49.2–59.4) and 49.3 (38.4–59.1) mo, respectively. ORR was 71.4% in cohort A and 74.5% in cohort B (Table). Grade ≥3 pneumonitis (primary endpoint) occurred in 9 pts (8.0%) in cohort A and 7 (6.9%) in cohort B. Grade 3–5 treatment-related AEs occurred in 73 pts (65.2%) in cohort A and 52 (51.0%) in cohort B. Of ~136 samples sent for sequencing, 73 pts (~53.7%) had samples evaluable for ctDNA at baseline. ORR was 68.7% in pts with ctDNA detectable (n = 67) vs 50.0% in pts with ctDNA non-detectable samples (n = 6) at baseline. Among 46 pts with ctDNA detectable at baseline and evaluated at cycle 7, 32 (69.6%) had cleared ctDNA at cycle 7; these pts had better trends in PFS and OS vs pts who had not cleared ctDNA at cycle 7 (n = 14). **Conclusions:** With ~4 y of follow-up, pembro + cCRT continues to demonstrate durable antitumor activity and manageable safety in previously untreated unresectable, locally advanced stage III NSCLC. ctDNA was evaluable in ~half of the samples assessed; most pts with detectable ctDNA at baseline had cleared ctDNA at cycle 7. Clinical trial information: NCT03631784. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

	Cohort A N = 112	Cohort B N = 102
ORR (95% CI), %	71.4 (62.1–79.6)	74.5 (64.9–82.6)
Median DOR (range), mo	46.5 (1.9+ to 54.5+)	NR (1.6+ to 54.6+)
Median PFS (95% CI), mo	29.0 (16.6–48.5)	37.9 (17.9–NR)
48-mo PFS rate (95% CI), %	40.6 (28.9–52.0)	46.4 (33.7–58.1)
Median OS (95% CI), mo	35.6 (26.1–44.2)	NR (41.1–NR)
48-mo OS rate (95% CI), %	40.2 (31.1–49.1)	54.6 (43.9–64.0)

'+' indicates no PD by the time of last assessment.

The safety and efficacy of induction chemoimmunotherapy in initially unresectable stage III non-small cell lung cancer.

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Background: Definitive concurrent chemoradiation followed by consolidation immunotherapy is the standard of care for unresectable stage III non-small cell lung cancer. Several studies demonstrated addition of induction immunotherapy may further improve outcome, and it is necessary to assess the response-adapted strategy based on early tumor retraction to induction therapy. This study evaluated safety and treatment outcomes of induction chemo-immunotherapy followed by surgery or RT in unresectable stage III NSCLC. **Methods:** Patients with previously untreated, unresectable, pathologically and radiologically confirmed stage III NSCLC, EGFR/ALK-wild-type, with measurable disease were included. Patients received 3 to 4 cycles (Q3W) of chemoimmunotherapy including carboplatin (area under the curve [AUC] 5mg/mL/min), nab-paclitaxel (squamous NSCLC, 260mg/m^2) or pemetrexed (non-squamous NSCLC, 500mg/m^2), and tislelizumab (200mg) . After Multi-Disciplinary Treatment, those operable patients after induction chemoimmunotherapy received radical minimally invasive surgery followed by 14 cycles of tislelizumab. The still unresectable patients received standard thoracic radiotherapy followed by 14 cycles of tislelizumab. Coprimary end points include 24-month progression-free survival (PFS) rate and incidence of grade 3 to 5 pneumonitis. **Results:** Between May 2020 and November 2023 , a total of 59 patients received treatment (54 men [91.5%]; median [range] age, 65 [46-82] years; 34 patients [57.7%] with programmed cell death ligand 1 [PD-L1] tumor proportion score ≥ 1%); 40 patients [67.8%] were squamous cell NSCLC; 33.9%, 45.8%, and 20.3% patients were stage IIIA, IIIB and IIIC. Sixteen patients received radical minimally invasive surgery (9 pCR), 42 patients received thoracic radiotherapy, and 1 patient had brain metastasis after 2 cycles of induction therapy. The median follow-up period was 20.1 (1.9-44.1) months, and median PFS was not reached, the 24-months PFS rate was 77.6% (95%CI, 59.9%-88.2%). The objective response rate was 93.2% (95%CI, 83.5%-98.1%), and DCR was 98.3% (95%CI, 90.9%-100.0%). Grade 3 pneumonitis occurred in 2 of 59 patients (3.4%). **Conclusions:** The findings of this study indicate encouraging antitumor activity and manageable safety of induction chemoimmunotherapy, and the response-adapted strategy requires further exploration in locally advanced unresctable non-small cell lung cancer. Clinical trial information: ChiCTR2200064104. Research Sponsor: None.

Treatment-related adverse events.

Adverse Events	Any Grade (No., %)	Grade 3-5 (No., %)
Pneumonitis	22 (37.3)	2 (3.4)
Dysphagia	16 (27.1)	2 (3.4)
Leukopenia	16 (27.1)	4 (6.8)
Fatigue	15 (25.4)	0
Vomiting	8 (13.6)	0
Rash	8 (13.6)	0
Diarrhea	8 (13.6)	1 (1.7)
Fever	4 (6.8)	0
Hypothyroidism	4 (6.8)	0
Increased transaminases	4 (6.8)	0
Pruritus	4 (6.8)	0
thrombocytopenia	1 (1.7)	0
Adrenal insufficiency	1 (1.7)	0
Hypophysitis	1 (1.7)	0
Myocarditis	1 (1.7)	1 (1.7)

The youngest population under 50 years old (P50) with lung cancer (LC) in the French nationwide real-life KBP cohorts: Evolution since 2000.

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Background: The KBP-CPHG studies are multicenter prospective real-life studies on LC, conducted in France each decade since 2000. We describe the characteristics of the LC in P50, which is a small population and rarely described [1], compare it to the oldest population with LC and describe the evolution since 2000. **Methods:** All patients with LC diagnosed in 2020, in non-academic public hospital were included in KBP 2020. The characteristics of the 8999 patients included in KBP-2020 have already been reported [2]. Only 428 (4.8%) were P50 and included in this cohort. Here, we describe their characteristics compared to the oldest patients from and over 50 years old and with the previous cohorts (KBP-2000 & 2010). **Results:** In KBP-2020, among the P50, the proportion of women is 41.1% vs 34.3% ($p = 0.004$). The proportion of active smokers is greater (79.4% vs 51.5%, $p < 0.0001$) including more cannabis users (28.3% vs 2.3%, $p < 0.0001$). P50 are symptomatic in 81.1% of cases, more often have adenocarcinomas 66.8% vs 55.6%, $p < 0.0001$ and metastatic at diagnosis (67% vs 57.9%, $p < 0.001$) with brain metastasis in 39.9% of cases. The molecular alterations are more often researched in P50 (72.2% vs 55.4%, $p < 0.0001$) and we found a significantly higher proportion of ALK rearrangement (7.2% vs 2.1% $p < 0.0001$) and ROS1 (4.2% vs 1.6 $p < 0.007$) and less KRAS rearrangement (26.8% vs 35.5% $p = 0.013$). P50 have significantly better 3-y overall survival (OS) than ≥ 50 years old, 39.2% [34.5 - 44.6] vs 31.5% [30.4 - 32.6], log-rank test for OS, $p = 0.0003$. Compared to KBP-2000 and 2010, the overall proportion of P50 have been decreasing for 20 years (respectively 12.3%, 8.7% and 4.8%, $p < 0.001$), with an increasing proportion of women (respectively 24.1%, 38.2% and 41.1%, $p < 0.001$). The ECOG PS at diagnosis improves (PS 0/1 = 74.3%, 81.0% and 84.0% respectively, $p = 0.002$). Among the P50, the proportion of non-smokers increases (respectively 4.4%, 9.8% and 11.7%) but there is still a large majority of smokers with a decreasing quantity of tobacco (respectively 35.3 PA, 33.1 PA, 29.1 PA). P50 have significantly better 3y survival in 2020 (39.2% [34.5 - 44.6]) compared to 2000 (19.1% [16.3 - 22.3]). The median OS was 9.8 months [8.9 - 11.2] in 2000, 11.7 [10.3 - 13.8] in 2010 and 21.6 [16.1 - 29.2] in 2020, log-rank test for OS, $p < 0{,}0001$. **Conclusions:** The proportion of P50 with LC has decreased over the last 20 years in France, with an increased proportion of women. In this young population, the proportion of tobacco smokers was still high but has decreased for 20 years and the cannabis consumption was high. Compared to older patients, the PS is better although metastatic diseases were more frequent, and patients were more often symptomatic. Adenocarcinoma was the most frequent histology type. Research Sponsor: Abbvie, AstraZeneca, Amgen, BMS, MSD, Janssen, Bayer, Boehringer Ingelhei, Lilly, Takeda, Sanofi, Roche, Chugai, Pfizer; Fondation du Souffle, Le Nouveau Souffle, Couleur espoir, the labeling of InCa and FHFCNCR Institutional Funding.

Next-generation sequencing (NGS) completion and timeliness using reflex testing protocol for patients with stage II-III non-squamous non-small cell lung cancer (NS-NSCLC).

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Background: Genomic testing is important for early-stage NSCLC due to benefits of adjuvant EGFR and ALK targeted therapies and implications for neoadjuvant immunotherapy decisions. The purpose of this study is to evaluate the completion rates and timeliness of NGS prior to treatment initiation for patients with stage II-III NS-NSCLC, with reflex NGS testing protocols in place. **Methods:** Patients with stage II-III NS-NSCLC diagnosed between 2015 and 2022 at UVA Cancer Center were identified retrospectively. A reflex tissue-based NGS testing protocol was initiated at UVA in early 2015 using in-house TruSight Tumor and later PGDx platforms. Targeted pyrosequencing was performed in cases of NGS failures. The primary outcomes of the study were to evaluate the NGS completion rate and median time from biopsy to results and to any first line treatment (1L), including surgery, radiation, or systemic therapy. Actionable mutation incidence, proportion of patients with test results prior to treatment, and overall survival (OS) were all assessed. Statistical analysis included both descriptive statistics and Kaplan-Meier methodology for overall survival (OS). **Results:** 171 patients met eligibility, 92 (54%) female, 80 (47%) stage II and 91 (53%) stage III. 159 (93%) had known 1L start dates and 99 (58%) received systemic therapy with known dates. Testing completion rates and time to results are shown in the table. Actionable mutations identified included: KRAS 39% (G12C 15%), EGFR 7%, BRAF 4%, MET 2%, RET 1%, and NTRK 1%. There was no difference in NGS success rates between patients with stage II and III diseases, X^2 (1, N = 171) = 2.667, p = 0.102. Median OS was 64.1 months in those with complete NGS testing and 53.4 months in those without complete NGS (p=0.222). **Conclusions:** Reflexive, in-house NGS resulted in a shorter median time from biopsy to results (17 days) and higher completion rate (NGS, 77%; at least limited testing, 92%) compared to historical controls. The majority of patients had NGS results available to inform systemic therapy decisions (69%). While OS was numerically higher for patients with complete NGS, this was not statistically significant. Reflex NGS testing protocols increase the likelihood of obtaining timely results in the new era of adjuvant tyrosine kinase inhibitors and neoadjuvant chemotherapy and immunotherapy. Research Sponsor: None.

	Stage II	Stage III	Total
Total patients	80	91	171
NGS successful - n (%)	65 (81)	66 (73)	131 (77)
NGS or pyrosequencing successful – n (%)	75 (94)	82 (90)	157 (92)
Median Time to Results – calendar days (range)			
NGS (n=131)	16 (9-47)	17 (9-56)	17 (9-56)
Pyrosequencing (n=26)	18 (9-49)	18 (9-64)	18 (9-64)
Timeliness of Completed NGS – n (%)*			
NGS prior to 1L	35 (46)	47 (57)	82 (52)
NGS prior to systemic therapy	27 (79)	41 (63)	68 (69)

*For patients with known treatment start dates.

Clinical outcomes of maintenance durvalumab after definitive concurrent chemoradiotherapy in unresectable locally advanced stage III non-small cell lung cancer according to epidermal growth factor receptor and anaplastic lymphoma kinase status: Korean Cancer Study Group LU-22-18.

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Background: The role of maintenance durvalumab after definitive concurrent chemoradiotherapy (CCRT) in unresectable locally advanced non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (*EGFR*) mutation or anaplastic lymphoma kinase (*ALK*) translocation remains unclear. We compared the effectiveness of durvalumab maintenance therapy in groups with *EGFR/ALK* wild-type versus those with *EGFR*or *ALK* mutations. **Methods:** In this retrospective multicenter observational study, patients with locally advanced NSCLC without progression after CCRT followed by maintenance durvalumab and available molecular test results (*EGFR* and *ALK*) were eligible. The primary objective was to compare progression-free survival (PFS) between *EGFR*/*ALK* wild-type and *EGFR*or *ALK*mutant NSCLC. Secondary objectives include overall survival according to *EGFR*or *ALK* mutation and programmed cell death-ligand 1 (PD-L1) expression. **Results:** Among 339 patients, 279 had wild-type *EGFR/ALK*, 41 had *EGFR* mutations and 19 had *ALK* translocations. The median age was 68 years with 276 males (81.4%) and 63 females (18.6%), 165 (49.3%) had adenocarcinoma, 149 (44.5%) had squamous cell carcinoma, and 21 (6.3%) had other histological types, 120 (35.4%) had stage IIIA, 168 (49.6%) stage IIIB, and 51 (15.0%) had stage IIIC. The majority of patients (n=288, 85%) achieved partial response to CCRT, 2 (0.6%) had a complete response, and 49 patients (14.4%) had stable disease. Excluding 4 patients with unknown PD-L1 tumor proportion score (TPS), 16 (4.8%) had a PD-L1 TPS of 0, 168 (50.1%) had 1-49, and 151 (45.1%) had 50 or higher. The median PFS was 21.4 months (95% CI 17.3–25.3) for the *EGFR*/*ALK* wild-type group and 21.0 months (95% CI 15.7–NA) for the *EGFR* or *ALK* mutant group with no significant difference (p=0.74). Significant differences occurred in PFS based on PD-L1 expression with values of 13.6 (95% CI 10.5–NA), 18.7 (95% CI 15.1–26.9), and 24.7 (95% CI 20.7–NA) months for TPS of 0, 1–49, and 50 or higher, respectively (p=0.02). **Conclusions:** Durvalumab maintenance therapy after definitive CCRT in unresectable locally advanced NSCLC patients with *EGFR*or *ALK* mutation demonstrates comparable clinical outcomes to those with wild-type *EGFR/ALK* when PD-L1 expression is present. Research Sponsor: None.

8062 Poster Session

Anlotinib plus docetaxel in advanced NSCLC progressing on immunotherapy: A pooled analysis of two randomized trials.

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Background: This analysis aimed to evaluate outcomes of anlotinib plus docetaxel versus docetaxel alone in patients with advanced non-small cell lung cancer (NSCLC) after progression on immune-checkpoint inhibitors (ICIs) using the pooled data from two randomized trials (ALTER-L016; ALTER-L018). **Methods:** Eligible patients for this pooled analysis were aged 18-75 years and had EGFR/ALK/ROS1 wild-type advanced NSCLC progressing after first-line ICIs therapy. Patients were randomly assigned to receive anlotinib (10 mg [L016] or 12 mg [L018] once daily on days 1-14) plus docetaxel (60 mg/m^2 [L016] or 75 mg/m^2 [L018], on day 1 every 3 weeks) or docetaxel alone. The primary endpoint was progression-free survival (PFS). Second endpoints included overall survival (OS), objective response rate (ORR), disease control rate (DCR), and safety. **Results:** Total of 71 patients (L016, n = 39; L018, n = 32) who progressed after ICIs were included in this pooled analysis, 40 of whom had received anlotinib plus docetaxel and 31 received docetaxel. Median follow-up for all patients was 27.0 months (IQR, 17.6-31.2). A significant PFS benefit was observed with anlotinib plus docetaxel (5.4 months; 95% CI, 5.0-9.3) over docetaxel alone (2.3 months; 95% CI, 1.4-2.9), with a hazard ratio (HR) of 0.34 (95% CI, 0.18-0.63; $P < 0.001$). Improvement in PFS was seen across most evaluated subgroups. Anlotinib plus docetaxel induced a higher ORR (25.0% vs. 12.9%) and DCR (82.5% vs. 45.2%) over docetaxel alone. Median OS was similar between two arms (16.2 vs. 13.7 months; HR = 0.82 [0.47-1.44]; P = 0.488). Subsequent therapy with ICIs was associated with a longer OS. The incidence of grade 3 or higher treatment-related adverse events was 32.5% with anlotinib plus docetaxel and 6.5% with docetaxel. **Conclusions:** Anlotinib plus docetaxel demonstrated survival and response improvements compared with docetaxel alone in patients with advanced NSCLC progressing after ICIs, with a manageable safety profile. This finding suggested anlotinib plus docetaxel might be effective and safe option in this setting. Clinical trial information: NCT03726736; NCT03624309. Research Sponsor: None.

8063 Poster Session

Lymph node metastasis prediction with non-small cell lung cancer histopathology imaging.

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Background: Lymph nodal metastasis (LNM) plays a critical role in the prognosis and treatment strategy formulation for non-small cell lung cancer (NSCLC). Initial diagnosis typically involves a CT scan, but its sensitivity for detecting mediastinal LNM is limited, sometimes as low as 51%. To improve detection, PET-CT, mediastinoscopy, and Endobronchial ultrasound-guided transbronchial needle aspiration are employed, with sensitivities of 74%, 78%, and 90%, respectively. The ability to anticipate nodal metastasis from primary tumor data could significantly influence clinical decisions, particularly for patients at risk from invasive procedures like EBUS. By leveraging the pathology data from the National Lung Screening Trial (NLST), this study aims to harness machine learning algorithms, with the goal of refining the staging process and individualizing patient care, thus enhancing the therapeutic outcome and potentially sparing patients from the morbidity associated with more invasive diagnostic techniques. **Methods:** This research used digital hematoxylin and eosin (H&E) stained histopathology slide images of NSCLC from the NLST provided by The Cancer Imaging Archive. It excluded cases with undefined nodal or distant metastasis status (Nx or Mx), as well as those with confirmed distant metastasis (M1). Cases were categorized as node positive if they had N1, N2, or N3 disease, and node negative if they had N0 disease. The analysis of pathology slide images was performed using the CLAM analysis pipeline, which operates by creating patches, extracting features via a ResNet-50 model pre-trained on ImageNet, and training models with attention modules that assign scores to each patch. The study was performed using Python 3.7 and the CLAM library. **Results:** 636 whole slide images were analyzed, comprising 453 cases without lymph node metastasis (node negative) and 183 cases with lymph node metastasis (node positive). The study revealed that the CLAM model could predict LNM with an average area under the curve (AUC) of 0.78 over a series of 10 folds. The median sensitivity of the model at the threshold values of 0.3, 0.5, and 0.7 was 0.78, 0.48, and 0.24, respectively. Correspondingly, the median specificity at these same cutoffs was 0.49, 0.91, and 1.00, respectively. **Conclusions:** The study provided a proof of concept that nodal metastasis can be predicted from H&E slide images of primary resections using solely deep learning methods. The integration of deep learning models into the diagnostic process could fundamentally transform how clinicians evaluate the risk of LNM, tailor treatment plans, and ultimately enhance survival rates and quality of life for patients with NSCLC. Research Sponsor: None.

8064 Poster Session

Five-year survival outcomes from the PIT-1 trial: Pemetrexed-cisplatin plus bevacizumab or concurrent thoracic radiation therapy followed by surgery in stage IIIA (N2) nonsquamous non-small cell lung cancer.

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Background: Personized Induction Therapy-1 (PIT-1) is a multicenter, randomized phase II selection design trial of pemetrexed-cisplatin plus bevacizumab (BEV arm) or concurrent thoracic radiation therapy (TRT arm) followed by surgery in patients with stage IIIA (N2) nonsquamous non-small cell lung cancer (NSCLC). The TRT arm was chosen as the investigational induction treatment strategy for a future phase III study based on the results of a numerically higher 2-year progression-free survival (PFS, primary endpoint) in the TRT arm and fatal postoperative complications observed only in the BEV arm. We report updated, exploratory analyses of survival, approximately 5 years after the last patient was randomly assigned. **Methods:** Patients with stage IIIA (N2) nonsquamous NSCLC were randomly assigned (1:1) induction therapy consisting of pemetrexed and cisplatin plus bevacizumab (n = 44) or concurrent TRT (n = 44) followed by surgery. Among them, 38 patients in the BEV arm and 37 patients in the TRT arm underwent surgery. Five-year overall survival (OS), 5-year PFS, and patterns of postoperative recurrence were compared between arms. Prognostic factors of OS were analyzed in surgically resected patients using Cox's proportional hazard model. **Results:** The median follow-up was 66.4 months. In 82 treated patients, the 5-year OS and PFS rates were 63.5% (95% CI: 46.9-76.1) and 26.2% (95% CI: 14.1-40.0) in the BEV arm (n = 42), and 57.2% (95% CI: 40.5-70.8) and 27.5% (95% CI: 14.9-41.7) in the TRT arm (n = 40), respectively. There were no statistical differences in OS (P = 0.572) and PFS (P = 0.356). In 75 surgically resected patients, pathological nodal down stage was the only significant prognostic factor of OS (P = 0.014). Age, sex, smoking status, clinical T stage, clinical N stage based on a computed tomography scan, preoperative serum CEA and CYFRA level, *EGFR* mutation status, pathological complete response, and major pathological response did not have a significant prognostic impact on OS. The patterns of postoperative recurrence were different between arms: locoregional only, in four (11%) and one (3%); distant metastasis only, in 16 (42%) and 21 (57%); and both, in five (13%) and four (11%) in the BEV and TRT arms, respectively. The recurrence rate of ipsilateral hilar or mediastinal lymph nodes (the irradiation field) was significantly lower in the TRT arm (3%) than in the BEV arm (21%, P= 0.01). **Conclusions:** Five-year survival outcomes were not different between the BEV and TRT arms. The TRT arm demonstrated sufficient local control, but insufficient control of distant metastasis so this is an important issue that requires improvement in the future. Clinical trial information: s031180402. Research Sponsor: None.

8065 Poster Session

A phase II, two-cohort study of neoadjuvant chemotherapy plus tislelizumab ± bevacizumab followed by hypofractionated radiotherapy, concurrent chemotherapy, and consolidative immunotherapy in locally advanced non-small cell lung cancer (GASTO-1086).

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Background: Neoadjuvant chemoimmunotherapy holds promise for enhancing clinical outcomes in patients with resectable non-small cell lung cancer (NSCLC). The assessment of Ki values, derived from dynamic total-body PET/CT scans, has emerged as a crucial determinant of treatment response to neoadjuvant chemoimmunotherapy. This study investigated the efficacy of neoadjuvant chemoimmunotherapy ± bevacizumab, guided by the Ki value, followed by hypofractionated radiotherapy, concurrent chemotherapy (hypo-CCRT), and consolidative immunotherapy in unresectalbe stage III NSCLC. **Methods:** Conducted as a phase II, two-cohort trial in patients with unresectable stage III NSCLC, the study involved dynamic total-body [^{18}F] FDG PET/CT scans to derive Ki values from primary tumors. Cohort A, comprising High FDG Ki patients (Ki $>$ 2.779 ml/min/100g), received neoadjuvant therapy with nab-paclitaxel, cisplatin, and tislelizumab 200mg every 3 weeks for 2 cycles. Meanwhile, Cohort B, consisting of Low FDG Ki patients (Ki $\leq$ 2.779 ml/min/100g), received nab-paclitaxel, cisplatin, tislelizumab 200mg, and bevacizumab 7.5mg/kg every 3 weeks for 2 cycles. Subsequently, hypo-CCRT was administered, and patients without disease progression and grade (G) 2+ pneumonitis received consolidative tislelizumab 200mg every 3 weeks for up to 12 months. Objective response rate (ORR) and toxicities were analyzed, with the trial registered under ClinicalTrials.gov, NCT05468242. **Results:** Enrollment occurred between July 21, 2022, and Nov 10th, 2023, with 29 patients in cohort A and 26 in cohort B. Cohort B exhibited a higher proportion of stage IIIC patients compared to cohort A (57.7% vs. 20.7%, P = 0.019). Post-neoadjuvant therapy, ORRs were 89.7% (26/29) in cohort A and 92.3% (24/26) in cohort B. Following hypo-CCRT, ORRs increased to 96.6% (28/29) in cohort A and 92.3% (24/26) in cohort B. During neoadjuvant therapy, G3 leukopenia occurred in 3.4% (1/29) of cohort A, with no G3+ toxicities in cohort B. In the hypo-CCRT phase, G3 neutropenia and G2 pneumonitis were observed in both cohorts (G3 neutropenia: 3.4% in cohort A vs. 3.8% in cohort B; G2 pneumonitis: 6.9% in cohort A vs. 7.7% in cohort B), with no Grade 3+ adverse events during the consolidative tislelizumab phase. **Conclusions:** The Ki value derived from dynamic total-body FDG PET/CT proved instrumental in guiding the addition of bevacizumab to neoadjuvant therapy. Both cohorts exhibited promising responses to neoadjuvant therapy, suggesting that neoadjuvant chemotherapy plus tislelizumab ± bevacizumab, followed by hypo-CCRT and consolidative tislelizumab, is effective and well-tolerated for unresectable, stage III NSCLC patients. Longer follow-up is essential to validate these findings. Clinical trial information: NCT05468242. Research Sponsor: None.

8066 Poster Session

Pre- and post-operative lung cancer recurrence prediction following curative surgery: A retrospective study using European radiomics and clinical data.

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Background: Accurately estimating the risk of lung cancer recurrence is vital for making informed treatment choices, both before surgery, such as the prescription of neo-adjuvant/peri-operative therapies and the extent of lung resection, and after surgery, such as the prescription of adjuvant therapies and planning follow-up strategies. In this study, we build on previous work demonstrating the predictive power of pre-operative patient demographic and imaging features and develop a machine-learning model using a combination of clinical and tumour radiomic features in the pre- and post-operative setting. **Methods:** We collected a dataset of 323 clinical stage I-IIIA lung cancer patients who underwent surgical treatment for lung cancer, of which 94 had lung cancer recurrence. This includes retrospectively collected CT images and associated patient demographic and diagnostic data from North Estonia Medical Centre (NEMC). The models were trained to predict the likelihood of recurrence on a diverse set of features, including radiomic features extracted from CT images and relevant clinical variables. Post-operative clinical factors such as pathological staging and tumor histology were only included in the post-operative model. An 8-fold cross-validation strategy was used, where, in each fold, 6 (of the 8 equally sized) subsets were used for training, one for model tuning, and one for validation. As a baseline, we compare the pre- and post-operative models to clinical and pathological staging, respectively. Performance was evaluated using the Area-Under-the-ROC-Curve (AUC) and sensitivity (at a fixed specificity of 90%). **Results:** Lung cancer recurrence classification results are tabulated below for the pre-operative models. We find that the pre-operative model (AUC=74.1%, Sens=35.29%) performs significantly better than clinical staging alone (AUC=65.4%, Sens=14.71%, p=0.025), and that the post-operative model (AUC=74.4%, Sens=26.47%) performs significantly better than pathological staging alone (AUC=67.3, Sens=22.4%, p=0.045). Top predictive features for both the pre-operative and post-operative models included clinical staging, tumor shape and textural radiomics, tumor size and tumor location. The post-operative model additionally included pathological staging and tumor histology. **Conclusions:** Based on this retrospective analysis, we find that the model outperforms staging prediction of lung cancer recurrence in pre- and post-operative settings. With further development, these algorithms could prove a valuable tool to aid the management of lung cancer patients. Research Sponsor: Optellum Ltd.

Predictors	AUC	Sensitivity	Specificity
cTNM	65.4 (59.0, 71.6)	14.7 (8.9, 43.5)	90.0
preop ML model	74.1 (68.0, 79.8)	35.3 (24.5, 49.0)	90.0
pTNM	67.3 (61.5, 73.3)	22.4 (13.5, 35.8)	90.0
postop ML model	74.4 (68.8, 79.9)	26.5 (16.2, 41.9)	90.0

Treatment outcomes in locally advanced, unresectable NSCLC treated with concurrent chemoradiation and PD-L1 consolidation: Real-world data from a NCI comprehensive cancer center with a racially diverse, high poverty catchment area.

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Background: The PACIFIC trial established concurrent chemoradiotherapy (CCRT) followed by consolidation durvalumab as standard of care for unresectable stage III non-small cell lung cancer (NSCLC). This study showed a progression free survival (PFS) of 16.9 mo and an overall survival (OS) of 47.5 mo. There is a paucity of real world data with PACIFIC, especially in diverse patient populations. We present real world outcomes of the PACIFIC regimen in a NCI-designated comprehensive cancer center (CCC) with a racially diverse, high poverty catchment area. **Methods:** Retrospective chart review identified patients treated with durvalumab for NSCLC after CCRT per PACIFIC. Demographic data included sex, race, age, stage, address, smoking status, immunotherapy adverse events (irAE). Poverty index was assessed using the SAIPE tool by percent of children in poverty at the school district level based off 2021 census and stratified to above and below 15.1%. Annual air particulate matter (PM) 2.5 was obtained at the zip code level from the Socioeconomic Data and Applications Center. PFS was from date of first dose durvalumab; OS was from date of NSCLC diagnosis to death or last follow up. **Results:** 203 patients with unresectable NSCLC were included. Of these, 18.2% were of Black race compared to 2.0% in the PACIFIC trial. 42.4% of patients lived in high poverty areas, 44.3% were current smokers. Patients had a median annual PM 2.5 exposure of 7.9 ug/m^3. 42.7% had PD-L1 expression >50%. The irAE rate was 27.6% (Table 1). Overall median PFS was 23 mo (95% CI 16.1-31.9) and 28.2 mo (95% CI 11.1-50.7) for patients of Black race. Overall median OS was 52.4 mo (95% CI 31.2-NR) and 52.4 mo (95% CI 18.2-NR) for Black patients. **Conclusions:** In this diverse cohort treated with the PACIFIC regimen at a NCI CCC, favorable real world PFS (23.0 vs. 16.9 mo), and OS (52.4 vs. 47.5 mo) were demonstrated. This cohort is more representative of the US patient population than that of a stringent clinical trial population with at least comparable results. This unexpected result may arise from institutional practices leading to equitable access to care and other biological characteristics of the population. Clinical trial enrollment representative of the broader population remains paramount for equitable care delivery. Research Sponsor: None.

Patient characteristics stratified by race.

Factor	Whole cohort (n = 203) (n%)	White Race (n = 161) (n%)	Black Race (n = 37) (n%)	p-value
Age	66.9	67.4	64.9	0.12
Male Sex	104 (51.2)	83 (51.6)	17 (45.9)	0.54
Current Smoker	90 (44.3)	65 (40.4)	22 (59.5)	0.07
ECOG 0-1	189 (93.1)	150 (93.2)	35 (94.6)	0.94
Comorbidity index	5.2	5.3	5.2	1.00
High Poverty (≥ 15.1)	86 (42.4)	57 (35.4)	28 (75.7)	<0.01
PM 2.5	7.9	7.8	8.3	0.01
PD-L1 TPS >50% (n=37 Not tested)	71 (42.8)	54 (41.2)	16 (51.6)	0.36
IrAE rate	56 (27.6)	47 (29.2)	8 (21.6)	0.35

8068 Poster Session

Preliminary results of the Lung Cancer Mutation Consortium LCMC4 evaluation of actionable drivers in early stage lung cancer (LEADER) screening trial.

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Background: Neoadjuvant chemotherapy and immunotherapy have become standard for patients with resectable non-small cell lung cancer with no targetable oncogenic driver. For patients with tumors driven by most actionable oncogenes, little benefit has been seen. The LEADER Screening Trial designed by the LCMC and supported by the Thoracic Surgical Oncology Group aims to determine the proportion of clinical Stage IA2-III lung adenocarcinomas and adenosquamous carcinomas with one of 12 actionable oncogenes, detected through tumor and blood genomics. This abstract presents data from the first 110 tumors, all tested at Foundation Medicine. **Methods:** This analysis includes eligible patients on the LEADER trial with recectable NSCLC (not purely squamous) tested centrally with FoundationOneCDx (F1CDx, tissue) and/or FoundationOneLiquidCDx (F1LCDx, liquid biopsy) prior to 15Dec2023. An actionable oncogene is defined as: *EGFR* sensitizing or exon 20; *KRAS G12C*; $BRAF^{V600E}$; *HER2* mutation or amplification, *MET* ex14 skipping mutation or amplification; or *RET*, *ROS1, ALK,*or *NTRK1/2/3* fusion. Detectable ct DNA was defined as tumor fraction > 0. **Results:** Of the 110 patients, 95% (105/110) had a successful tissue and/or liquid profiling. Of samples received, 91% (64/70) yielded successful tissue profiling, and 86% (91/ 106) successful blood profiling. All unsuccessful tests were due to inadequate DNA extraction. Some ctDNA was present in 37% (34/91) of blood samples; 62% (56/91) had no detectable. We found an actionable oncogenic driver in 35% (38/ 110, 95% confidence interval 26-44%) of patients tested. If any ctDNA was detected in blood, there was a 100% agreement with tumor tissue whether a driver was present or absent. In blood samples without paired tumor, an actionable alteration was found in 19% of cases (8/42). Identified driver alterations included: 12 *EGFR* sensitizing, 12 *KRAS G12C*, 4 *EGFR*exon 20 insertions, 2 $BRAF^{V600E}$, 2 RET fusions, 2 *HER2* mutations, 1 *ALK* fusion, 1 *HER2* amplification, 1 *MET* ex14 skipping, and 1 *ROS1* fusion. Alterations detected on liquid biopsy included *EGFR*exon 20 insertion, *EGFR* sensitizing mutations, *KRAS G12C*, *RET*fusion, and *HER2* mutation. **Conclusions:** In this national study using both tissue and blood NGS testing, actionable oncogenic drivers were found in 35% of patients with clinical stages IA2-III lung adenocarcinoma at diagnosis. Blood testing identified an actionable driver 19% of the time when tumor testing was not done. Comprehensive genomics testing on patients with early-stage lung cancer should be standard. It identifies relevant oncogenic drivers and provides important 'negative selection' to identify the patients appropriate for neoadjuvant chemo-immunotherapy. Accrual to the LEADER trial continues. Clinical trial information: NCT04712877. Research Sponsor: Lung Cancer Research Foundation.

LBA8069 **Poster Session**

Overall survival following heterogeneous FDG-guided dose-escalation for locally advanced NSCLC in the international phase III NARLAL2 trial.

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The impact of HIV and CD4 count stratification on all cause mortality for adenocarcinoma and squamous cell lung cancers in the antiretroviral therapy era: Analysis of National Veterans Affairs and Kaiser Permanente Northern cohorts.

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Background: Since the widespread introduction of antiretroviral therapy (ART), people living with HIV (PWH) have experienced substantially decreased morbidity and mortality. However, PWH are at higher risk for lung cancer and have decreased cancer survival rates compared to people without HIV (PWoH). Few studies have evaluated histology-specific lung cancer survival by stage and HIV immune control. **Methods:** A retrospective cohort study was conducted with newly diagnosed non-small cell lung cancer (NSCLC), including PWH with PWoH, identified between 2008 and 2020 from the US Department of Veterans Affairs and Kaiser Permanente, California. Adjusted hazard ratios for 5-year survival by CD4 count ($\geq$ 500 cells/mm^3, <500 cells/mm^3, ref: PwOH) were estimated using Cox models stratified by subtype (adenocarcinoma, squamous) and TNM (I, II/III, IV) stage. **Results:** This cohort consisted of 562 PWH (53% adenocarcinoma, 33% squamous cell) and 91,370 PWoH (52% adenocarcinoma, 33% squamous cell, 15% not specified). The PWH cohort tended to be younger (62 vs. 69 years), male (97% vs. 83%), and non-Hispanic Black race (48% vs. 14%), compared to PWoH. Among PWH, 41% had CD4 $\geq$500 cells/mm^3, 59% had CD4 <500 cells/mm^3 . The median survival in years for PWoH, PWH CD4 count $\geq$500 cell/mm^{3}and <500 cells/mm^3 were: 2.4 $\pm$0.10, 2.3 $\pm$ 0.17, 2.0$\pm$0.17, respectively for adenocarcinoma, and 2.1$\pm$0.01, 2.3$\pm$0.21, 1.6$\pm$0.17 respectively for squamous cell carcinoma. The table shows the adjusted HR for all-cause mortality for Adenocarcinoma and Squamous Cell Carcinoma comparing PWH $\geq$500 and PWH<500 to PWoH (as reference) stratified by stage. **Conclusions:** Although it is well known that low CD counts (<200) are associated with poor cancer outcomes, higher CD4 counts (CD<500) at the time of lung cancer diagnosis may still play a role in the treatment outcomes of NSCLC. PWH who have CD4 counts $\geq$500 appear to have similar survival compared to PWoH, but CD4<500, those with (vs. without) HIV have higher rates of mortality for both adenocarcinoma and squamous cell histologies. Adjusted hazard ratios (HR)* with 95% confidence intervals (CI) for 5-year all-cause-mortality associated with HIV by CD4 count (reference: PWoH), across Adenocarcinoma and Squamous Cell Cancer histology and baseline cancer stage. Research Sponsor: U.S. National Institutes of Health; R01CA260689.

TNM Stage	Adenocarcinoma				Squamous Cell			
	CD4 ≥ 500		CD4 <500		CD4 ≥ 500		CD4 <500	
	HR	95%CI	HR	95%CI	HR	95%CI	HR	95%CI
I	0.7	0.39 - 1.43	2.4†	1.57 - 3.80	1.0	0.60 - 1.73	1.8†	1.03 - 3.08
II or III	1.1	0.74 - 1.66	0.9	0.58 - 1.30	1.2	0.81 - 1.74	1.9†	1.35 - 2.67
IV	1.1	0.87 - 1.46	1.4†	1.09 - 1.83	1.4	0.89 - 2.26	1.1	0.74 - 1.55

*Adjusted model includes: age, sex, race/ethnicity, year of diagnosis, Deyo comorbidity index, smoking, alcohol abuse, time-dependent treatment, and organization.
†Hazard ratios significant at a =0.05 level.

Feasibility of induction chemoimmunotherapy (ID chemo-IO) followed by chemo-radiation for locally advanced unresectable non-small cell lung cancer (NSCLC).

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Background: Data from the PACIFIC study demonstrated a 5-yr median progression free survival (PFS) and overall survival (OS) of 16.9 and 47.5 months respectively for patients with stage 3A and stage 3B NSCLC demonstrating a high risk of relapse. The 8th ed. of the IASLC staging project reports that the 60-month OS for stage 3A, B and C disease is 41%, 24% and 12% respectively, indicating that improved treatment options are needed for this patient population. Induction chemo-IO (ID chemo-IO) followed by concurrent chemo-radiation (CRT) has not been fully investigated due to concerns regarding the toxicity profile, but this may representant an important unexplored avenue for research. We aim to describe the outcomes of patients who received ID chemo-IO followed by CRT with or without maintenance IO. **Methods:** We conducted a retrospective study across all Mayo Clinic sites. Patients were included if they were diagnosed with Stage 3 NSCLC deemed ineligible for resection and/or requiring raditation over a large-field] by a multidisciplinary team with plans for ID chemo-IO prior to CRT and maintenance IO. A total of 927 cases of stage 3 NSCLC patients were screened and those receiving ID chemo-IO followed by CRT were extracted (n = 36). Clinical endpoints are PFS, OS, overall response rate (ORR) and treatment related adverse events (TrAE) defined using CTCAE 5.0. **Results:** The median age was 67 years, 52.8% were female, all patients were past smokers and 97.2% identified as white. The tumor histologies were adenocarcinoma (66.67%), squamous (27.8%), mucinous adenocarcinoma (2.8%) and sarcomatoid (2.8%). Majority were Stage 3B (47.2%) followed by 3C (38.9%) and 3A (13.9%). N2 and N3 disease was noted in 36.1% and 55.6% of patients respectively. PD-L1 by IHC was $>$ 1-49% (47.2%), $>$ 50% (22.2%) and $<$ 1% (19.4%). Patients received ID chemo-IO with pembrolizumab (83.3%), nivolumab (11.1%) and atezolizumab (2.78%). Average number of ID chemo-IO cycles were 3.67 cycles. The ORR to ID chemo-IO was 86.11%. The median PFS was 23.67 mths and the median OS was 32.07 months. About 94% of patients received CRT afterwards and 66.67% received maintenance IO with pembrolizumab (53.17%) or durvalumab (45.83%). Any grade TrAE occured in 58.33% of patients. Pneumonitis was the most common event (38.9%). Grade 3 -4 pneumonitis was noted in 28.5% (4/11) patients. Other toxicities included hepatitis (8.3%), colitis (11.1%) and myasthenia gravis (2.8%) and 22% of these TrAE's were grade 3 or 4. **Conclusions:** Our results indicate that ID chemo-IO shows promise as a therapeutic approach for patients with unresectable stage III NSCLC, especially for patients deemed ineligible or high risk for upfront radiation. Further investigation is needed through a randomized clinical trial to systematically explore and validate the safety and efficacy of ID chemo-IO. Research Sponsor: None.

Assessing quality of care in early stage resected stage non-small cell lung cancer (NSCLC): An evaluation of epidermal growth factor receptor (EGFR) testing and adjuvant (adj) therapy (tx).

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Background: In December 2020, the FDA approved the use of osimertinib in the treatment of stage IB-IIIA (ES) NSCLC patients (pts) with EGFR exon 19 deletions and exon 21 L858R mutations (EGRFm) following tumor resection. Using real-world data, we sought to understand EGFR testing rates among ES pts and whether pts received osimertinib in the adjuvant setting based on EGFRm. **Methods:** We used the Integra Connect PrecisionQ real-world de-identified database of over 3 million cancer pts across 500 sites of care. From this database, we identified Stage IB – IIIA pts evaluated via medical chart curation who underwent lung cancer resection (R) between 12/1/2021 to 7/31/2023 (N = 803). We assessed adj treatment by stage, EGFR testing rates overall and by stage, EGFR testing rates by adjuvant treatment and non-adj treatment pts, timing of EGFR testing, and treatment rates with an EGFR TKI among EGFRm pts. Descriptive analyses were used and proportions were compared using a chi-squared test. **Results:** The mean age of the 803 ES R pts in the sample was 69 (SD = 8.3), 53.3% of the pts were female, , and 12% never smoked. We found adj treatment rates among ES R pts to be 56%; these were highest among stage IIIA (N = 245) pts at 70.2%, compared to stage IIB (N = 241) at 68.8%, stage IIA (N = 69) at 53.6% and stage IB (N = 240) at 31.7% ($p < 0.001$). Among ES R pts, 70% (N = 563) were tested for EGFR; this rate was 78% (N = 455) among ES pts who were R and received adj treatment, compared to 59% (N = 348) among ES R pts who did not receive adj treatment ($p < 0.001$). EGFR testing rates were highest among stage IIB pts at 76%, compared to stage IIIA pts at 73%, stage IIA pts at 72%, and stage IB pts at 60% ($p < .001$). Among ES pts who were R and tested for EGFR (N = 563), 14% were tested before surgery, 38% were tested after surgery but before adj treatment, and 48% were tested after initiating adjuvant therapy. EGFRm was found in 10.4% of EGFR tested pts. Among EGFRm ES R pts (N = 59), 54% were treated with an EGFR TKI. EGFRm ES R pts treated with an adj EGFR TKI were highest among stage IIB pts (N = 14) at 93%, compared to stage IIA pts (N = 5) at 60%, stage IB pts (N = 20) at 45%, and stage IIIA pts (N = 20) at 35% ($p < 0.01$). However, only 69% (N = 41) of EGFRm ES R pts received adj treatment (either chemotherapy or EGFR TKI) and among those pts, 78% (N = 32) received an EGFR TKI. **Conclusions:** Based on our findings using real-world data for EGFR testing and adjuvant osimertinib use, and in light of the published results from the ADAURA trial which showed disease free survival benefit (HR 0.2) and overall survival benefit (HR 0.49) of adjuvant osimertinib in ES NSCLC, we have identified an opportunity to improve patient outcomes following resection of ES NSCLC by increasing EGFR testing and encouraging treatment with EGFR TKI in exon 19 deletion or exon 21 L858R mutated pts. Research Sponsor: None.

8073 Poster Session

Efficacy and surgical safety of sequential surgical resection after neoadjuvant chemoimmunotherapy for unresectable stage III NSCLC.

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Background: Neoadjuvant chemoimmunotherapy has been successfully used in resectable non-small cell lung cancer (NSCLC) patients. However, its application in advanced stage unresectable NSCLC remains a topic of debate. This retrospective study was designed to evaluate the efficacy and safety of neoadjuvant chemoimmunotherapy followed by surgical resection in patients with initial unresectable stage III NSCLC, focusing on the surgical resection rate and the survival benefits of surgery. **Methods:** Patients unresectable stage III NSCLC who received 2-4 cycles of neoadjuvant chemoimmunotherapy between January 2021 and December 2022 were retrospectively identified. Data on characteristics, radiological and pathological responses, and survival outcomes were collected. **Results:** In total, 148 patients with unresectable stage III NSCLC were recruited. After the last cycle of neoadjuvant therapy, 105 (70.9%) patients were evaluated to be eligible for surgery, and 102 patients ultimately underwent surgery. The rate of complete (R0) resection was 100%, with a major pathological response (MPR) observed in 63.7% and a pathologic complete response (pCR) in 41.2%. Postoperative complications were observed in 9 patients (8.8%), and there was no surgical-related mortality within 30 days. With a median follow-up of 21.9 months, the median progression-free survival (PFS) was 19.6 months in the non-surgery group and not reached in the surgery group. The median overall survival (OS) was not reached in either group. **Conclusions:** The use of neoadjuvant chemoimmunotherapy is effective in converting unresectable stage III NSCLC into resectable NSCLC. Subsequent radical surgery is safe with low complications and surgical-related mortality. Research Sponsor: Natural Science Foundation of Shandong Province.

ALK testing patterns in early-stage non-small cell lung cancer: A real-world evidence study.

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Background: Comprehensive biomarker testing in advanced non-small cell lung cancer (aNSCLC) is standard of care, but disparities exist. As new clinical data emerge in early disease (eNSCLC), the set of actionable lung driver mutations (LDMs) and therefore the testing landscape in that setting will change. In particular, following the results of the ALINA trial, therapies that target ALK fusions are anticipated to become part of routine treatment of eNSCLC in 2024.This study thus sought to identify the factors associated with receipt of timely ALK testing in eNSCLC, prior to this shift. **Methods:** We retrospectively analyzed patients with resected stage I-IIIa NSCLC diagnosed between 2018-2023 using the expanded nationwide (US-based) de-identified Flatiron Health EHR-derived database; data were consolidated from approximately 280 US cancer clinics (≅800 sites of care), using natural language processing with machine learning (ML) to extract patient characteristics. The primary endpoint was ALK testing results (by any modality) within 90 days of initial diagnosis. We used multivariable logistic regression to assess the association between clinico-demographic characteristics and likelihood of testing. **Results:** The sample contained 21,982 stage I-IIIa patients. Of these, 6,685 (30%) were tested within 90 days, and 15,297 (70%) were not. Patients were more likely to be tested within 90 days if they were diagnosed in more recent years (2023 vs. 2018 odds ratio (OR) 2.12); had no history of smoking (OR 1.21); had highest socioeconomic status (SES) quintile (OR vs. lowest SES 1.14); had more advanced disease (stage IIIa vs. stage I OR 2.43); or were treated in a community setting (OR vs. academic 1.13), all $p < 0.05$. Patients with Medicare insurance (OR vs. commercial insurance 0.89, $p = 0.014$) or squamous histology (OR vs. non-squamous 0.46, $p < 0.01$) were less likely to be tested. There were no significant differences between black and white patients (OR 0.91, p = 013). **Conclusions:** In this real-world analysis of patients diagnosed between 2018-2023 most patients did not have testing within 90 days of diagnosis. Our data show variation in the baseline probability of testing with respect to clinico-demographic factors. Given that barriers to testing persist in aNSCLC, this suggests that once ALK inhibitors become part of routine care in eNSCLC, some groups might be less likely to be tested and therefore to receive efficacious targeted treatment. Preemptive measures such as education of patients, providers, payers, and policy makers could help prevent disparities from emerging. Research Sponsor: Genentech, Inc.

8075 Poster Session

Comparative survival after neoadjuvant vs adjuvant systemic therapy in resectable stage II and stage III non-small cell lung cancer: A retrospective study using the National Cancer Database.

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Background: Resectable Stage II and III Non-small Cell Lung Cancer (NSCLC) are managed with surgery and perioperative systemic therapy [Chemo/Chemo-Immunotherapy (IO)]. However, there lacks a consensus in optimal selection between neoadjuvant and adjuvant approaches. Hence, it underscores the necessity to undertake a comparative survival outcome associated with systemic therapy in these distinct settings. **Methods:** We conducted an analysis, of individuals aged 18 and above diagnosed with stage II and stage III NSCLC between 2004 - 2020, using data from the National Cancer Database (NCDB). Overall survival (OS) was compared for both Neoadjuvant and Adjuvant systemic therapy using Cox proportional hazards models after adjusting for sociodemographic (e.g., age, sex, race-ethnicity, and income) and health (e.g., insurance and facility type) related factors. The inclusion criteria involved restricting the analysis to individuals with no more than one lifetime cancer diagnosis and excluding those who received radiation therapy. **Results:** Among approximately 2 million total patients with NSCLC in NCDB, 8.38% and 20% were stage II and III respectively. After we identified a total of 137,473 eligible patients, 27,115 had relevant treatment information with 2,550 Neoadjuvant Chemo, 112 Neoadjuvant chemoIO, 24,175 Adjuvant chemo and 278 Adjuvant chemoIO. A statistically significant association between OS and treatment group was observed [$\chi 2(3) = 55.5$, $p < .001$]. The OS was notably higher in the Neoadjuvant chemoIO group (78.57%) compared to Adjuvant chemoIO group (55.76%), whereas the Neoadjuvant chemo-only group exhibited lower OS (45.41%) compared to the Adjuvant chemo group (47.98%). The Cox proportional hazards model showed 70% higher mortality risk in the Adjuvant chemoIO group compared to the Neoadjuvant chemoIO group (p=0.030, 95% CI 1.05-2.77). The 2-year and 5-year OS rates for Neoadjuvant ChemoIO were 77.9% and 68.8%, respectively versus 68.7% and 42.8% for Adjuvant chemoIO group. **Conclusions:** Our analysis reveals that Neoadjuvant chemoIO demonstrates superior survival outcomes compared to Adjuvant chemoIO. Additionally, our findings suggest the potential predictive value of Immunotherapy in combination with chemotherapy in the Neoadjuvant setting. Key Words: NSCLC, Neoadjuvant treatment, Adjuvant treatment, Chemotherapy, Immunotherapy, OS. Research Sponsor: None.

A multi-center cohort study Examining risk factors for central nervous system metastases (CNSm) in patients with stage III non-small cell lung cancer (NSCLC) treated with definitive chemoradiation (ChemoRT) followed by durvalumab (Durva).

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Background: In the PACIFIC trial, 6.3% of patients with unresectable stage III NSCLC receiving durva after chemoRT developed CNSm. In a single center study, we previously reported real-world incidence of CNSm is higher at 19.8%. Risk factors for development of CNSm post-durva are incompletely understood. **Methods:** We conducted a multi-center retrospective study of patients with unresectable stage III NSCLC treated with durva after chemoRT from 2018 to 2022 with no CNSm on baseline brain MRI to assess for incidence of CNSm. Patient characteristics were compared between cohorts with and without CNSm to assess for risk factors for CNSm using Fisher's exact test for categorical variables and two-sample t-test or Wilcoxon Mann-Whitney U-test for continuous variables. Overall survival was compared using log-rank test. **Results:** Of 193 patients in our study, 32 (16.6%) developed CNSm with median time to CNSm of 6.4 mo (IQR 4.5 - 13.7). Twenty-five (78%) had CNSm within one year. Patients with CNSm had a longer interval between baseline brain MRI and start of durva (median 3.7 mo vs 3.3 mo, p=0.02) and received fewer doses of durva compared to those without CNSm (median 7 vs 12, p=0.03). As some patients received Q2 week and others Q4 week durva, we also compared median durva treatment duration, which was consistent (3.7 mo vs 8.3 mo, p=0.02). There was no association between CNSm and age, sex, histology, T/N stage, PDL1 status, or chemoRT regimen (Table). Patients with CNSm had shorter median survival (19.6 mo vs 36.4 mo, p=0.008). **Conclusions:** Real-world incidence of CNSm is higher than that seen in PACIFIC. Patients with CNSm received less durva, likely due to early disease progression, and had longer intervals between baseline brain MRI and starting durva. Minimizing treatment delays may improve outcomes. Further research is needed to understand optimal surveillance strategies for CNSm in this patient population. Research Sponsor: None.

Characteristics of patients with unresectable stage III NSCLC managed with chemoRT followed by durva according to development of CNSm.

Variable		CNSm (n=32)	No CNSm (n=161)	P-Value
Age	Mean (SD)	63.5 (8.7)	64.3 (9.8)	0.65
Gender	Male	16 (50.0%)	92 (57.1%)	0.56
Histology	Squamous	13 (40.6%)	83 (51.6%)	0.33
T stage*	1 or 2	13 (41.9%)	73 (49.0%)	0.56
	3 or 4	18 (58.1%)	76 (51.0%)	
N stage**	N0	4 (12.9%)	32 (20.5%)	0.46
	N1+	27 (87.1%)	124 (79.5%)	
PDL1***	<1%	9 (29.0%)	49 (33.8%)	0.68
	≥1%	22 (71.0%)	96 (66.2%)	

CNS = central nervous system, SD=standard deviation, IQR = interquartile range, PDL1 = programmed cell death ligand-1.
*T stage data were missing for 12 patients who did not and 1 patient who did develop CNSm.
**N stage data were missing for 5 patients who did not and 1 patient who did develop CNSm.
***PDL1 expression data were missing for 16 patients who did not and 1 patient who did develop CNSm.

Phase I trial of aurora kinase A (AURKA) inhibitor VIC-1911 plus osimertinib for TKI-resistant, EGFR-mutant non-small cell lung cancer (NSCLC).

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Background: ARUKA has been implicated in the emergence of resistance to osimertinib. VIC-1911 is a highly selective ARUKA inhibitor that has minimal activity in EGFR-mutant (mt) cell lines as a monotherapy. Preclinical data show synergy of VIC-1911 with osimertinib across in vitro and in vivo osimertinib-resistant models. Sustained tumor control after drug withdrawal is observed in both osimertinib-naïve and -resistant xenograft models. This trial evaluated the safety and efficacy of VIC-1911 plus osimertinib in patients with TKI-resistant, EGFRmt NSCLC (NCT05489731). **Methods:** This is a phase I trial with a 3+3 dose escalation stage and a dose expansion stage. Eligible patients should have advanced NSCLC with EGFR 19del/L858R and failure after ≥1 lines of EGFR-TKIs. Patients enrolled into the dose escalation stage were treated with VIC-1911 150mg or 200mg BID intermittently (4 days on, 3 days off) plus osimertinib 80 mg QD consecutively. Patients enrolled into the dose expansion stage were treated with VIC-1911 at the recommended phase 2 dose (RP2D) plus osimertinib 80 mg QD. Toxicity was assessed by the NCI CTCAE V5. Efficacy was evaluated per RECIST v1.1. **Results:** As of 18 December 2023, a total of 24 patients were treated. Median lines of prior treatment were 3 (range,1-8). Seven patients were enrolled during the dose escalation stage (150mg = 4, 200mg = 3). No DLT was observed and 200mg was selected as the RP2D. The most common AEs related to VIC-1911 at RP2D were diarrhea (52.3%), leucopenia (38.1%), neutropenia (33.3%), and thrombocytopenia (28.6%). Efficacy was evaluable in 23 patients. Among them, 10 patients were osimertinib-naïve (T790M-negative = 8,T790M-positive = 2) and 13 were osimertinib-resistant. For osimertinib-naïve patients, confirmed objective response rate (ORR) was 50% (5PRs, T790M-negative = 4, T790M-positive = 1) and disease control rate (DCR) was 80% (3SDs). For osimertinib-resistant patients, ORR was 0% and DCR was 53.8% (7SDs). Among patients with disease control, 66.7% (10/15) stayed on treatment as of data cutoff. The median follow-up duration was 5.5 months. Median duration of response (DOR) was not reached. The 6-month (6m) DOR rate was 50%. Median progression-free survival (PFS) was not reached and 4.3months for osimertinib- naïve and -resistant patients, respectively. The 6m PFS rate was 70.0% and 38.5%, respectively. Updated DOR and PFS data will be presented. **Conclusions:** VIC-1911 in combination of osimertinib is well-tolerated in previously-treated EGFRmt NSCLC. The combination demonstrates sustained antitumor activity, which indicates the potential of AURKA blockade in delaying the emergence of resistance to osimertinib. Clinical trial information: NCT05489731. Research Sponsor: None.

Ultrasensitive circulating tumor DNA (ctDNA) minimal residual disease (MRD) detection in early stage non-small cell lung cancer (NSCLC).

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Background: Translation of ctDNA MRD in NSCLC has been hampered by suboptimal sensitivity of 1st-generation assays. Here, we explore how improvements in analytical sensitivity can drive improved clinical sensitivity for MRD after surgery in NSCLC. **Methods:** To understand MRD kinetics, we analyzed longitudinal ctDNA in early stage NSCLC using data from the TRACERx study. Patient-specific mathematical models were generated to predict MRD levels at the postsurgical landmark and estimate the impact of an assay's 95% limit of detection (LOD95) on clinical sensitivity. To test these predictions, tumor-informed ctDNA testing was performed using an SNV-based assay (CAPP-Seq) and a phased variant-based assay (PhasED-Seq, Foresight Diagnostics) on 269 samples from 46 patients. We also assessed MRD performance for predicting 1) patient outcomes at the landmark timepoint and 2) the effect of adjuvant treatment. **Results:** ctDNA MRD dynamics were assessed in 23 patients from TRACERx with $\geq$3 consecutive samples with detectable ctDNA without intervening therapy. MRD kinetics strongly correlated with exponential growth, with a median ctDNA doubling time of 51 days. Extrapolating MRD levels to the postsurgical landmark predicted that improving MRD assay LOD95 from 100 ppm (0.01%) to 1 ppm could increase clinical sensitivity by 2.1-fold. We then evaluated 46 NSCLC cases using two assays. The median LOD95 was 1 ppm for PhasED-Seq and 84 ppm for CAPP-Seq. Twelve cases were MRD+ by PhasED-Seq, all of whom recurred (100%), with MRD levels as low as 0.19 ppm. In contrast, 6 cases were MRD+ by the SNV-based approach, of whom 5 (83%) recurred. Accordingly, PhasED-Seq had a higher clinical sensitivity than the SNV-based method (12/18 [67%] vs. 5/18 [28%], P = 0.022). Kaplan Meier analysis for freedom from recurrence revealed significantly worse outcomes for patients with detectable MRD regardless of the method used; however, outcomes were better stratified using PhasED-Seq (HR 3.1 vs. 11.4). Patients who were MRD- after surgery by both assays had similar outcomes regardless of adjuvant therapy (chemotherapy and/or radiotherapy). However, MRD+ patients by PhasED-Seq receiving adjuvant therapy had significantly better outcomes than those who did not (HR 8.2, P = 0.00035). A similar benefit for adjuvant therapy was not observed with the SNV-based assay. Using PhasED-Seq, 80% (4/5) of MRD+ patients receiving adjuvant therapy cleared their MRD, compared to 0% (0/3) without adjuvant treatment. **Conclusions:** Ultrasensitive ctDNA detection improved the clinical sensitivity of MRD at key landmarks in early stage NSCLC. PhasED-Seq detected MRD at levels below 1 ppm and was associated with significantly better outcomes, revealing potential benefits of adjuvant therapy in MRD+ patients. This suggests that ultrasensitive MRD detection is promising for use in risk-adapted trials in early stage NSCLC. Research Sponsor: None.

8079 Poster Session

An interpretable AI-derived radiology signature to identify patients at risk of progression on the PACIFIC regimen for unresectable non-small cell lung cancer.

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Background: Advances in the treatment of unresectable NSCLC have emerged through the combination of chemotherapy, radiotherapy, and immune checkpoint inhibitors (ICI), also known as the PACIFIC regimen. Despite this protocol's benefits, it lacks predictive biomarkers and many patients will ultimately fail to respond. Artificial intelligence (AI) has shown promise in identifying patients responsive to ICI, but its ability to identify patients who may not benefit from such combination regimens remains underexplored. We introduce an AI-enabled approach leveraging interpretable imaging biomarkers, such as tumor heterogeneity and twistedness of the tumor-associated vasculature, to identify patients who will fail to benefit from chemo-radio-immunotherapy (CRIT) using pretreatment scans. **Methods:** We analyzed CT data from 148 NSCLC patients with predominantly stage III (91%) disease from two institutions. Target lesions were delineated by a trained radiologist. The Picture Health Px platform was utilized to segment the lungs and pulmonary vessels. Subsequently, a number of interpretable imaging features from the tumor and surrounding tissues were extracted. A Cox proportional hazards model of feature clusters was developed on the training set (n = 101) to stratify patients into benefit groups associated with progression-free survival (PFS). A cohort of 47 patients receiving CRIT were held out for testing. **Results:** The imaging-derived high-risk group defined by the model was associated with decreased PFS in the test set, with a hazard ratio (HR) of 4.99 (95% CI: 2.04-12.18; $p < 0.005$) and concordance index (C-index) of 0.66. The risk groups identified by the model outperformed PD-L1 negative status in identifying likely progressors (C-index = 0.52; HR = 1.49 [0.51-4.54], p = 0.47), and were additionally independently prognostic of PD-L1 status when compared in a multivariable analysis ($p < 0.001$). The primary features driving the model were measurements of the radius and tortuosity of the tumor-associated vasculature, as well as heterogeneity metrics of the tumor. Conclusions: An AI imaging tool that stratifies patients by risk after CRIT from baseline radiology was developed. The tool was able to strongly identify a subset of patients at very high risk of progression if treated with CRIT. These risk groups outperformed PD-L1 and thus may address biomarker gaps in the CRIT setting. With further clinical validation, radiology-based risk stratification could be used to identify a subset of unresectable NSCLC patients for whom alternatives to the standard of care should be explored. Research Sponsor: Picture Health Inc.

Integration of circulating tumor DNA and metabolic parameters for outcome prediction in unresectable locally advanced non-small cell lung cancer.

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Background: An effective biomarker to direct precise consolidation treatment after CRT is still lacking. Circulating tumor DNA (ctDNA) molecular residual disease (MRD) following curative-intent treatment strongly predicts recurrence in multiple tumor types, but whether further treatment can improve outcomes in patients with MRD remains unclear. Hereby, we applied CAPP-Seq ctDNA analysis to plasma samples collected before and after definitive chemo-radiotherapy (CRT) or radiotherapy (RT) in unresectable LA-NSCLC. **Methods:** A total of 62 unresectable LA-NSCLC patients were prospectively enrolled, providing 62 baseline and 49 post-definitive CRT/RT plasma samples. All patients underwent a PET/CT scan at baseline and 33 patients received a mid-treatment PET/CT scan upon reaching a RT dose of 40Gy/20f during therapy. These 33 patients were randomly assigned to either receive or not receive adaptive dose-escalated RT. A group of patients who received immune checkpoint inhibitor (ICI) consolidation after CRT/RT was compared with patients who were ctDNA-/high △TMTV post-treatment. **Results:** ctDNA was detected at baseline in 44 (71.0%) patients. Pre-treatment ctDNA concentration was significantly correlated with TMTV (p = 0.004) and TLG (p = 0.010). Baseline ctDNA detection and concentration were not able to differentiate patients with varying treatment responses or predict survival. However, patients with undetectable ctDNA and low TMTV exhibited significantly better PFS (p = 0.024). One month after completing CRT or RT, ctDNA was detected in 25 (47.2%) patients. While the concentration of circulating free DNA (cfDNA) remained relatively stable (p = 0.652), both the mean ctDNA Variant Allele Frequency (VAF) (p = 0.002) and ctDNA concentration (p = 0.043) showed a significant decrease. Patients with undetectable ctDNA post-treatment exhibited significantly longer PFS and OS. A lower ∆TMTV was significantly associated with longer PFS and OS. Compared to the non-response group, the response group exhibited significantly lower change in △SUVmax (p = 0.024), with a trend towards lower change in TMTV, although not significant (p = 0.064). Compared with the matched 30 patient receiving ICI consolidation, those with negative ctDNA and high △TMTV after CRT demonstrated significantly better PFS (p = 0.042) and OS (p = 0.039). **Conclusions:** Baseline ctDNA combined with TMTV can enhance the predictive ability for survival. Post-CRT ctDNA and △TMTV possess strong prognostic capabilities. Patients who are ctDNA- and with high △TMTV may be exempt from ICI consolidation therapy. Research Sponsor: None.

8081 Poster Session

EGFR-TKI as neoadjuvant treatment in patients with NSCLC with EGFR sensitive mutation: A retrospective real-world analysis.

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Background: This study aimed to evaluate the efficacy and outcome of Epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs) as preoperative neoadjuvant treatment in patients with NSCLC and EGFR sensitive mutation. **Methods:** A retrospective analysis was conducted. Patients with resectable stage I-III NSCLCs and received neoadjuvant treatment with any generation of EGFR-TKI before surgical resection were enrolled. The primary endpoint were major pathological response (MPR) and objective response rate (ORR), the second endpoints included diseases down staging, surgical outcomes, disease-free survival (DFS) and overall survival (OS). **Results:** A total of 58 patients were enrolled. Female accounted for 62.1% and most of them (77.6%) were never-smoker. Forty-five (77.6%) patients received the first generation of EGFR-TKI and 11 received the third. The median duration of EGFR-TKI before surgery was 3.6 months (0.7-19.5m). Nine (15.5%) patients achieved MPR and one patient (1.71%) achieved pathological complete response (pCR). The ORR was 60.3% (35/58) according to RECIST v1.1. Eighteen patients achieved TNM downstaging with T downstaging occurred in 44.8% of patients and N downstaging was about 32.8%. Majority of patients (96.6%) underwent thoracoscopic surgery and the rate of R0 resection was 82.8% (48/58). The DFS and OS of the whole cohort was 25.7months and not reached respectively. Patients with MPR had statistically improved outcomes than those without. What noticeable was that patients with tumor regression grade 3 (13/58) (residual viable tumor cells counts for 10% to 50%) also demonstrated a significant benefit from EGFR-TKI preoperative treatment than those with TRG4 or 5 (residual viable tumor cells > 50%) ($p = 0.01$). We define patients with TRG1 to TRG3 as deep pathological regression (DPR) and the rest as non-DPR, and the DPR cohort showed significantly prolonged DFS than those with non-DPR (median DFS, 60.9 vs 16.7 months; HR, 0.29 (95%CI: 0.11-0.74), $p = 0.006$), the data of OS was not mature. Subgroup analysis validated DPR was an independent predictive factor for DFS. **Conclusions:** EGFR-TKI as neoadjuvant therapy had good effect on tumor pathological regression and disease down-staging, DPR patients were more likely to achieve long-term disease-free survival. Patients with NDPR should be closely followed up and appropriate adjuvant therapy was necessary after surgery due to the high risk of reccurence. Research Sponsor: None.

Neoadjuvant SHR-1701 with or without chemotherapy in unresectable stage III NSCLC (TRAILBLAZER): Efficacy, safety and feasibility of surgical conversion outcomes from a proof-of-concept, phase 2 trial.

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Background: Consolidation immunotherapy after chemoradiation is the standard of care for unresectable stage III NSCLC. Addition of immunotherapy-based induction treatment may further improve outcome, partly by enabling surgery. We conducted a proof-of-concept, phase 2 trial to assess neoadjuvant SHR-1701 (an anti-PD-L1/TGF-β bifunctional fusion protein) with or without chemotherapy, followed by surgery or radiotherapy in unresectable stage III NSCLC and without *EGFR*/*ALK* alterations. **Methods:** Patients with MDT-assessed surgically unresectable disease were given 3 cycles of neoadjuvant SHR-1701 (30 mg/kg Q3W) with or without chemotherapy (paclitaxel 175 mg/m^2 Q3W + carboplatin AUC = 5 Q3W).Patients with PD-L1 TPS $<$ 50% received combination therapy (arm A) and those with PD-L1 TPS $\geq$50% were randomized (1:1) to receive combination therapy (arm B) or SHR-1701 alone (arm C). After reassessment by MDT, patients received either surgery or definitive radiotherapy (60 Gy/30 fractions) plus concurrent cisplatin (30 mg/m^2 QW), all followed by consolidation SHR-1701 for 16 cycles. The primary endpoints were post-induction objective response rate (ORR) and 18-month event-free survival (EFS) rate. Arm A+B (patients receiving neoadjuvant chemo-immunotherapy) was the primary analysis cohort. **Results:** Between Nov. 20, 2020 and Jan. 27, 2022, 107 patients were enrolled (arm A/B/C, n = 88/9/10). Median follow-up was 22.2 months. In arm A+B, both primary endpoints were met, with a post-induction ORR of 58% (95% CI 47-68) and an 18-month EFS rate of 56.6% (95% CI 45.2-66.5). In arm C, the post-induction ORR was 40% (95% CI 12-74) and 18-month EFS rate was 77.1% (95% CI 34.5-93.9). 24-month overall survival rate was 78.3% (95% CI 68.0-85.7) in arm A+B and 100% in arm C. Overall, 27 (25% of 107; arm A+B/C, n = 24/3) patients underwent surgery; all achieved R0 resection. Among them, 12 (44%) MPR and seven (26%) pCR were recorded. The 18-month EFS rate was 74.1% (95% CI 53.2-86.7) in resected patients and 57.3% (43.0-69.3) in those receiving radiotherapy. Across arms, all grade $\geq$3 TRAEs with frequency $\geq$10% were hematological toxicities. No new safety signals were identified. **Conclusions:** NeoadjuvantSHR-1701 with chemotherapy, followed by surgery or radiotherapy, showed promising anti-tumor activity with a tolerable safety profile in unresectable stage III NSCLC. We provided first evidence that surgical conversion was feasible in a notable proportion of patients, and was associated with better survival outcomes. Clinical trial information: NCT04580498. Research Sponsor: None.

8083 Poster Session

Combining a WT1 cancer vaccine (galinpepimut-S) with checkpoint inhibition (nivolumab) in patients with WT1-expressing diffuse pleural mesothelioma (DPM): A phase I study.

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Background: Diffuse pleural mesothelioma (DPM) is an aggressive malignancy with poor outcomes and only two FDA-approved therapeutic regimens. The Wilms' tumor suppressor protein (WT1) is often presented on the surface of DPM and is an ideal therapeutic target. A phase I study confirmed the safety and immunogenicity of galinpepimut-S (GS), a tetravalent, non-HLA restricted, heteroclitic WT1-specific peptide vaccine, in patients with WT1-expressing cancers, and our prior randomized Phase II study of adjuvant GS in patients with DPM suggested an improvement in median overall survival. Vaccine-dependent upregulation of T cell suppressive programmed death-ligand 1 (PD-L1) has been observed in the tumor microenvironment of other malignancies. To further enhance the immunogenicity of GS by reversing the effect of T cell suppression by PD1/PD-L1, we combined GS with checkpoint inhibition using nivolumab, an anti-PD1 monoclonal antibody. This open-label, non-randomized phase I study, examined the tolerability and immunogenicity of GS in combination with nivolumab in patients with previously treated DPM. **Methods:** We enrolled patients with WT1-positive metastatic or recurrent and measurable DPM treated with at least one course of pemetrexed-based chemotherapy. Patients received 2 doses of GS followed by 4 dose of GS with intravenous nivolumab every 2 weeks, and up to six additional cycles until disease progression, as measured by mRECIST 1.1 on CT imaging, or unacceptable toxicity. Primary endpoint was tolerability of the combination with < 3 patients with severe toxicity. Peripheral blood mononuclear cells (PBMC) were collected every 2 weeks for immune correlative testing. Toxicity was graded by the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0. Eliciting of antigen-specific T cells responses was evaluated via WT1 vaccine peptide pool expansion culture of PBMC samples for 10 days in the presence of IL-2 and IL-15 followed by short-term (6 hour) peptide pool restimulation and flow cytometry evaluating CD4/CD8 T cell intracellular cytokine production. **Results:** Ten patients were treated; 70% experienced treatment-related adverse events which were mostly mild; 2 experienced a grade ≥ 3 adverse event. Four (50%) of 8 patients had T-cell responses to WT1 peptides. There were no partial responses, but three patients had prolonged stable disease with up to 17% decrease in tumor volume. Median overall survival was 13.5 months from the most recent prior line of therapy. **Conclusions:** Coadministration of galinpepimut-S and nivolumab demonstrated a tolerable toxicity profile and induced immune responses in a subset of patients as indicated by immunophenotyping and disease control rate of 30% at 8 weeks but initial response and survival benefit were limited which may be due to the small sample size. Clinical trial information: NCT04040231. Research Sponsor: Bristol Myers Squibb; Sellas Life Sciences.

8084 Poster Session

Final analysis of the BIMES trial, a phase II single arm study assessing efficacy and safety of bintrafusp alfa in previously treated advanced malignant pleural mesothelioma (GECP 20/09).

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Background: Transforming growth factor β (TGF-β) is involved in tumor immune evasion and epithelial–mesenchymal transition (EMT). As TGF-β upregulation and EMT are associated with resistance to anti-PD1 therapy, we evaluated the efficacy of bintrafusp alfa, a bifunctional fusion protein targeting TGF-β and PD-L1, in malignant pleural mesothelioma (MPM). **Methods:** Patients with advanced MPM who were previously treated with platinum-based chemotherapy were enrolled and received bintrafusp alfa 1200mg/m^2 every 2 weeks until progression or for a maximum of two years. The primary objective was to determine the progression-free survival (PFS) by modified RECIST v1.1. assessed by the investigators. The expected median PFS was 4.5 months. Secondary objectives were overall response rate, duration of response, overall survival (OS) and safety. **Results:** Between October 2021 to March 2023, 47 patients were enrolled. Mean age was 70 years (41-84) and 36 (78.3%) were males. Most patients had epithelioid histology (82.9%) and had received only 1 prior line of therapy (84.8%). With a median follow-up of 11.5 months, 43 patients had disease progression and 24 patients died. The median number of doses administered was 4 (1-21) and reasons for treatment discontinuation were disease progression (82.6%), toxicity (6.5%), investigator decision (4.4%) and death (6.5%) by tumor progression. The median PFS was 1.9 months (95% CI 1.7 – 5.4) and the 6 month-PFS rate was 15.9%. Disease control rate was 34.8% (95% CI 22.2-49.9) consisting of 2 patients with partial response and 13 patients with stable disease as best response. The median OS was 11.9 months (95% CI 4.4 – not reached) and 6, 12 and 18-month OS rate was 65.3%, 46.5% and 26.6%, respectively. No significant differences in OS and PFS were observed based on MPM histological subtype. Grade 3-4 treatment-related adverse events occurred in 16 (34%) patients, anemia being the most common (n = 5); skin toxicity (n = 3); colitis (n = 2); adrenal insufficiency, acute kidney injury, allergic reaction, lipase, and amylase increased (n = 1 each). **Conclusions:** Bintrafusp alfa did not reach the expected efficacy in patients with advanced malignant pleural mesothelioma previously treated with platinum-based chemotherapy. Clinical trial information: NCT05005429. Research Sponsor: None.

8085 Poster Session

Efficacy of nivolumab/ipilimumab as first-line treatment of pleural mesothelioma in the German real-world setting.

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Background: The approval of nivolumab/ipilimumab (IO) has extended the first-line treatment options in unresectable pleural mesothelioma (PM). In the Checkmate 743 trial, first-line IO treatment resulted in similar survival benefit for both non-epithelioid (NE) and epithelioid (E) subtype with median survival of 18 months. However, data about efficacy in unselected populations from the real-world setting are scarce. **Methods:** We retrospectively collected clinical data of patients (pts) with PM diagnosed between 2010-2023 from twelve centers in Germany and analyzed cases that received at least one cycle of IO in the first-line setting. Median progression-free (mPFS) and overall survival (mOS) were estimated using Kaplan-Meier method and compared using the log-rank method. All statistical analyses were conducted using R software (4.3.2). **Results:** Overall 1574 patients were collected, of which 931 received any first-line systemic treatment and 135 were treated with IO in the first-line. The latter were mostly male (85%), older than 65 years (78%), current or former smokers (54%), and had E histology (67%). Mean age was 72 (standard deviation [SD] 8.4) years. The ECOG PS score (PS) was ≥2 in 5 cases only, but not available in 23. Only 64/135 (47%) pts went on to receive any second-line treatment, i.e. platinum/pemetrexed in 47, monochemotherapy (pemetrexed, gemcitabine or vinorelbine) in 15, IO re-challenge in 1 and nivolumab in 1. With median follow-up of 9 months (IQR 4.8-14.5), the mOS for the entire cohort was 13.6 mo (95% confidence interval [CI] 10.64-17.35). By histology, the mOS in NE was 16.6 mo vs. 13.6 mo in E histology [HR 0.89 (95%CI 0.54-1.48), p=0.65]. The mOS difference in pts with PS 0 vs 1 vs. >=2 was 16.6 mo vs. 12.8 mo vs. 3.5 mo [HR 1.45 (95% CI 0.90-2.36); p=0.13]. 2/5 pts with PS ≥ 2 died within first 4 months. When age at diagnosis was considered, mOS in age group "< 65", "≥ 65 to <75" and "≥75"-years were 18.8 mo, 16.6 mo, and 9.6 mo [HR 1.37 (95%CI 1-1.88), p=0.047], respectively. The mOS in never (N=42) vs. current or past smokers (N=52) was 10 mo vs. 14 mo [HR 0.67 (95%CI 0.39-1.14), p=0.14], respectively. The mPFS for the entire cohort was 4.76 mo (95% CI 3.7-6.7), 5.6 mo for the NE and 4.2 mo for E histology [HR 0.77 (95% CI 0.51 -1.16); p=0.21]. Subsequent treatment with Platin/Pemetrexed yielded a numerically longer mOS of 10 mo compared to 6.3 mo with monochemotherapy [HR 1.96 (95%CI 0.88-4.3), p=0.09]. **Conclusions:** In this real-world analysis of unselected patients, survival benefit with nivolumab/ipilimumab was somewhat less pronounced in both non-epithelioid and epithelioid subtypes compared to the Checkmate 743 trial. Older patients had worse prognosis, while there was also a tendency for shorter survival of never smokers and patients with worse ECOG performance status. Further analysis of larger real-world datasets with longer follow-up will be essential to validate these results. Research Sponsor: None.

Programmed cell death ligand 1 (PD-L1) inhibitors versus programmed cell death 1 (PD-1) inhibitors for the first-line therapy of extensive-stage small cell lung cancer: A propensity score-matched study.

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Background: Addition of programmed cell death ligand 1 (PD-L1) inhibitors or programmed cell death 1 (PD-1) inhibitors to etoposide-platinum (EP) chemotherapy has become the standard first-line regimen for ES-SCLC. The clinical efficacy and safety between the two types of immune checkpoint inhibitors (ICIs) remain controversial. We conduct the retrospective study and propensity score-matched analysis to explore the potential differences between them. **Methods:** Patients diagnosed with ES-SCLC and treated by EP plus PD-L1 or PD-1 inhibitors at Shandong Cancer Hospital between March 2019 and November 2022 were reviewed retrospectively. According to PD-L1 or PD-1 inhibitors, they were divided into two groups. Propensity score matching (1:1) was performed to balance the baseline characteristics of the two groups. The baseline characteristics and adverse events between the two groups were compared using the chi-squared test. The survival curves of overall survival (OS) and progression-free survival (PFS) were plotted by the Kaplan-Meier method and differences were analyzed by the log-rank test.The primary endpoints were OS and PFS. **Results:** As a result, 448 patients were analyzed in this study. 264 patients received PD-L1 inhibitors plus EP and 184 received PD-1 inhibitors plus EP. The median follow-up was 17.6 months. The median OS and PFS was 20.4 months and 7.8 months in the overall population. Before propensity score matching, the median OS was 20.1 months in PD-L1 inhibitor plus EP group and 20.7 months in PD-1 inhibitor plus EP group, respectively (HR 1.043, 95%CI 0.776-1.401; p= 0.781). The median PFS was 7.6 months in the PD-L1 inhibitor plus EP group and 8.5 months in PD-1 inhibitor plus EP group (HR 1.099, 95%CI 0.886-1.364; p= 0.390). After propensity score matching, the median OS and PFS were 20.4 months and 7.8months in PD-L1 inhibitor plus EP group, and those were 20.1 months and 8.6 months in PD-1 inhibitor plus EP group. There was no significant difference in OS and PFS between PD-L1 inhibitors plus EP and PD-1 inhibitors plus EP in the matched population (HR 1.104; p= 0.578 and HR 1.072; p= 0.602, respectively). The overall adverse events were comparable in the two groups. Only ≥3 grade neutropenia was more frequent in the PD-L1 inhibitors plus EP group (77.7% vs 69.0%, p= 0.040). **Conclusions:** In conclusion, the overall efficacy and safety profile was similar between PD-L1 inhibitors and PD-1 inhibitors for the first-line treatment of ES-SCLC. Research Sponsor: National Natural Science Foundation of China; Natural Science Foundation of Shandong; ZR2022LZL008.

8087 Poster Session

Outcome of chemo-immunotherapy for extensive-stage small-cell lung cancer according to potential clinical trial eligibility: 3-year outcomes from prospective cohort study.

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Background: Chemo-immunotherapy is the standard 1st-line therapy for patients with extensive-stage small-cell lung cancer (ES-SCLC). Our large previous real-world prospective analysis showed outcomes of chemo-immunotherapy for these patients according to potential clinical trial eligibility with a minimum follow-up period of 1 year. However, long-term outcomes have not been studied in the real-world setting. **Methods:** We conducted a 32-hospital prospective cohort study of consecutive patients with ES-SCLC who received carboplatin and etoposide with atezolizumab as 1st-line therapy between September 2019 and September 2020. Patients who met eligibility criteria for pivotal phase 3 clinical trials were considered "trial-eligible." We present 3-year outcomes from this study. **Results:** In total, 207 patients with ES-SCLC were analyzed. The median (range) time from the start of treatment to data cutoff (September 30, 2023) was 42.2 (35.8.-48.2) months. The median age was 72 years, and 64 patients (31%) were elderly (≥75 years). Most patients (89%) had a performance status (PS) of 0 or 1. As a result, 132 (64%) were categorized as trial-eligible patients. The 3-year PFS and OS probability of all patients was 6.1 % (95%CI:3.5-10.4%) and 20.9 % (95%CI:15.6-27.3%), respectively. Patients achieving 3-year OS included significantly higher proportions of trial-eligible patients (30 out of 132 versus 5 out of 75, respectively; p = 0.002). Kaplan-Meier estimates of the 3-year OS rate were 26.7% for the trial-eligible group and 9.5 % for the trial-ineligible group. **Conclusions:** This is the first real-world study to show the long-term efficacy of chemo-immunotherapy for ES-SCLC by using the largest prospective cohort of its kind. Additionally, this study demonstrated that trial eligibility was associated with long-term efficacy. Our study suggests that long-term clinical outcomes among trial-eligible patients may not translate to ineligible patients. Research Sponsor: chugai pharmaceutical.

Multidimensional analysis of B7 homolog 3 (B7-H3) RNA expression in small-cell lung cancer (SCLC) molecular subtypes.

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Background: SCLC is an aggressive cancer with a poor prognosis. B7-H3, a transmembrane protein showing low expression in normal tissues but overexpression in SCLC and other tumors, is a promising target for antibody–drug conjugates. We performed a multidimensional analysis of *B7-H3/CD276* expression in SCLC molecular subtypes (SCLC-A, -N, -P, and -I) and its relationship with expression of other immune-related genes. **Methods:** Clinical and molecular data for a cohort of patients (pts) with SCLC were derived from a real-world database (Caris Life Sciences, Irving, TX, USA). Tumor RNA expression was used to assign the SCLC molecular subtype derived from non-negative matrix factorization. Programmed death ligand-1 (PD-L1) protein expression was assessed by immunohistochemistry (IHC; antibody 22c3; positive cut-off: tumor proportion score >1%). Demographic, clinical, and molecular data were summarized by SCLC subtype or *B7-H3* expression quartile (Q). Spearman's *r* evaluated correlations between expression of *B7-H3* and other immune-related genes/signatures. **Results:** The cohort included 1721 pts (52.5% female; 98.9% [434/439] smokers; median age, 67 years [range, 18–90+]). Across the subtypes, *B7-H3* expression was high and remarkably consistent ($q>0.05$; Table). Other biomarker genes, including *DLL3* ($q<0.05$), had lower and more variable expression. Median (range) *B7-H3* expression across all samples was 16.75 (0–68.2) transcripts per million (TPM). Across *B7-H3* expression Qs, the proportion of PD-L1-positive pts by IHC was similar (Q1, 39.8%; Q2, 46.5%; Q3, 40.7%; Q4, 39.2%). Median (95% confidence interval) *B7-H3* expression was similar between pts with prior immunotherapy ($n=24$; 14.43 [11.64–21.17] TPM) and pts without ($n=208$; 14.20 [13.00–15.91] TPM); treatment information was not available for the remaining samples in this cohort. *B7-H3* expression was not strongly correlated with any other immune-related genes/signatures, although several had moderate correlation (*HAVCR2/TIM3*, $r=0.59$; *PDCD1LG2/PD-L2*, $r=0.56$; M2 macrophages, $r=0.56$; CD86, $r=0.56$). **Conclusions:** In pts with SCLC, *B7-H3* showed high and consistent expression across subgroups defined by molecular subtype or prior immunotherapy. The relative expression of *B7-H3* was higher and less variable among molecular subtypes than for other key molecular targets in this tumor type, including *DLL3*. *B7-H3* expression had limited association with *PD-L1* expression, supporting a role as a distinct therapeutic target. Research Sponsor: Daiichi Sankyo, Inc.

***B7-H3* and *DLL3* expression by SCLC subtype.**

	SCLC-A	SCLC-N	SCLC-P	SCLC-I	Equivocal
n	848	202	142	291	238
B7-H3 expression, median TPM (range)	16.98 (1.03–68.21)	16.22 (3.91–63.24)	16.93 (1.44–62.25)	16.4 (0.91–52.57)	17.05 (0–65.73)
DLL3 expression, median TPM (range)	10.6 (0.16–153.39)	4.19 (0.03–93.11)	0.74 (0–39.41)	7.98 (0.04–179.88)	8.29 (0.19–88.92)

8089 Poster Session

Tifcemalimab combined with toripalimab and chemotherapy as 1st line treatment for extensive-stage small cell lung cancer (ES-SCLC): A phase Ib/II, open-label study.

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Background: Tifcemalimab, a humanized IgG4 monoclonal antibody against B and T lymphocyte attenuator (BTLA), has shown preliminary anti-tumor activities in combination with toripalimab (anti-PD-1) as a later line treatment for patients with extensive-stage small cell lung cancer (ES-SCLC). We further conducted a multi-cohort phase Ib/II study (NCT05664971) to evaluate the safety and efficacy of tifcemalimab combined with toripalimab and chemotherapy as a 1st line treatment for patients with advanced lung cancer. Here, we report the preliminary results from the ES-SCLC cohort. **Methods:** Patients without previous systemic anti-tumor therapy for ES-SCLC were eligible. Patients received tifcemalimab 200mg in combination with toripalimab 240mg and standard chemotherapy (etoposide + carboplatin/cisplatin) intravenously once every three weeks (Q3W) for 4 cycles, then followed by tifcemalimab plus toripalimab maintenance therapy until disease progression, intolerable toxicity, or completion of 2 years treatment. Primary endpoints included safety and objective response rate (ORR) by investigators per RECIST v1.1. **Results:** From 7/12/2023 to 12/6/2023, a total of 44 ES-SCLC patients were enrolled. As of Dec 28, 2023, the median follow-up duration was 8.3 weeks. The median age of the patients was 65.5 (range 48-73) years, and 84.1% (37/44) were males. Forty-one (93.2%) patients experienced treatment-emergent adverse events (TEAEs), and 26 (59.1%) experienced ≥ grade 3 TEAEs. The most common TEAEs included leukopenia (65.9%), neutropenia (63.6%), anemia (40.9%) and thrombocytopenia (40.9%). No treatment-related adverse events led to discontinuation of tifcemalimab and toripalimab. Four (9.1%) patients experienced immune related AE (irAEs), and 1 experienced ≥ grade 3 irAE. Among 37 evaluable patients, 32 PR and 5 SD were observed. The ORR was 86.5% (32/37) and the DCR was 100% (37/37). By the data cut-off date, 94.6% of the responses were ongoing and the median duration of response was not reached. The preliminary biomarker analysis of tumor tissue suggested 100% ORR was observed among patients with either PD-L1 or HVEM positive expression. Further biomarker analysis will be updated. **Conclusions:** Tifcemalimab in combination with toripalimab and chemotherapy showed a promising objective response rate with a manageable safety profile as a 1st line treatment for patients with ES-SCLC. Continued follow-up is ongoing for additional safety and efficacy (PFS and OS) evaluation after extended exposure. Clinical trial information: NCT05664971. Research Sponsor: Shanghai Junshi Biosciences.

8090 Poster Session

Updated results from a phase 1/2 study of HPN328, a tri-specific, half-life (T1/2) extended DLL3-targeting T-cell engager in patients (pts) with small cell lung cancer (SCLC) and other neuroendocrine cancers (NEC).

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Background: Delta-like canonical Notch ligand 3 (DLL3) is highly expressed on the cell surface of neuroendocrine carcinomas, which have few approved treatment options in the refractory, metastatic setting. HPN328 is DLL3-targeting T-cell engager. HPN328 has 3 binding domains including anti-DLL3 for target engagement, anti-albumin for half-life extension, and anti-CD3 for T cell engagement and activation. **Methods:** Pts with relapsed/refractory, metastatic SCLC, neuroendocrine prostate cancer (NEPC) and other NEC associated with DLL3 expression are eligible. Primary objectives are safety, maximum tolerated dose (MTD) and pharmacokinetics (PK). Secondary objectives are immunogenicity and efficacy. Overall response rate (ORR) is determined using modified RECIST v1.1 to include extracranial response assessment for pts treated with radiotherapy for brain metastases while on treatment. HPN328 is administered IV QW or Q2W with priming dose preceding target dose in higher dose cohorts. **Results:** As of January 5, 2024, 86 pts received HPN328 doses of 0.015-24 mg across 14 cohorts (SCLC [n = 54; 63%]; other NEC [n = 32;37%]). The median (range) number of prior regimens was 3 (1-7); 83% previously received a PD-1/PD-L1 blocker. Treatment is ongoing in 24 of 46 (52%) pts in the dose optimization cohorts (1 mg priming dose with 12 or 24 mg target doses QW or Q2W). Treatment-related AEs in $\geq$ 10% of pts included CRS (59% [30% G1, 26% G2, 3% G3+]), dysgeusia (36%), fatigue (34%), diarrhea (19%), nausea (17%), vomiting (14%), decreased appetite and decreased neutrophil count (13% each), and weight decreased (11%). No G3-4 CRS was seen at target doses. Immune effector cell-associated neurotoxicity syndrome (ICANS) occurred in 9% of pts, all G1-2. The maximum tolerated priming dose was 1 mg; dose escalation of target dose continued up to 24 mg QW without reaching a maximum tolerated target dose. Among efficacy evaluable pts treated in dose optimization cohorts, the confirmed ORR in SCLC was 50% (12/24), with one complete response (CR). In NEC (other than NEPC) the confirmed ORR was 44% (4/9), with one CR. Four of eleven pts with NEPC had unconfirmed PRs in 1 mg priming dose cohorts, with 5 NEPC pts remaining on treatment $>$ 20 weeks. HPN328 exhibited linear PK with dose-proportional increases in exposure and a median $T_{1/2}$ of 71 hrs. Transient increases in cytokines up to 24 hrs post-dose and T-cell activation were observed. **Conclusions:** HPN328 is well tolerated and clinically active in SCLC, NEC, and NEPC. Current dose optimization cohorts have completed enrollment and data continue to mature; selection of a recommended phase 2 dose will be made based upon complete mature data. Updated safety and efficacy results will be presented. Clinical trial information: NCT04471727. Research Sponsor: Harpoon Therapeutics, Inc.

8091 Poster Session

Surrogate endpoints and outcomes in modern small cell lung cancer trials.

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Background: Overall Survival (OS) may not always be a feasible primary endpoint. Endpoints such as Overall Response Rate (ORR), Disease Control Rate (DCR=CR+PR+SD), Progression Free Survival (PFS), are frequently used in the assessment of treatments. However, improvements in DCR, ORR, PFS may not translate into OS benefit. Resilient trial showed a doubling of ORR to PEGylated liposomal irinotecan[1] compared to control but no improvement in PFS/OS. Furthermore, these associations may differ between 1st line (1L) and relapsed (2L) disease settings. This study analyzes the relationship between ORR, DCR, PFS, and OS in extensive-stage SCLC. **Methods:** MEDLINE, Embase, ClinicalTrials.gov were searched to identify randomized, phase III trials between 2014-2024. PRISMA guideline was followed. DCR, ORR, OS, PFS data were extracted. Weighted linear regression models investigated the association between treatment effects on DCR, ORR, OS, PFS. Weighted Pearson correlation analyses were performed under logarithmic transformation of DCR/ORR odds ratio besides DCR/ORR difference between treatment arms, with weights equal to the inverse of variance of DCR/ORR associated with the log PFS HR and the log OS HR. Logistic regression models were used to derive DCR/ORR odds ratios. Hazard ratios (HR) estimated from Cox proportional hazards regression models were used. All tests are two-sided; p-value < 0.05 is significant. **Results:** 115 trials were identified. 22 met the criteria. DCR: 1) 1L and 2L: DCR difference between arms and the log odds ratio and log PFS HR were strongly correlated: −0.63 (P = 0.001) for the DCR difference model; −0.64 (P = 0.0008) for the log odds ratio model. No correlation was found between DCR and OS; 2) 1L: No correlation between DCR and PFS & OS was found; 3) 2L: DCR difference between arms and the log odds ratio and log PFS HR were correlated: −0.84 (P = 0.01) for the DCR difference model; −0.84 (P = 0.01) for the log odds ratio model. ORR:1) 1L and 2L: ORR difference between arms and the log odds ratio and log PFS HR were correlated: −0.43 (P = 0.036) for the ORR difference model; −0.51 (P = 0.011) for the log odds ratio model; 2) 1L: No correlation between ORR and PFS & OS was found; 3) 2L: No correlation between ORR and PFS & OS was found. PFS:1)1L and 2L: The Pearson correlation coefficients between log HR of PFS and log HR of OS: 0.6 (p = 0.002); 2) 1L: The Pearson correlation coefficient between log HR of PFS and log HR of OS: 0.77 (p = 0.0005) 3) 2L: The Pearson correlation coefficients between log HR of PFS and log HR of OS: -0.14 (p = 0.732). **Conclusions:** In the 1L setting, neither DCR nor ORR predict PFS and OS. However, PFS predicts OS. In the 2L, ORR does not predict either OS or PFS; however, DCR predicts PFS and shows a trend with OS. Unlike in the frontline setting, PFS does not predict OS in the second-line setting. Reference: [1] Rudin CM, Dowlati A, Chen Y, et al.1610 RESILIENT part 2: A randomized, open-label phase III study of liposomal irinotecan versus topotecan in adults with relapsed SCLC. Research Sponsor: None.

J-TAIL-2: A prospective, observational study of atezolizumab (atezo) combined with carboplatin and etoposide (CE) in patients (pts) with extensive-stage small cell lung cancer (ES-SCLC) in Japan.

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Background: Atezo + CE is approved for the first-line treatment of ES-SCLC based on IMpower133 (IMp133; NCT02763579). Due to the limited data available in Japanese pts, J-TAIL-2 (NCT04501497) is evaluating the efficacy and safety of atezo + CE in Japanese pts in the clinical setting. **Methods:** Pts from Japan had ES-SCLC, were aged ≥20 y and were scheduled to start atezo + CE in clinical practice. The primary endpoint was 12-mo OS rate. Secondary endpoints included OS, PFS and safety. Efficacy and safety were evaluated in these subgroups: IMp133-unlike (e.g., ECOG PS 2-4, CNS metastases, history/complication of autoimmune or interstitial lung disease, previous treatment for ES-SCLC) vs IMp133-like (met IMp133 eligibility criteria), age <70 vs ≥70 y and geriatric score (G8) < median vs ≥ median. G8 was assessed in pts aged ≥70 y at baseline, with lower vs higher scores indicating poorer health status. **Results:** From Aug 21, 2020, to data cutoff (Feb 3, 2023), 403 pts were enrolled from 150 sites. Baseline characteristics are shown in the Table. In the efficacy analysis population (n=399), the 12-mo OS rate was 63.7% (95% CI: 58.6, 68.3), median OS (mOS) was 16.5 mo and mPFS was 5.1 mo. In the IMp133-unlike vs -like groups, mOS was 15.5 vs 19.1 mo (HR, 1.32; 95% CI: 0.98, 1.77) and mPFS was 4.8 vs 5.4 mo (HR, 1.14; 95% CI: 0.90, 1.45). In pts aged <70 vs ≥70 y, mOS was 17.9 vs 16.4 mo (HR, 1.18; 95% CI: 0.90, 1.55) and PFS was 5.1 vs 5.1 mo (HR, 1.07; 95% CI: 0.86, 1.33). The median G8 score was 12; in pts with a G8 score < median vs ≥ median, mOS was 11.1 vs 18.4 mo (HR, 1.95; 95% CI: 1.38, 2.77) and mPFS was 4.8 vs 5.2 mo (HR, 1.25; 95% CI: 0.94, 1.67). In the safety analysis population (n=400), treatment-related AEs occurred in 36.0% of pts, Grade (Gr) ≥3 AEs in 66.3% and Gr 5 AEs in 2.8%. Safety outcomes were similar for the IMp133-unlike vs -like and age <70 vs ≥70 y groups. In pts with a G8 score < median vs ≥ median, Gr ≥3 AEs occurred in 70.8% vs 63.5% of pts and Gr 5 AEs occurred in 5.2% vs 0.8% of pts. **Conclusions:** The efficacy and safety of atezo + CE in Japanese pts treated in clinical practice were consistent with those seen in IMp133. Subgroup analyses support the use of atezo + CE in pts who would have been ineligible for IMp133, although clinical outcomes favored the IMp133-like group. Efficacy and safety were similar for pts aged <70 vs ≥70 y but were worse for those with lower vs higher G8 scores, suggesting that this assessment may be a useful tool for therapeutic strategies. These data support the use of atezo + CE in Japanese pts with ES-SCLC, including in subgroups excluded from IMp133. Clinical trial information: NCT04501497. Research Sponsor: Chugai Pharmaceutical Co, Ltd.

	n=403
Median age (range), y	71.0 (39-91)
Age ≥70 y, n (%)	245 (60.8)
Male, n (%)	323 (80.1)
ECOG PS ≥2, n (%)	67 (16.6)
Brain metastases, n (%)	108 (26.8)
History of autoimmune disease, n (%)	5 (1.2)
Interstitial lung disease, n (%)	28 (6.9)
IMp133 unlike, n (%)	293 (72.7)
G8 score < median [12], n (%)	96 (23.8)

ARTEMIS-001: Data from a phase 1a/b study of HS-20093 in patients with relapsed small cell lung cancer (SCLC).

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Background: SCLC is characterized by a high rate of proliferation and poor prognosis, and new therapies are urgently needed. B7-H3 is highly expressed in SCLC. HS-20093, a B7-H3-targeted antibody-drug conjugate (ADC), demonstrated antitumor activity in advanced solid tumors in the dose escalation part of ARTEMIS-001 study (Jie Wang et al., JCO, 2023) (NCT05276609). Here, we present results on the efficacy and safety of the expansion doses in patients (pts) with SCLC from phase 1a/b. **Methods:** ARTEMIS-001 study consisted of dose escalation (1a) and expansion (1b) part. Pts were treated with doses of 1.0 to 16.0 mg/kg HS-20093 every 3 weeks in dose escalation, and were treated with doses at 8.0 mg/kg and 10.0 mg/kg randomly in dose expansion. Pts with SCLC were required to have received prior platinum-based standard therapy. B7-H3 expression was retrospectively evaluated by IHC. **Results:** As of data cutoff November 30th 2023, a total of 56 pts with extensive stage SCLC (ES-SCLC) were enrolled and received ≥1 dose of HS-20093 with doses at 8.0 mg/kg (n=31) or 10.0 mg/kg (n=25). Median prior lines of therapy was 2.0 (range: 1-6). All pts received platinum plus etoposide and 73.2% (41/56) received immunotherapy. Safety profile was consistent with previous reports. The most common grade≥3 treatment-related adverse events (≧10%) were neutropenia, leukopenia, lymphopenia, thrombocytopenia and anemia. Out of 56 pts, 52 pts were efficacy evaluable (8.0 mg/kg: 31 pts; 10.0 mg/kg: 21 pts). HS-20093 showed encouraging efficacy in relapsed ES-SCLC (Table). Tumor shrinkage in target lesions occurred in 96.2% (50/52) pts with a post-baseline scan. Deep response defined as tumor shrinkage ≥50% was obtained in 44.2% (23/52) pts. Median overall survival has not yet reached. Responses were observed regardless of B7-H3 expression. Pharmacokinetic (PK) showed approximately dose-proportional increase in exposure with a half-life of 3-7 days. PK profiles of total antibody and ADC were similar and exposure to payload was considerably low. **Conclusions:** HS-20093 demonstrated promising antitumor activity and manageable safety in pts with previously-treated SCLC. Phase 3 study is planned to compare the efficacy and safety of HS-20093 with standard-of-care chemotherapy in relapsed SCLC. Clinical trial information: NCT05276609. Research Sponsor: Hansoh Pharmaceutical Group Co, Ltd.

	8.0 mg/kg Q3W (n=31)	10.0 mg/kg Q3W (n=21)
ORR, n (%), (95% CI)	18 (58.1%)* (39.1, 75.5)	12 (57.1%)# (34.0, 78.2)
DCR, n (%), (95% CI)	25 (80.6%) (62.5, 92.5)	20 (95.2%) (76.2, 99.9)
Median DOR, month, (95% CI)	4.3 (3.3, NA)	NA (3.1, NA)
Median PFS, month, (95% CI)	5.6 (3.4, NA)	NA (4.4, NA)
Median follow-up time, month, (95% CI)	4.8 (3.6, 5.6)	4.9 (4.1, 5.6)

*Fifteen pts were confirmed PRs, 3 pts are awaiting confirmation.
#Ten pts were confirmed PRs, 2 pts are awaiting confirmation. ORR: objective response rate, DCR: disease control rate, DOR: duration of response; PFS: progression free survival, CI: confidence interval, PR: partial response.

Efficacy and safety of lurbinectedin (LUR) with irinotecan (IRI) in patients (Pts) with relapsed small cell lung cancer (SCLC): Results from a phase 2 expansion cohort.

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Background: LUR has been approved in the US and elsewhere for treatment of adult pts with metastatic SCLC and disease progression on or after platinum-based chemotherapy. Preclinical studies found synergy for LUR with IRI (Galmarini C. *Cancer Res* 2013; 73: Abst 5499). The phase 1b/2 study PM1183-A-014-15 (NCT02611024) evaluated the LUR/IRI combination in pretreated pts with advanced solid tumors. The phase 1b part defined the recommended dose at LUR 2.0 mg/m^2 on Day (D)1 + IRI 75 mg/m^2 on D1,D8 every three weeks with primary G-CSF prophylaxis, and found promising results for the combination in SCLC pts after first-line therapy (Ponce Aix S. *Ann Oncol* 2019; 30: Abst 471P). **Methods:** Eligibility criteria for this cohort of the phase 2 part of this study included: confirmed SCLC, progression after one platinum-containing regimen, controlled brain metastases and ECOG PS ≤ 1. The primary endpoint was overall response rate (ORR). **Results:** 101 evaluable pts were enrolled. Baseline characteristics included: median age 63 (range, 45-77 y), 60.4% males, 76.2% ECOG PS 1, 28.7% CNS involvement, 39.6% bulky disease and 41.6% pretreated with immunotherapy. Chemotherapy-free interval (CTFI) was <90 d in 51.4% of pts (26.7% had CTFI<30 d. Median CTFI was 85 d (range, 0-323 d). Median number of cycles per pt was 6 (range, 1-34); 25.7% received >10 cycles. Efficacy results by independent review committee are summarized in the table. Treatment-related adverse events (AEs) were observed in 99.0% of pts (grade ≥3 in 69.3%). Most relevant grade ≥3 events/abnormalities were neutropenia (52.5%), anemia (27.7%), diarrhea (19.8%), fatigue (18.8%), and febrile neutropenia (9.9%). Treatment-related SAEs occurred in 25.0% of pts and 5.0% discontinued due to treatment-related AEs. No treatment-related deaths occurred. **Conclusions:** The LUR/IRI combination showed promising antitumor activity and a manageable safety profile in these pts with poor prognosis, particularly those with CTFI>30 d. These encouraging results reinforce the rationale for including this combination as an experimental arm in the ongoing pivotal phase 3 LAGOON trial (NCT05153239) in relapsed SCLC with CTFI>30 d. Clinical trial information: NCT02611024. Research Sponsor: None.

	All pts (n=101)	CTFI<90 d (n=52)	CTFI≥90 d (n=49)	CTFI>30 d (n=74)
ORR, % (95% CI)	42.6% (32.8-52.8%)	25.0% (14.0-38.9%)	61.2% (46.2-74.8%)	51.4% (39.4-63.1%)
DoR (mo), median (95% CI)	7.6 (5.4-9.7)	6.3 (3.9-9.7)	8.4 (4.6-12.7)	8.2 (5.4-11.7)
PFS (mo), median (95% CI)	4.7 (3.8-6.0)	3.3 (2.6-5.0)	6.2 (4.2-9.6)	5.6 (4.1-7.2)
OS (mo), median (95% CI)	9.7 (8.5-13.4)	7.8 (3.5-8.9)	14.0 (10.1-16.1)	12.7 (9.1-14.1)
OS rate at 12 mo, % (95% CI)	44.6% (33.9-55.3%)	28.0% (14.2-41.8%)	61.7% (46.6-76.7%)	52.3% (39.8-64.7%)

CI, confidence interval; CTFI, chemotherapy-free interval; d, days; DoR, duration of response; mo, months; ORR, overall response rate; OS, overall survival; PFS, progression free survival.

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Results of a phase III clinical trial with anti-PDL1 treatment in combination with chemotherapy for extensive stage small cell lung cancer.

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Background: In China, small cell lung cancer (SCLC) accounts for over 15% of lung cancers. The morbidity of SCLC has been continuously increasing. SCLC is invasive, fast-growing cancer that distinctly differs from other cancers. Approximately 70% of cases present with metastasis at diagnosis and the median overall survival rate is about 8 to 11 months with a 5-year survival rate of less than 5%. Although being sensitive to chemotherapy and radiotherapy, SCLC patients are liable to relapse and often present with drug resistance. Here we study the combination of Socazolimab, an anti-PDL1 antibody, carboplatin and etoposide to treat extensive stage small cell lung cancer. **Methods:** The study is a randomized, double-blinded, placebo-controlled multicenter Phase III clinical trial. Patients who have extensive-stage SCLC are eligible to the trial. Patients are randomly assigned to the study group (Socazolimab + carboplatin + etoposide) or control group (placebo + carboplatin + etoposide) at 1:1 ratio, with a treatment cycle of every 3 weeks. There are 4 cycles of chemotherapy followed by Socazolimab or placebo alone until termination events occurred or for up to 2 years. The primary endpoint is overall survival (OS). The major secondary endpoint is progression free survival (PFS). **Results:** There were a total of 498 patients recruited for the study with average age of 61.9 amount which 449 patients were diagnosed with stage IV SCLC. All the analysis was based on intent-to-treat (ITT). The median baseline performance status score was 1.0. The median OS of study group and control group are 13.90 months (95% CI: 12.22-15.34) and 11.58 months (95% CI: 10.64-12.81) respectively, with a P-value of 0.0316. The 24 month survival rate of study group and control group are 20.7% (95% CI:14.8-27.3) and 5.9 %(95% CI: 0.8-18.9). The median PFS of the two groups are 5.55 months (95% CI:5.06-5.82) and 4.37 months (95% CI: 4.27-4.70) with a P-value < 0.0001. The treatment related adverse event were similar in both groups. **Conclusions:** These results show that Socazolimab plus chemotherapy continued to provide clinically meaningful improvements in OS for patients with extensive stage small cell lung cancer. Clinical trial information: NCT04878016. Research Sponsor: None.

Survival outcomes of patients with extensive-stage small cell lung cancer who received treatment with atezolizumab in combination with carboplatin and etoposide: A propensity score adjusted cohort study.

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Background: Small cell lung cancer (SCLC) is an aggressive type of lung cancer. Most patients (pts) are diagnosed with extensive-stage disease (ES-SCLC). The cornerstone treatment of ES-SCLC has been platinum-based chemotherapy and etoposide. Combining atezolizumab with carboplatin plus etoposide (Carbo-E) improved overall survival (OS) in ES-SCLC pts and became a new standard for first-line treatment. However, there is a paucity of real-world outcomes in ES-SCLC. Herein, we present the largest and longest follow-up retrospective study analyzing atezolizumab in combination with chemotherapy for treatment of ES-SCLC. **Methods:** We conducted a retrospective study and included all adult pts (≥ 18 years) with ES-SCLC treated at Cleveland Clinic between 1/2010-12/2022. ES-SCLC was defined as stage IIIB or stage IV. We collected treatment regimens and baseline characteristics including age, sex, race, smoking, alcohol intake history, and comorbidities. Responses were assessed using RECIST response criteria. Both OS and progression-free survival (PFS) were calculated from treatment initiation. We used propensity score (PS) weighting and multivariable Cox proportional hazards ratio (CPH) to adjust for baseline confounding. **Results:** We identified 561 ES-SCLC pts who received treatment, 375 (67%) received Carbo-E and 160 (29%) received Carbo-E + Atezolizumab (Carbo-E-Atezo). The table describes the baseline characteristics of Carbo-E and Carbo-E-Atezo groups. The median follow-up was 30 months (mo) (IQR: 14 - 59). In the Carbo-E arm, 45 patients (12%) received second-line immune therapy (nivolumab +/- ipilimumab or pembrolizumab). On PS-adjusted logistic regression, pts who received Carbo-E-Atezo had a 1.1 odds ratio (95%CI: 0.85-1.43, P>0.05) to respond compared to pts who received Carbo-E. There was no difference in PS-adjusted median OS between pts who received Carbo-E-Atezo (9.2 mo (95%CI: 8.1-11)) vs. Carbo-E (8.4 mo (95%CI: 7.7-9.0)) (log-rank P>0.05). Similarly, there was no difference in adjusted median PFS between pts who received Carbo-E-Atezo (5.9 mo (95%CI: 5.3-6.9)) vs. Carbo-E (5.5 mo (95%CI: 4.7-5.9)) (P>0.05). Using CPH model, the addition of atezolizumab to Carbo-E did not decrease mortality (Hazard Ratio: 0.84, 95%CI: 0.68-1.04, P>0.05). Male gender and increasing age were predictors of worse OS (P<0.05). **Conclusions:** Among pts with ES-SCLC, the addition of atezolizumab to the standard chemotherapy regimen of Carbo-E showed no significant difference in PFS or OS in our real-world study. Research Sponsor: None.

	Carbo-E	Carbo-E-Atezo
Age (median, IQR), years	67 (60, 74)	65 (59, 71)
Gender, Female (%)	194 (53%)	75 (48%)
Race: White (%)	336 (91%)	145 (92%)
Race: African American (%)	33 (9%)	12 (8%)
Smoking Current + Former (%)	357 (96%)	153 (97%)
Heart Disease (%)	85 (23%)	34 (22%)
CKD 3/4 (%)	14 (3%)	7 (4%)

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Cost-effectiveness study of atezolizumab (ATZ) vs. durvalumab (DUR): Real-world data (RWD) on first-line chemotherapy combined with immune-checkpoint inhibitors (Chemo-ICIs) for extensive disease small-cell lung cancer (ED-SCLC).

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Background: Chemo-ICI is the standard of care in first-line therapy for ED-SCLC. Although there is no comparative data on ATZ vs. DUR, their efficacies appear to be equivalent based on results from IMpower133 and CASPIAN trials. On the other hand, the drug price of DUR is higher than that of ATZ, suggesting a different cost-effectiveness. **Methods:** This is a multicenter retrospective study of RWD. Clinical outcomes and safety information of ED-SCLC patients (pts) who had received Chemo-ICIs were collected from electronic medical records, and the total cost incurred during ICIs was obtained from the receipts of each hospital. Propensity score matching (PSM) was performed to adjust difference of pts' backgrounds of two groups (ATZ-G vs. DUR-G). The total monthly medical costs incurred during ICI administration for both groups were compared by cost minimization analysis to evaluate cost-effectiveness. **Results:** From August 2018 to December 2022, 274 pts (ATZ/DUR: 176/98) were extracted from 8 hospitals in Japan. After PSM and exclusion of cisplatin-treated pts, total 128 pts: 64 pts in each group were evaluated. The mean total medical costs per month during ICIs were 1,003,922 (±310,192) JPY (6,783 USD) in the ATZ-G and 1,596,511 (±371,405) JPY (10,787 USD) in the DUR-G (Wilcoxon rank sum test: $p < 0.001$). Mean ICI drug costs per month during ICIs were 799,079 (±89,555) JPY (5,399 USD) in the ATZ-G and 1,570,744 (±371,405) JPY (10,163 USD) in the DUR-G ($p < 0.001$). Response rate was 73.4% for ATZ-G and 75.0% for DUR-G. Median overall survivals (OSs) of ATZ-G vs. DUR-G were 13.9 (95% confidence interval [CI]: 11.7-17.5) vs. 13.6 (95% CI: 11.0-20.0) months, respectively ($p = 0.919$). Median progression-free survivals of ATZ-G vs. DUR-G were 4.9 (95% CI: 4.4-5.6) vs. 5.6 (95% CI: 5.0-6.7) months, respectively ($p = 0.060$). Cox-proportional hazard model identified poor performance status (hazard ratio [HR]: 5.5, $p < 0.001$) and bone metastases (HR: 1.8, $p = 0.029$) as significant factors for shorter OS, while ATZ vs. DUR was not significant. ATZ-G revealed lower incidences of immune-related adverse events (irAEs) ≥grade 2 (10.9 vs. 31.3%, $p = 0.009$) and any grade interstitial lung disease (ILD) (3.1 vs. 20.3%, $p = 0.004$) than DUR-G. Number of hospitalizations in ATZ-G (median 1, range 0-6) was lower than that in DUR-G (median 2, range 0-7) ($p = 0.005$). **Conclusions:** Our RWD demonstrated a superior cost-effectiveness of ATZ to that of DUR. Total efficacies were similar, whereas the safety profiles, including irAE and ILD were more favorable in ATZ-G. Further discussion is required regarding not only cost-effectiveness but also clinical practicality such as: dose schedule of 3 weeks vs. 4 weeks; regimen flexibility of carboplatin vs. cisplatin; and etoposide dose adjustment of 100 mg/m^2 vs. 80 mg/m^2. Clinical trial information: 000053483. Research Sponsor: Healthcare Consulting, Inc.

A randomized phase II study of toripalimab consolidation or observation after concurrent chemoradiotherapy in limited-stage small cell lung cancer.

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Background: In recent years, the use of immune checkpoint inhibitors has led to significant progress in the treatment of extensive-stage small cell lung cancer. However, there is limited data on the efficacy of immunotherapy in patients with limited-stage disease (LS-SCLC). Therefore, we conducted a phase II randomized study to verify the efficacy and safety of Toripalimab consolidation following definitive concurrent chemoradiotherapy (CCRT) in patients with LS-SCLC (ClinicalTrials.gov ID: NCT04418648). **Methods:** Patients with LS-SCLC who had achieved complete or partial response after definitive CCRT (including four to six cycles of etoposide and cisplatin, and curative-intent thoracic radiotherapy) were randomly assigned (1:1) to receive Toripalimab consolidation (240mg intravenously, every 3 weeks for 6 months) or observation. Prophylactic cranial irradiation (PCI) was recommended but not mandatory. The primary endpoint was progression-free survival (PFS) calculated from randomization, and secondary endpoints included overall survival (OS) and toxicity. **Results:** As of data cutoff (November 30, 2023), a total of 64 eligible patients (intent-to-treat population) were randomly assigned to the Toripalimab group (n = 31) or the observation group (n = 33), respectively. With the median follow-up of 25 months, PFS was significantly improved with Toripalimab (hazard ratio [95% CI]: 0.47 [0.22-1.02]; P = 0.04). The median PFS in observation group was 12.3 months (95% CI, 0.04-24.50), while the median PFS in the Toripalimab group has not been reached. The 24-month PFS rate was 61.6% (95% CI, 43.0%-88.3%) in the Toripalimab group and 34.8% (95% CI, 21.5%-56.3%) in the observation group. The 24-month OS was 82.7% (95% CI, 65.2%-100%; P = 0.23) in the Toripalimab group and 59.1%(95% CI, 44.2%-79.1%) in the observation group. There were 5(16.1%) and 3 (9.1%) patients in the Toripalimab group and observation group experiencing G2+ pneumonitis respectively. No G4+ toxic events occurred in either group. **Conclusions:** Our preliminary results suggested Toripalimab consolidation following definitive CCRT was effective and tolerable in LS-SCLC. Clinical trial information: NCT04418648. Research Sponsor: None.

	Toripalimab Group (n = 31)	Observation Group (n = 33)	Total (n = 64)	P-value
Age, median(range)	62(29-71)	59(39-71)	59(29-71)	0.79
Gender, n(%)				0.66
Male	25(80.6)	28(84.8)	53(82.8)	
Female	6(19.4)	5(15.2)	11(17.2)	
ECOG, n(%)				0.61
0	5(16.1)	7(21.2)	12(18.8)	
1	26(83.9)	26(78.8)	52(81.2)	
Disease Stage, n(%)				0.94
II	3(9.7)	3(9.1)	6(9.4)	
III	28(90.3)	30(90.9)	58(90.6)	
Chemotherapy cycle, n(%)				0.92
4	26(83.9)	28(84.8)	54(84.4)	
5	1(3.2)	1(3.1)	2(3.1)	
6	4(12.9)	4(12.1)	8(12.5)	
Radiation Dose, n(%)				0.46
45Gy/30f	25(80.6)	24(72.7)	49(76.6)	
60-65Gy/24-26f	6(19.4)	9(27.3)	15(23.4)	
PCI				0.46
Yes	25(80.6)	24(72.7)	49(76.6)	
No	6(19.4)	9(27.3)	15(23.4)	
Median cycle of Toriplimab (range)	5(1-8)			

8099 Poster Session

BIOLUMA: A phase II trial of nivolumab and ipilimumab in lung cancer—Results from the SCLC TMB^{high} cohort.

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Background: Therapeutic options and prognosis for patients with small-cell lung cancer (SCLC) remain poor. Treatment with checkpoint inhibition can achieve remarkable responses, but this holds true for a small percentage of SCLC patients only. While tumor mutation burden (TMB) emerged as possible predictive biomarker for nivolumab and ipilimumab combination therapy in SCLC patients, to our knowledge, tissue-based TMB has never been evaluated prospectively in SCLC patients. Here, we present the results of the cohort 2b of the BIOLUMA trial, which evaluates efficacy and safety of nivolumab in combination with ipilimumab in SCLC patients with high tumor mutation burden. **Methods:** BIOLUMA is an investigator initiated multicentre non-randomised phase II trial in 2nd line patients with SCLC. The initial all-comer SCLC cohort was amended for inclusion of patients with high TMB only. FFPE tumor tissue was used for TMB pre-screening by whole exome sequencing (WES) at time of first diagnosis. TMB^{high} was defined as the upper tertile of total missense mutations. After progression on platinum-based therapy, patients received 4 cycles of nivolumab 1 mg/kg q3w in combination with ipilimumab 3 mg/kg q3w and subsequently nivolumab 240 mg flat dose as monotherapy. Primary endpoint was overall response rate (ORR) of the combination therapy. Additionally, exploratory analyses of sequential tumor biopsies and blood samples were performed at different time points. **Results:** TMB analysis was feasible for most patients without necessity of performing additional tumor biopsy. Evaluation of TMB on FFPE tumor tissue obtained at first diagnosis was sufficient for TMB analysis in 92.5% of cases. TMB status was determined for 297 patients: 45.8% belonged to the TMB high group, while 54.2% had low or medium TMB. In total, 45 TMB^{high} patients were enrolled in the study with 44 subjects evaluable for primary endpoint analysis. Six patients (13.6%) showed response to therapy, of whom in 4 patients (9%) response could be confirmed according to RECIST 1.1 criteria. One patient, who is not evaluable for endpoint analysis experienced a remarkably long lasting PR, which is still ongoing for more than three years. This patient received concomitant palliative radiation during induction with nivolumab and ipilimumab. Disease control rate (DCR) was 20.4% (n=9), three more patients showed unconfirmed SD. Three patients with confirmed PR or SD experienced long lasting treatment benefit, which is still ongoing at data cut-off. **Conclusions:** This represents the first trial to prospectively evaluate the combination therapy of nivolumab and ipilimumab in TMB^{high} SCLC patients. The primary endpoint ORR was not reached. However, we observed an impressive clinical benefit in single patients, which warrants further investigation in order to get more insight into the mechanisms leading to these long-lasting tumor responses. Clinical trial information: NCT03083691. Research Sponsor: None.

8100 Poster Session

Serplulimab vs. placebo combined with chemotherapy as first-line treatment for extensive-stage small-cell lung cancer: Extended follow-up results and patient-reported outcomes from the international phase 3 ASTRUM-005 study.

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Background: ASTRUM-005 is a randomized, double-blind, phase 3 trial comparing efficacy and safety of serplulimab (a novel anti-PD-1 antibody) plus chemotherapy (chemo) vs. placebo plus chemo as first-line therapy for extensive-stage small-cell lung cancer (ES-SCLC). Interim analysis presented at 2022 ASCO Annual Meeting showed significantly prolonged overall survival (OS) in the serplulimab arm. Continuing improvements were seen in all efficacy endpoints in an updated analysis reported at ESMO Asia Congress 2022. Here we present the updated results with an extended follow-up duration of 31.6 months and the previously undisclosed patient-reported outcomes (PROs). **Methods:** 585 patients with ES-SCLC who had not received prior systemic therapy were randomized 2:1 (serplulimab arm, n = 389; placebo arm, n = 196) to receive serplulimab 4.5 mg/kg or placebo intravenously every 3 weeks. All patients received up to 4 cycles of intravenous carboplatin and etoposide every 3 weeks. Stratification factors were PD-L1 expression level, brain metastases, and age. The primary endpoint was OS. PROs were assessed using EORTC QLQ-C30, EORTC QLQ-LC13, and EQ-5D-5L questionnaires. **Results:** By the data cutoff of June 13, 2023, 267 (68.6%) patients in the serplulimab arm and 160 (81.6%) in the placebo arm had died. Median OS was markedly longer in the serplulimab arm than that in the placebo arm (15.8 vs.11.1 months; stratified HR 0.61, 95% CI 0.50–0.74). Subgroup analysis by race showed similar trends of a prolonged median OS in Asians (unstratified HR 0.61, 95% CI 0.48–0.77) and non-Asians (all were White; unstratified HR 0.57, 95% CI 0.39–0.83). Estimated OS rate at 3 years was 24.6% (95% CI 19.5–30.1) and 9.8% (95% CI 5.6–15.4) in the respective arms. By-visit longitudinal changes in all domains of the 3 questionnaires were comparable between arms. Least square mean (LSM) changes from baseline to week 18 in QLQ-C30 functional and symptom domains, QLQ-LC13 symptom domains, and EQ-5D-5L VAS were similar and generally improved in both arms, with more pronounced and persistent amelioration in "pain in other parts" symptom domain for the serplulimab arm (difference in LSM change, −6.37 [95% CI −11.59 to −1.15], p = 0.0170). Time to deterioration was similar between arms: median, not reached (NR) vs. NR for global health status/quality of life (HR 0.90, 95% CI 0.59–1.39), physical functioning (HR 1.01, 95% CI 0.61–1.65), and role functioning (HR 1.17, 95% CI 0.74–1.87). **Conclusions:** With extended follow-up, the survival benefits brought by the addition of serplulimab were maintained in the first-line therapy of ES-SCLC. PROs were not adversely impacted, and pain in other parts was significantly improved. All these results support serplulimab plus chemo as a promising first-line treatment option for ES-SCLC. Clinical trial information: NCT04063163. Research Sponsor: Shanghai Henlius Biotech, Inc.

Safety and efficacy of durvalumab plus carboplatin and etoposide for patients with previously untreated extensive-stage small-cell lung cancer (ES-SCLC) with a poor performance status: The results from phase II single-arm study (NEJ045A study).

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Background: Although the combination of an anti-PD-L1 antibody and platinum-based chemotherapy has become the standard care for ES-SCLC patients (pts), its safety and efficacy for those with a poor PS are unclear. Since SCLC is highly sensitive to chemotherapy, we hypothesized that ES-SCLC pts with a poor PS may benefit from anti-PD-L1 antibody therapy because tumor shrinkage by cytotoxic agents is expected to improve PS and tumor immune responses. This study aims to assess the safety and efficacy of durvalumab plus carboplatin (CBDCA) and etoposide (ETP) in ES-SCLC with a poor PS. **Methods:** This is an open-label, single-arm, multicenter phase II study. Previously untreated ES-SCLC pts with a poor PS (PS 2–3) were enrolled. Eligible pts received 1500 mg durvalumab plus CBDCA and ETP every 3 to 4 weeks for up to 4 cycles, followed by 1500 mg durvalumab every 4 weeks until progression or unacceptable toxicity. Initial dosages of CBDCA and ETP were AUC 4 and 80 mg/m^2 in PS 2 cohort and AUC 3 and 60 mg/m^2 in PS 3. The dosages for the second and subsequent cycles were adaptively determined based on the adverse events of the first cycle allowing for dose escalation to a maximum CBDCA AUC of 5 and ETP of 100 mg/m^2. The primary endpoint was the tolerability, which was evaluated based on the percentage of pts who completed four cycles of durvalumab plus CBDCA and ETP. The expected completion rates were 50% for each cohort, and the threshold completion rates were 33% for PS2 and 20% for PS3. **Results:** From April 2021 to October 2023, 57 pts (43 pts with PS 2 and 14 pts with PS 3) were enrolled. At data cutoff (Dec 31th, 2023), the median follow-up period was 7 months (range 1.1-32) in the ITT population. The median age is 74 years old (range 55-86), 79% male. 68% (80% CI, 56-77) in PS2 and 50% (80% CI, 27-73) in PS3 pts completed four cycles of durvalumab plus CBDCA and ETP. The ORRs in PS 2 and PS 3 were 52% (95% CI, 36-68) and 45% (95% CI, 17-77). The median PFSs in PS 2 and PS 3 were 4.7 months (95% CI, 3.8-6.4) and 5.1 months (95% CI, 1.4-10.6). The median OS in PS 2 and PS 3 were 9.5 months (95% CI, 6.6-26.7) and 5.1 months (95% CI, 1.4-not reached). The ratios of PS improvement in PS2 and PS3 were 57% (95% CI, 42-71) and 45% (95% CI, 21-72). Grade ≥3 adverse events (AEs) were reported in 93% in PS 2 and 100% in PS 3 pts, and 11 pts (20%) had discontinued study treatment due to AE. **Conclusions:** The current study met its primary endpoint. Durvalumab plus CBDCA and ETP showed tolerability and promising efficacy as first-line treatment for ES-SCLC pts with a poor PS. These data support the combination therapy of immune checkpoint inhibitor and chemotherapy with dosage adjustment for ES-SCLC with a poor PS. Clinical trial information: jRCTs031200319. Research Sponsor: AstraZeneca.

An open-label, multicenter, phase Ib/II study of the ATR inhibitor SC0245 in combination with irinotecan in patients with relapsed and refractory extensive stage small cell lung cancer (ES-SCLC).

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Background: Ataxia telangiectasia and Rad3 related (ATR) is activated in response to replication stress induced by topoisomerase 1 inhibitors (TOP1i) and other DNA damaging agents. SC0245 is a novel potent ATR inhibitor, showing synergistic inhibitory effects when combined with TOP1i in DMS-114 and H446 small cell lung cancer. This is the first report on an ongoing phase Ib/II study of SC0245 in combination with irinotecan (IRI) in patients (pts) with ES-SCLC (ClinicalTrials.gov: NCT05731518). **Methods:** Multiple escalating doses of SC0245 are being administered orally with a fixed dose of IRI. Pts are being enrolled into five escalating dose cohorts (80 mg once daily (QD), 120 mg QD, 80 mg twice daily (BID), 120 mg BID, 160 mg BID) using a BOIN design. SC0245 is administered daily for 3 days weekly x 3 (e.g, Days 1-3, 8-10 and 15-17) with IRI 80 mg/m^2 on Days 1, 8 and 15. Cycles are repeated every 4 weeks. The primary endpoint is the rate of dose-limiting toxicity (DLT). Tumor assessments are being performed every 8 weeks using RECIST v1.1. Dose expansion in ES-SCLC patients will follow after definition of the recommended phase 2 dose (RP2D). **Results:** As of the data cut-off-date (December 21, 2023), 15 pts (median age, 65; male, 73.3%) with previously treated solid tumors have been enrolled, with 3, 4, 3 and 5 pts in 80mg QD, 120mg QD, 80mg BID and 120 mg BID dose cohorts, respectively. 12 of 15 pts were DLT evaluable, and one DLT event (Grade 3 febrile neutropenia) occurred in the 80 mg QD dose cohort. Cytopenia, diarrhea, and liver function test elevations, were the main adverse events (AEs) experienced in 73.3%, 46.7% and 40% pts, respectively. Most AEs were grade 1 or 2 in severity and manageable. The only ≥ Grade 3 TRAEs experienced by more than 2 subjects has been leukopenia (3/15, 20.0%). No drug-related deaths occurred. Among the 9 pts who were evaluable for tumor response, one confirmed partial response (PR) was reported in a pt with ES-SCLC (progressed on prior 1st line of etoposide + carboplatin + serplulimab treatment) treated in the 120mg QD dose cohort, and the response sustained for 32+ weeks; five pts (5/9, 55.6%) had stable disease (SD) as their best response. PK characteristics indicated that SC0245 was rapidly absorbed (median $T_{max,}$ 1.0 to 2.0 h), and drug exposure was proportional to dose for the QD and BID regimens. No drug-drug interactions (DDI) between SC0245 and either IRI or its active metabolite SN38 were observed. **Conclusions:** SC0245 exhibited favorable safety and PK characteristics when administered in combination with IRI at doses ranging from 80mg QD to 120mg BID and the regimen has demonstrated preliminary antitumor activity in ES-SCLC, supporting further evaluation of the regimen in ES-SCLC and other relevant malignancies. Clinical trial information: NCT05731518. Research Sponsor: Biocity Biopharmaceutics Co,.Ltd, Wuxi, China.

8103 Poster Session

Tumor-derived serum proteotypes to predict response to immune therapy in patients with limited disease small-cell lung cancer.

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Background: The STIMULI clinical trial (NCT02046733) tested the combination of ipilimumab and nivolumab (IPI/NIVO) after standard chemoradiotherapy in patients with limited disease small cell lung cancer (LD-SCLC). The study showed no improvement in the primary endpoint of progression-free survival (PFS) in unselected patients. Accessing tumor samples is challenging in LD-SCLC after chemoradiotherapy; hence, we analyzed serum and whole blood RNA samples as biomarkers to stratify patients for clinical benefit. **Methods:** We used a semi-quantitative large-scale proteomic assay (SomaScan) to analyze more than 7000 proteins. We also profiled whole-blood RNA collected before and after chemoradiotherapy and performed Bulk RNA barcoding and sequencing (BRBseq). We analyzed 131 serum samples, of which one failed quality control. 119 whole blood Paxgene RNA before chemoradiotherapy and 124 after were also analyzed. We performed unsupervised hierarchical clustering on protein and RNA samples and defined differentially expressed proteins/transcripts and pathway enrichment in specific clusters. We also performed RNA deconvolution with CibersortX. In addition, we performed organ-specific aging prediction from serum proteomics using the orange Python pipeline. **Results:** We identified five patient proteotype clusters. Unexpectedly, the proteotypes corresponded to three types of clinical outcomes. Clusters 1, 3, and 4 were linked with a lack of benefit from immune therapy. Patients in cluster 2 had improved outcomes from immune therapy (HR: 0.436 CI: 0.1976 to 0.9078, p: 0.0272) and likely benefited most. In contrast, patients in cluster 5 had a decreased survival (HR: 5.53, CI: 1.261 to 24.28, p: 0.0234). These patients might represent a hyper-progression phenotype on immune therapy. Protein-based pathway analysis showed that cluster 1 patients had upregulated TGF?, and IL-6 signaling, whereas patients in cluster 5 activated the complement pathway. In addition, preliminary analysis of organ aging showed that the patient clusters could also be linked with differential immune aging. Together, our prototypes suggest differential proteomic states of patients' underlying responses. In contrast with the protein data, RNA analysis did not lead to outcome predictors. We compared the protein signatures to single-cell RNAseq data of SCLC and found that these proteins might originate from the tumors. **Conclusions:** Proteotypes based on large-scale proteomic analysis could predict both the benefit and lack thereof for IPI/NIVO therapy in limited disease small cell lung cancer. The clusters also provide clues into differential pathway activation and could serve as potential new biomarkers and targets for precision adjuvant immune therapy of SCLC and beyond. Research Sponsor: Sophien-Stiftung zur Foerderung der klinischen Krebsforschung.

A phase II, open-label, combination therapy of durvalumab and ceralasertib in relapsed and refractory small cell lung cancer (SUKSES-N4).

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Background: In extensive stage small-cell lung cancer (SCLC), the standard first-line treatment is an immune checkpoint inhibitor (ICI) combined with chemotherapy. However, in the relapsed or refractory setting, the benefits of ICI-based combinations are modest, regardless of prior ICI exposure. Ceralasertib, a selective ATR inhibitor, not only enhances DNA damage, inducing apoptosis, but also affects immune and inflammatory pathways. This study assesses the safety and efficacy of combining durvalumab with ceralasertib in SCLC patients. **Methods:** This open-label, phase II, multi-cohort umbrella trial recruited relapsed and refractory SCLC patients independent of biomarker status. Initially, patients received 1500mg of durvalumab on day 1, followed by 240mg of ceralasertib twice daily from day 15 to 28 of a 28-day cycle (Dose A). An amendment aligned the dosing regimen to other studies to 240mg of ceralasertib twice daily from day 1 to 7, with 1500mg of durvalumab administered on day 8 (Dose B). The primary endpoint was the objective response rate (ORR), with a target enrollment of 40 evaluable patients. **Results:** Between June 2022 and May 2023, forty-two patients were recruited (Dose A: 27; Dose B: 15). The median age was 67 (range: 43-83), with a predominance of males (n = 36) and smokers (n = 40). ECOG PS scores were 0 (n = 1) or 1 (n = 41), and nearly half (n = 20, 47.6%) had prior ICI exposure. The ORR per RECIST was 9.5%, with a disease control rate of 26.2%, including 4 partial responses (PR) and 7 cases of stable disease (SD). Median progression-free survival (PFS) was 1.64 months (95% CI: 1.61-1.97), and overall survival was 7.16 months (95% CI: 6.07-13.9). The duration of responses was notable, showing PFS of 4.8, 17.0, and 18.3 months in ICI-naïve PR patients and 14.1 months in ICI-exposed patient currently still ongoing on treatment. A sustained clinical benefit of up to 10.7 months was observed in an ICI-naïve patient with SD. Hematologic adverse events (AEs) included thrombocytopenia as grade 4 (n = 9) and grade 3 (n = 3), anemia as grade 3 (n = 3), and neutropenia as grade 4 (n = 3) and grade 3 (n = 1). Other AEs were mostly grades 1 or 2 and manageable. Exploratory biomarker analysis is in progress and will be presented. **Conclusions:** Ceralasertib and durvalumab combination therapy have demonstrated durable responses in select patients with manageable hematologic toxicity. Biomarker research is ongoing to identify patients most likely to benefit from this treatment strategy. Clinical trial information: NCT04361825. Research Sponsor: AstraZeneca.

Exploring systemic treatment approaches for advanced pure large cell neuroendocrine carcinoma (LCNEC): A multicenter retrospective analysis.

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Background: Due to lack of prospective data, the optimal first line treatment approach for patients (pts) with pure LCNEC histology remains uncertain. **Methods:** Across 17 centers, we conducted a retrospective analysis of metastatic pure LCNEC (diagnosed at local institutions) who received 1st-line systemic therapy between 2015-2023. Pts were either treated with chemotherapy (chemo), immunotherapy (IO), or a combination (chemoIO). Clinical outcomes were progression-free survival (PFS), overall survival (OS), objective response rates (ORR), and treatment-related adverse events (trAE) as defined using CTCAE 5.0. Survival analysis by genomic alteration status (*TP53, RB1, STK11, KEAP1, KRAS*) and PD-L1 status were performed. **Results:** We identified 161 pts with median age of 67 years (IQR: 58-83) at 1st line systemic therapy; 54% (n = 87) were males. Median follow-up was 55 months (mo), 62 mo, and 29 mo for the chemo, IO, and chemoIO groups, respectively. 79% (n = 127) were former or current smokers. 1st-line treatments were chemo (n = 94), IO (n = 11), or chemoIO (n = 56). Of 85 pts with PD-L1 status, 58 (68%) were 0% and 27 (32%) were ≥1%. The most common chemo regimen was platinum-etoposide (n = 72, 78%). ChemoIO regimens included carboplatin/etoposide/atezolizumab (n = 23, 43%) and carboplatin/pemetrexed/pembrolizumab (n = 17, 31%). In the IO group, 1 patient received dual IO. Lung (n = 74, 46%) and liver (n = 71, 41%) were the most common sites of metastasisThere was no significant difference in PFS across the groups (median PFS [mPFS] chemoIO: 5.7 mo, 95% CI: 5.0-6.3, chemo: 5.1 mo, 95% CI: 3.1-5.9; IO: 3.6 mo, 95% CI: 1.7-6.5) on multivariable analysis adjusting for ECOG and "M" stage (p = 0.2 and 0.24 for chemoIO-chemo and chemoIO-IO comparisons, respectively). There was no difference in OS (mOS chemo: 11 mo, 95% CI: 7.6-17.4; IO: 13.6 mo, 95% CI: 5.9-not reached; chemoIO: 12.2 mo, 95% CI: 7.4-20.6, p = 0.5 and 0.8 for chemoIO-chemo and chemoIO-IO comparisons, respectively). ORR was 35.2% (31/88) in chemo, 25% (2/8) in IO, and 35.7% (20/56) in chemoIO (*p*= 0.46). There were no significant differences in PFS and OS outcomes by treatment group when divided by genetic profile (n = 79, methods), or by PD-L1 status (0% vs ≥1%). Any grade trAE occurred in 48 (51%), 5 (45%), and 28 (50%) pts treated with chemo, IO, and chemoIO, respectively. Grade ≥3 toxicity profiles are shown (table). **Conclusions:** For 1st-line treatment of LCNEC, similar PFS, OS, and ORR were seen for chemo, IO, and chemoIO. This questions the added benefit of chemoIO compared to chemo alone, and warrants future clinical trials to discern the optimal 1st line treatment. Research Sponsor: None.

Grade ≥3 (n,%)	Chemo	IO	ChemoIO
Any trAE	22 (23)	0 (0)	10 (18)
Fatigue	6 (6.4)	0 (0)	2 (3.6)
Anemia/thrombocytopenia	6 (6.4)	0 (0)	4 (7.1)
Nausea/vomiting	2 (2.1)	0 (0)	1 (1.8)
Diarrhea	3 (3.3)	0 (0)	0 (0)
Steroids	2 (2.1)	1 (9.1)	6 (11)
Discontinued due to toxicity	12 (23)	1 (17)	6 (11)

8107 Poster Session

Comprehensive analysis of the value of dynamic changes in ctDNA in SCLC.

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Background: Dynamic changes in circulating tumor DNA (ctDNA) have not been studied in small-cell lung cancer (SCLC). Here, we assessed the changes of ctDNA over time and clinical outcomes. **Methods:** We performed a 105-gene, hybrid-capture, next-generation sequencing (NGS) liquid biopsy assay that detects SNVs, in/dels, CNVs, and chromosomal rearrangements. Patients had ctDNA assessed at 3 time points: 1) before initiation of front-line therapy; 2) at remission (within 3-6 weeks of 4th cycle of chemotherapy+/- immunotherapy), and 3) at the time of relapse (based on radiographic imaging). Study outcome measures include OS, PFS, DFS *(duration of response from completion of 4th cycle of systemic treatment until relapse)*, and overall response rate (ORR). Survivor distribution was estimated using Kaplan-Meier methods. Cox model was also used to estimate the effects on OS, PFS and DFS. The effects of predictors on ORR were estimated using logistic regression. The T-test was used to examine the difference in continuous measures between the two groups, and the chi-square test was used to examine the association between two categorical factors. All tests were two-sided, and p-values < 0.05 were considered significant. **Results:** 62 patients were enrolled. The median follow-up was 12.3 mos. Patients were treated with standard-of-care chemotherapy +/- immunotherapy for 4 cycles. 71% had extensive stage disease. At baseline, 100% of patients had detectable variant alleles in *TP53,*and 70% had variant *RB1*. Patients with ES-SCLC had significantly higher maximum (max) Variant Allelic Fraction (VAF) (alteration with highest VAF) compared to LS-SCLC (59.1 vs 27.2%, p = 0.04). Median max VAF at baseline was 52.3%, 0.3% at remission, and 38.4% at relapse, indicating a response to therapy. However, ORR did not correlate with baseline max VAF (p = 0.2). Baseline max VAF (comparing those $<$ or $>$ VAF of 45%) was not associated with OS (19.4 vs 12.2 mos, p = 0.6) but highly impacted PFS (11.2 vs. 6.1 mos, p = 0.02) and DFS (12.1 vs 2.2 mos, p = 0.004). Baseline max VAF was an independent predictor of PFS and DFS. A drop in max VAF from pretreatment to remission (comparing those with a $>$ or $<$ 99% decrease) also did not associate with OS, PFS, or DFS. Patients with *RB1* alterations at pretreatment that had residual *RB1* alterations at the time of clinical remission had significantly worse PFS (6.3 vs 12.1 mos) and DFS (1 vs 8 mos, p = 0.02). **Conclusions:** Baseline max VAF ctDNA levels strongly correlate with PFS and DFS (duration of remission from completion of 4th cycle of treatment) but not OS and ORR. Most strikingly, those with detectable residual *RB1* alterations at completion of proscribed chemotherapy have an extremely short DFS of 1 month that justifies early assessment for clinical trials. This approach has led to a near 90% success rate in enrollment on 2nd line clinical trials or SOC options. Research Sponsor: None.

8109 Poster Session

Cytoreductive surgery followed by hyperthermic intrathoracic chemotherapy for the treatment of thymic epithelial malignancies with pleural spread or recurrence.

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Background: The purpose of this phase II study was to evaluate perioperative results and short-term oncological outcomes of cytoreductive surgery and hyperthermic intrathoracic chemotherapy (S-HITOC) for thymic epithelial malignancies (TETs) with pleural spread or recurrence. **Methods:** In this open, single-arm, prospective trial, 43 consecutive patients were recruited and treated by surgical cytoreduction (Day 0) followed by HITOC with 25mg/m^2 of doxorubicin (Day 1) and 50mg/m^2 of cisplatin (Day 2). HITOC was performed over a period of 60 minutes with a flow rate of 400 to 600 mL/min at an inflow temperature of 43°C. This study was registered with ClinicalTrials.gov (NCT05446935). **Results:** There were 22 women and 21 men with a median age of 55 years. Twelve patients (27.9%) were presented with myasthenia gravis (MG). Predominately, 34 cases (79.1%) were TETs with distant pleural recurrence and 9 cases (20.9%) were TETs with de novo pleural spread. Cytoreduction surgery was performed via pleurectomy/decortication (P/D) alone (5/43, 11.6%) or extended P/D (eP/D) (38/43, 88.4%). These resection procedures resulted in 21 cases (48.8%) of complete cytoreductive surgery without residual visible disease, 6 cases (14.0%) of optimal cytoreductive surgery with residual tumors measuring no more than 10 mm or 16 cases (37.2%) of incomplete cytoreductive surgery with residual lesions measuring more than 10 mm in diameter. The median length of post-operative hospital stay were 5.0 days. Eight patients (18.6%) had grade 3-4 treatment-related complications, including 2 cases of atelectasis, 2 cases of hydrothorax, 1 case of pneumonia, 1 case of hemothorax, 1 case of atrial fibrillation, and 1 case of chest pain. Patients had moderate level of pain on Day 3 [mean visual analog pain scale (VAS) score = 5.5]. However, the VAS scores decreased significantly on the Day 5 (mean VAS score = 2.8). The health-related quality-of-life (QoL) outcomes had continue improvement during the follow-up period, with the mean QoL scores of 59.0 at Day 3, 70.2 at Day 33, and 77.6 at Day 63, according to the EORTC QLQ-C30. The 90-day mortality rate was 0%. At median follow-up of 11 (3-37) months, 39 patients (90.7%) were free of tumor progression. The 1-, 2-, and 3-year PFS rate was 96.6, 82.8, and 70.9%. While two cases died, as one patient developed multiple organ failure and one case with pulmonary fungal infection. The 1-, 2-, and 3-year OS rate was 100.0, 100.0, and 85.7%. Importantly, overall remission rate of MG was 100%, with complete stable remission rate of 25.0%, pharmacological remission rate of 41.7% and minimal manifestation status rate of 33.3%. **Conclusions:** S-HITOC is a safe and feasible procedure with acceptable complication rate. Early clinical outcomes confirm S-HITOC offers encouraging oncological benefits for TETs and satisfactory control of MG. Clinical trial information: NCT05446935. Research Sponsor: Zhongshan Hospital, Fudan University; 2021ZSYQ28.

S1701: A randomized phase II trial of carboplatin-paclitaxel with and without ramucirumab in patients with locally advanced, recurrent, or metastatic thymic carcinoma.

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Background: Thymic carcinoma, a rare malignancy, presents treatment challenges due to its aggressiveness and poor response to standard chemotherapy. Angiogenic pathway activation is implicated in its pathogenesis. S1701 evaluated the efficacy and safety of ramucirumab, an anti-angiogenic monoclonal antibody, in combination with carboplatin-paclitaxel. **Methods:** We conducted a randomized phase II trial with patients having histologically confirmed, unresectable thymic carcinoma and no prior therapy for recurrent or metastatic disease. Patients were randomized to receive carboplatin-paclitaxel with or without ramucirumab for 6 cycles, followed by maintenance ramucirumab for patients without progression. The primary endpoint was progression-free survival (PFS), assessed by RECIST 1.1. Secondary endpoints included response rate, safety and toxicity. The primary analysis was done using a 1-sided 10% level log-rank test. Target sample size was 66 patients. **Results:** Between 2018-2022, 21 patients enrolled to ramucirumab plus carboplatin-paclitaxel (RCP, n = 8) and to the control arm (CP, n = 13). Three patients in the control arm were excluded from the efficacy analysis, as one was ineligible and 2 had non-measurable disease. No grade 4 or higher treatment-related adverse events occurred in the RCP arm, although 50% (4 out of 8) experienced grade 3 adverse events and 2 patients discontinued ramucirumab due to toxicity. There were no grade 3 or higher thromboembolic or bleeding events in the RCP arm. Among 9 evaluable patients for safety in the control arm (3 withdrew consent prior to initiating therapy), 11% encountered grade 4 neutropenia and 11% reported grade 3 thromboembolic events. Response rate favored the RCP arm, with an 88% [80% CI 59% - 99%] partial response rate compared to 40% [80% CI 19%-65%] in the control arm (Figure, p = 0.04). Disease control rate was higher in the RCP arm (100% vs 70%, p = 0.0897). At median follow-up time of 16.7 months, PFS was not different (hazard ratio [80% CI]: 0.51 [0.24 – 1.09]; p = 0.13). Median PFS was 8 months for RCP and 7 months for the control arm. At this time, OS remains immature. **Conclusions:** The addition of ramucirumab to CP led to higher response rates than CP alone. At this early analysis, PFS was not significantly improved; OS is pending. High-grade adverse events necessitate careful patient selection. Insights from S1701 emphasize the potential of targeting the angiogenic pathway, although larger trials are needed to confirm these findings. Future research should consider exploring larger multicenter trials and other combinations to improve outcomes. Challenges in enrollment emphasize the need for innovative strategies and larger collaborations in rare malignancies like thymic carcinoma. *Funding:* NIH/NCI/NCTN grant awards U10CA180888 and U10CA180819 and in part by Eli Lilly. Clinical trial information: 03694002. Research Sponsor: Southwest Oncology Group; U10CA180888 and U10CA180819; Eli Lilly and Company.

A retrospective study of 157 patients comparing platinum-anthracycline to other platinum combination for untreated unresectable thymoma: NEJ023B.

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Background: The optimal primary treatment for unresectable thymoma remains unclear to date. **Methods:** We enrolled patients with unresectable or recurrent thymomas that were confirmed between April 1, 2000, and March 31, 2020, and had received palliative radiotherapy and/or chemotherapy, from 38 facilities in Japan. **Results:** A total of 204 cases were registered, with 157 receiving platinum-based chemotherapy as first-line chemotherapy. The median age of these 157 cases was 58 years (range 24-79), with 74 females (47%). The histological types were: A in 3 (2%), AB in 13 (8%), B1 in 27 (17%), B2 in 60 (38%), B3 in 41 (26%). Out of 157 cases, 97 (62%) recurred after radical surgery or chemoradiotherapy. Of the remaining cases, 4 (3%) in Masaoka stage III, 44 (28%) in stage IVa, and 12 (8%) in stage IVb. At the start of first-line chemotherapy, 48 (31%) had paraneoplastic syndrome, and the performance status was 0 in 81 (52%). As first-line chemotherapy, platinum plus anthracycline combination was used in 104 cases (66%) (doxorubicin + cisplatin + vincristine + cyclophosphamide: ADOC in 76, cisplatin + doxorubicin + cyclophosphamide: CAP in 10), and other platinum combinations in 53 cases (34%) (carboplatin + paclitaxel in 31, cisplatin + etoposide in 11, carboplatin + nab-paclitaxel in 7). The response rates for platinum plus anthracycline and other platinum combinations were 57% and 30% (p = 0.0024), and disease control rates were 96% and 100% (p = 0.18), respectively. During a median observation period of 50.5 months (range 2.0-191.8 months), patients received a median of 2 chemotherapy regimens (range 1-9), one radiation (range 0-4), and one salvage or volume-reduction surgery (range 0-3). The median progression-free survival (PFS) was 13.4 months for platinum plus anthracycline vs. 15.0 months for other platinum combinations (hazard ratio 0.932, p = 0.72), and after propensity score matching (46 cases in each group), it was 11.7 months vs. 12.1 months (hazard ratio 1.02, p = 0.92). The median overall survival (OS) was 111.9 months for platinum plus anthracycline vs. 84 months for other platinum combinations (hazard ratio: 0.733, p = 0.23), and after propensity score matching (46 cases in each group), it was 113.5 months vs. 93.8 months (hazard ratio: 0.711, p = 0.34). Of the 157 cases, 67 deaths were observed, with the causes being progression of the primary disease in 47, infections in 9, and cardiac diseases in 4. **Conclusions:** Platinum plus anthracycline showed better response rates than other platinum combinations as a first-line chemotherapy, but there was no significant difference in PFS and OS. The median PFS for primary treatment was about one year, whereas the overall survival was nearly ten years, indicating the need for long-term multidisciplinary approach. Clinical trial information: UMIN000048181. Research Sponsor: None.

Combining SBRT with GM-CSF and Peg-IFNα to induce abscopal effects in previously treated patients with stage IV thymic tumors.

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Background: After the failure of multi-line treatment, patients with stage IV thymic tumors have a poor prognosis and few therapeutic options. Combining stereotactic body radiotherapy (SBRT) with granulocyte-macrophage colony-stimulating factor (GM-CSF) and Pegylated interferon-α (Peg-IFNα) may induce abscopal effects and improve prognosis. **Methods:** We conducted this open-label, single-arm, phase II trial to evaluate SBRT plus GM-CSF and Peg-IFNα in previously treated patients with stage IV thymic tumors. A 21-day treatment cycle consisted of SBRT delivered to one metastatic lesion with 30 Gy in 5 fractions from day 1, synchronous subcutaneous injection of GM-CSF 125 μg/ m^2 once daily for 14 days, and subcutaneous injection of Peg-IFNα 90 μg on day 8. If the patient has more than two metastatic lesions, another treatment cycle was repeated. After the completion of 1 or 2 treatment cycles, Peg-IFNα therapy was maintained for at least half a year with a subcutaneous injection of 90 μg once a month. The two primary endpoints were the proportion of patients with abscopal effects and the objective response rate (ORR). The secondary endpoints included overall survival (OS), progression-free survival (PFS), and therapeutic safety. **Results:** A total of 20 patients from March 2021 to September 2022, were enrolled in this trial, with 1 (5.0%) type A thymoma, 2 (10.0%) type B1 thymoma, 2 (10.0%) type B2 thymoma, 1 (5.0%) type B3 thymoma, 12 (60.0%) thymic squamous cell carcinoma and 2 (10.0%) thymic neuroendocrine tumor. At a median follow-up of 18.6 months, 8 (40.0%) out of 20 patients had abscopal effects, and the ORR was 45.0%. The median OS had not been attained yet. The median PFS was 9.0 months. We observed that patients with abscopal effects tended to have longer OS and PFS than those without abscopal effects (Figure 1). 3 patients (15.0%) experienced Grade 3 treatment-related adverse events (CTCAE version 5.0), among which cardiac insufficiency compelled 1 patient (5.0%) to drop out of treatment. **Conclusions:** Combining SBRT with GM-CSF and Peg-IFNα was well tolerated with acceptable toxicity and may represent a promising salvage therapy for previously treated patients with stage IV thymic tumors. The occurrence of abscopal effects is likely to improve patient outcomes. Clinical trial information: NCT04517539. Research Sponsor: None.

Comprehensive molecular characterization of thymic epithelial tumors.

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Background: Thymic epithelial tumors (TETs), which include thymomas (T) and thymic carcinomas (TC), are rare, yet they are the most common neoplasms in the anterior mediastinum. TETs can lead to significant morbidity and mortality. To develop more effective therapeutics for TETs, it is necessary to better understand their molecular underpinnings. Herein, we present the findings from an in-depth molecular characterization of TETs. **Methods:** TETs samples (n = 138; 55 from thymus and 78 from metastatic sites) were profiled using next generation sequencing (NGS) of DNA (592-genes/WES) and RNA (WTS) at Caris Life Sciences (Phoenix, AZ). Prevalence was calculated for pathogenic SNVs/Indels, deficient mismatch repair/microsatellite instability (dMMR/MSI) status assessed by IHC and NGS, PD-L1 expression measured by IHC (SP142; positive: $\geq$ 2+, $\geq$ 5%), and high tumor mutational burden (TMB-High) defined as $\geq$ 10 mut/Mb. The relative expression (transcript per million -TPM) of surface antigens (surfaceome) were evaluated. Pathway enrichment was determined by Gene Set Enrichment Analysis (GSEA). Mann-Whitney U, chi-square, and Fisher exact tests were applied where appropriate. **Results:** Central pathology review showed that the 138 TET samples were comprised of 34.8% (n = 48) thymic carcinomas (TC) and 65.2% (n = 90) thymomas (T). Thymomas were further stratified into the WHO classification subtypes (n = 10 A, 13 AB, 6 B1, 15 B2, and 46 B3). Median patient age was 60.5 years (range: 17-88). *TP53* was the most frequently mutated gene in TETs. *GTF2I* mutations were found in 8 cases exclusively in thymomas. *KIT* mutations were identified in B3 and TC. *KRAS*, *HRAS*, and *PIK3CA* mutations were present in $<$ 3% of all TETs patients. Genomic alterations in cell cycle-related genes (n = 19, 13.8%), the DNA repair pathway (n = 11, 8.0%), and chromatin remodeling (n = 27, 19.6%) were also observed in TETs, with these alterations more prevalent in TC compared to T. dMMR/MSI-H was detected in a subset of TETs, specifically B3 thymoma (n = 1) and TC (n = 4), showing a correlation with TMB-H in 80% of these cases. GSEA revealed that the MYC, angiogenesis, and mTORC1 pathways are more enriched in TC than in T. Surfaceome genes (*ERBB2*: fold change (FC) = 1.51, *ERBB3*: FC = 1.45, *TROP2*: FC = 1.45, *NECTIN-4*: FC = 1.77 and *MESOTHELIN*: FC = 5.25) were significantly highly expressed in TC compared to T. **Conclusions:** Our findings offer insights into the molecular characteristics of TETs and reveal potential therapeutic targets. The relatively high prevalence of dMMR/MSI-H status in TC underscores the potential utility of assessing dMMR/MSI-H in patients with TC. Research Sponsor: None.

Molecular Alterations (%)	A (n = 10)	AB (n = 13)	B1 (n = 6)	B2 (n = 15)	B3 (n = 46)	Thymic Carcinoma (n = 48)
TP53	0	0	0	6.7	10.9	29.2
GTF2I	30.0	23.1	0	6.7	2.2	0
KIT	0	0	0	0	15.2	6.3
KRAS	0	0	0	0	4.3	0
HRAS	10	0	0	0	0	6.3
PIK3CA	0	7.7	0	0	2.2	2.1
TMB-H	0	0	0	0	6.8	8.3
dMMR/MSI-H	0	0	0	0	2.2	8.3
High PD-L1 (≥ 50%)	37.5	60	20	87.5	51.2	28.3

A phase II clinical trial of selinexor in patients with advanced thymoma and thymic carcinoma.

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Background: Thymomas (T) and thymic carcinomas (TC) are rare thymic epithelial tumors (TET). Effective treatment options are needed for patients with progressive disease after platinum-based chemotherapy. Preclinical studies demonstrated antitumor activity of selinexor, an oral selective inhibitor of nuclear export (SINE) targeting exportin 1 (XPO1/CRM1), supporting the clinical development of XPO1 targeted therapy for the treatment of TET. To further assess the safety and efficacy of selinexor in TET, we conducted two parallel phase II clinical trials. **Methods:** The study included two parallel almost identical phase II trials conducted in the U.S. (NCT03193437), and Europe (Denmark and France; NCT03466827). Analysis was performed on data pooled from both trials. Both trials were non-randomized, open-label, two-armed phase II trials (Arm A: thymoma, Arm B: thymic carcinoma) with the same study design. Patients with histologically confirmed, advanced, inoperable TETs who had progressive disease after treatment with at least one platinum-containing chemotherapy regimen were included. In each 4-week cycle, patients received selinexor 60 mg twice weekly for 3 weeks. Due to poor tolerability, the starting dose was reduced to 40 mg twice weekly during the study. The primary objective was overall response rate (ORR) assessed by RECIST 1.1, with secondary objectives including progression free survival (PFS), overall survival (OS), and adverse events (AEs) assessed per CTCAE v4.03. **Results:** A total of 31 patients were enrolled in the study: 16 with T and 15 with TC. The median age was 57 years (range: 41-81), with 17 men and 14 women. The median number of prior systemic therapies was 2 (range: 1-9). The starting dose was 60 mg twice weekly for 29 (93.5%) patients, and 40 mg twice weekly for 2 (6.5%) patients. There was one complete response in the TC group (ORR 6.7%; 95% CI: 1.2-29.8%) and two partial responses (ORR 12.5% 95% CI: 3.5-36.0%) in the T group. Stable disease as the best response was observed in 11 (68.6%) patients with T and 12 (80%) patients with TC. The median duration of selinexor therapy was 4.5 months (mo) (range: 0.1-44.3). The most common treatment-related adverse events (TRAEs) were nausea (83.8%), vomiting (45.2%), anemia (41.9%), and fatigue (38.7%). The most common grade 3 or higher TRAEs were anemia (16.1%), thrombocytopenia (12.9%), and asthenia (9.7%). Twenty (64.5%) patients required dose reductions due to AEs, and 20 (64.5%) required dose interruptions. Median PFS was 7.8 mo (95% CI: 4.3 – 15.5) in the TC group and 13.6 mo (95% CI: 6.3 – 44.3) in the T group. Median OS was 15.5 mo (95% CI: 13.0-29.9) in the TC group and not reached in the T group. Due to low ORR, the trials did not proceed to the planned second phase. **Conclusions:** Selinexor demonstrated modest anticancer activity in patients with pretreated advanced TET. ORRs were low but prolonged stable disease was noted in a subset of patients. Clinical trial information: NCT03193437 and NCT03466827. Research Sponsor: Karyopharm Therapeutics.

TPS8115 **Poster Session**

LIBRETTO-432: A phase 3 study of adjuvant selpercatinib or placebo in stage IB-IIIA *RET* fusion-positive (*RET*+) NSCLC.

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Background: Around 30% of NSCLC patients (pts) present with stage IB-IIIA disease. Standard treatment options are definitive locoregional therapies w/wo chemotherapy (CT) and/or immunotherapy, followed by surveillance until disease recurrence. Targeted therapies are standard for metastatic NSCLC with driver alterations and recent Phase III trial data has emerged in support of their use in the adjuvant setting for stage IB-IIIA (ADAURA and ALINA). *RET* is a key oncogenic driver in NSCLC and a promising target for adjuvant targeted therapy. Selpercatinib, a highly selective, potent and CNS active RET inhibitor, recently demonstrated longer PFS than platinum-based CT as 1L treatment in pts with *RET*+ advanced NSCLC (Zhou et al. NEJM 2023). LIBRETTO-432 is a Phase 3, global, multicenter, randomized, double-blind, controlled trial evaluating efficacy and safety of adjuvant selpercatinib v Placebo in pts with *RET*+ Stage IB-IIIA NSCLC following completion of definitive therapies with curative intent, and other adjuvant therapy if indicated (NCT04819100). **Methods:** Pts (n≈170) will be randomized (1:1) to selpercatinib BID [160mg ≥50kg; 120mg < 50kg], or Placebo, in continuous 28-day cycles for a maximum treatment duration of 3y. Stratification factors include disease stage (IB/II/IIIA) and prior definitive therapy. Treatment will continue until disease recurrence/progression, unacceptable toxicity, or another protocol-defined reason. Crossover is allowed for Placebo pts who experience disease recurrence/progression. Key eligibility criteria include age ≥18 y; histologically confirmed Stage IB/II/IIIA NSCLC; *RET*+ tumor by PCR/NGS; prior definitive locoregional therapy with curative intent (surgery, radiotherapy) for Stage IB/II/IIIA NSCLC; and ECOG performance status 0-1. Maximum time allowed from definitive therapy completion to randomization is 26 w. Key exclusion criteria are evidence of other known oncogenic drivers; SCLC; and disease recurrence/progression following definitive therapy. Primary endpoint is investigator-assessed event-free survival (IAEFS) in the primary analysis population (pts with Stage II-IIIA). EFS is defined as time from randomization until locoregional disease recurrence with histopathological confirmation, distant disease recurrence per RECIST v1.1 or histopathological confirmation, or death. Gated secondary endpoints include IAEFS in the overall population (pts with Stage IB-IIIA) and OS in both primary analysis and overall populations. Non-gated secondary efficacy endpoints include BICR-assessed EFS, BICR and investigator-assessed time to distant disease recurrence in the CNS, and PFS on next line of treatment. Recruitment is ongoing, with enrollment across ~170 sites and 30 countries. Results from this trial will further inform the value of RET inhibition and genomic testing for adjuvant NSCLC pts. Clinical trial information: NCT04819100. Research Sponsor: Loxo Oncology Inc.

TPS8116 **Poster Session**

The phase 3 INTerpath-002 study design: Individualized neoantigen therapy (INT) V940 (mRNA-4157) plus pembrolizumab vs placebo plus pembrolizumab for resected early-stage non–small-cell lung cancer (NSCLC).

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Background: Pembrolizumab (pembro; anti–PD-1) is indicated as adjuvant monotherapy following resection and adjuvant chemotherapy in patients (pts) with stage IB (T2a ≥4 cm), II, or IIIA NSCLC (per AJCC v7). However, many pts experience disease recurrence, and have limited treatment options available. V940 (mRNA-4157) is a novel individualized neoantigen therapy that encodes up to 34 neoantigens that is specifically tailored and manufactured for each pt derived from their tumor. V940 as monotherapy and in combination with pembro has shown preliminary antitumor activity in the phase 1 KEYNOTE-603 study in several solid tumor types, including NSCLC. Additionally, in pts with completely resected, high-risk stage IIIB/C/D and IV cutaneous melanoma in the KEYNOTE-942 primary analysis, V940 plus pembro demonstrated significant improvements in recurrence-free survival (HR, 0.561 [95% CI, 0.309–1.017]; P = 0.0266) and distant metastasis-free survival (HR, 0.347 [95% CI, 0.145–0.828]; P = 0.0063) vs pembro alone. Here we present the design of the phase 3, randomized, double-blind INTerpath-002 study (NCT06077760) of adjuvant V940 plus pembro vs placebo plus pembro in pts with completely resected and chemotherapy-treated stage II–IIIB (N2) NSCLC (AJCC v8). **Methods:** Eligible pts aged ≥18 years with completely resected stage II, IIIA, or IIIB (N2) squamous or nonsquamous NSCLC (per AJCC v8.0) where EGFR-directed therapy is not indicated as primary therapy (ie, absence ofsensitizing *EGFR* mutations e.g. DEL19 or L858R), who have received 1–4 doses of adjuvant platinum-doublet chemotherapy, have ECOG PS 0 or 1, and have available tumor tissue for next-generation sequencing and PD-L1 testing will be enrolled. Pts must not have received previous neoadjuvant therapy for NSCLC and must not have received or be candidates for adjuvant radiotherapy. Pts will be randomized 1:1 to receive V940 1 mg IM or placebo Q3W for up to 9 doses plus pembro 400 mg IV Q6W for up to 9 cycles or until disease recurrence, pt withdrawal, unacceptable toxicity, or an additional malignancy requiring treatment. Randomization will be stratified by histology (squamous vs nonsquamous), PD-L1 TPS (< 1% vs 1%–49% vs ≥50%), disease stage (II vs III), and geographic location (North America/Western Europe/Australia vs rest of world). The primary endpoint is disease-free survival per investigator review. Secondary endpoints include distant metastasis-free survival per investigator assessment, OS, lung cancer–specific survival, patient-reported outcomes, and safety. Tumor imaging will occur at baseline, every 12 wk until wk 48, every 24 wk through year 3, and every 48 wk thereafter. Enrollment began in October 2023 and is ongoing globally (NCT06077760). The abstract was originally presented and published in: Proceedings of the American Association for Cancer Research Annual Meeting 2024; Part 2 (Late-Breaking, Clinical Trial, and Invited Abstracts); 2024 Apr 5-10; San Diego, CA. Philadelphia (PA): AACR; Cancer Res 2024;84(7_Suppl):Abstract nr CT281. Clinical trial information: NCT06077760. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA and Moderna, Inc., Cambridge, MA, USA.

TPS8117 **Poster Session**

Efficacy and safety of aumolertinib combined with or without chemotherapy as an adjuvant treatment for stage II-IIIA non-small cell lung cancer following complete tumour resection: The first third-generation EGFR-TKI versus chemotherapy phase III clinical study (APEX).

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Background: Patients with stage II-III A non-small cell lung cancer (NSCLC) can benefit from adjuvant targeted therapy. ADAURA study shows a remarkable advantage of disease-free survival (DFS). However, there are still unresolved clinical issues. Firstly, the control group in the trial is received placebo, making it impossible to directly compare the efficacy of adjuvant targeted therapy with the traditionally recommended adjuvant chemotherapy in guidelines. Thus, it cannot address the direct comparison of third-generation TKIs with the current standard therapy (chemotherapy). Secondly, the necessity of combining chemotherapy with adjuvant targeted therapy need to explored. Aumolertinib is a third-generation epidermal growth factor receptor- tyrosine kinase inhibitor (EGFR-TKI) that potently and selectively inhibits EGFR sensitizing and EGFR T790M resistance mutations. This study aims to evaluate the efficacy and safety of aumolertinib combined with or without chemotherapy as adjuvant treatment for EGFR-sensitive mutations stage II-III A non-squamous NSCLC patients. **Methods:** This is a multicenter, randomized, open label, phase III study. Patients with histologically confirmed stage II-III A non-squamous NSCLC harboring EGFR mutations without prior EGFR TKI treatment and R0 resection are eligible for this study. The performance status (Eastern Cooperative Oncology Group) is 0 or 1. This trial prepared to enroll approximately 606 patients, will be randomized (3:2:1) to receive either aumolertinib alone (110mg, po, once daily) or aumolertinib (110mg, po, once daily) plus pemetrexed (500mg/m2, iv) and cisplatin (500mg/m2, iv) or pemetrexed (500mg/m2, iv) plus cisplatin (500mg/m2, iv). The first patient was enrolled on August 2, 2021. The primary end point is DFS, The secondary endpoints include 2, 3, 4, 5-year DFS rates, 5-year overall survival (OS), OS, safety and quality of life. Adverse effects were graded per CTCAE v.4.0. This trial is registered as NCT04762459. Clinical trial information: NCT04762459. Research Sponsor: Hansoh Pharmaceutical Group Company Limited.

TPS8118 **Poster Session**

A randomized phase II trial of adjuvant pembrolizumab versus observation following curative resection for stage I non-small cell lung cancer (NSCLC) with primary tumors between 1-4 cm: Big Ten Cancer Research Consortium BTCRC-LUN18-153.

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Background: Each year, approximately 35,000 patients are diagnosed with stage I lung cancer in the United States. Despite early detection, the 5-year overall survival for this population remains disappointing, ranging between 73-86% with recurrence rates from 18-38%. The current standard of care for stage I NSCLC is surgery alone followed by observation as prior trials of adjuvant chemotherapy in this subgroup have failed to show benefit. More modern therapies such as programmed death-1 (PD-1) inhibitors have not been evaluated in the stage I setting but have demonstrated significant improvements in pathologic complete response, event free survival, and overall survival when added to chemotherapy for patients with fully resected stage II and III disease. The use of PD-(L)1 inhibition has also demonstrated clinically and statistically significant improvements in OS in both unresectable stage III NSCLC following chemoradiation and in the metastatic setting. Given the activity of PD-(L)1 inhibition in nearly every other subset of NSCLC patients, we aimed to evaluate this therapy following resection in stage I NSCLC patients. **Methods:** This study is a randomized phase II multicenter trial of adjuvant Pembrolizumab versus observation alone following complete resection of stage I NSCLC with tumors between 1-4cm. The trial randomizes patients 1:1 to either Pembrolizumab 400mg IV every 6 weeks for up to 9 cycles or observation alone. Patients are stratified by PD-L1 score (PD-L1 $\geq$50% vs. $<$ 50%) and tumor size (1-2cm vs. $>$ 2-4cm), and they undergo repeat CT imaging every 12 weeks. The study is being conducted through the Big Ten Cancer Research Consortium, and there are currently 11 sites open to accrual with one additional site pending activation. The primary endpoint is disease free survival with secondary endpoints including OS, DFS at multiple timepoints (1-, 2-, and 3-years), and safety. The trial initially opened to accrual at the lead site, Indiana University, in May 2020, and enrollment is currently at 95 patients with a planned enrollment of 244. (NCT04317534) Clinical trial information: NCT04317534. Research Sponsor: Merck.

TPS8119 **Poster Session**

Olaparib, AZD1390, ceralasertib, saruparib and consolidation durvalumab (CONCORDE) phase Ib platform study of novel DNA damage response inhibitor (DDRi) agents in combination with radiotherapy in non-small cell lung cancer (NSCLC).

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Background: Lung cancer is the leading cause of cancer mortality globally, with cases projected to exceed 62,000 by 2035. Outcomes remain poor despite advances in radiotherapy (RT) technologies. Combining novel mechanism-based agents with RT could improve the therapeutic index. DNA inhibition of cellular response to radiation-induced DNA damage can overcome intrinsic radio resistance and poses a promising strategy. **Methods:** CONCORDE is an open label, randomised, multi-arm, phase Ib, clinical trial opened to accrual in 11 UK hospitals designed to assess multiple DDRi in combination with radical thoracic RT (60Gy in 30 fractions over 6 weeks). Patients are randomised 3:1 to RT+/-DDRi. The study utilises an adaptive Bayesian model-based approach to dose escalation aiming to identify the recommended phase II dose for each treatment combination. Two arms will deliver up to 12 months consolidation durvalumab+/-DDRi following RT. Patients are eligible based on key criteria: not suitable for concurrent chemotherapy RT, inoperable, stage IIB/III NSCLC, performance status (KPS≥70). The dose limiting toxicity (DLT) period for treatment-related toxicities is 13.5 months post start of RT treatment, with most toxicities expected within the first 4.5 months (short DLT period). At least one patient must complete the short DLT period before dose escalation. A RT-alone calibration arm aids toxicity attribution. This trial is in progress: CONCORDE-A (olaparib (PARP inhibitor)), CONCORDE-B (AZD1390 (ATM inhibitor)), CONCORDE-C (ceralasertib (ATR inhibitor) followed by consolidation durvalumab+/-ceralasertib) and CONCORDE-E (AZD5305/saruparib (PARP1select inhibitor) followed by consolidation durvalumab) are open to accrual as of 24/11/2023. 57 of 74 registered participants have been randomised across 4 study arms. Of those 57 randomised: 55 started treatment: 20 received RT-alone, 12 received olaparib+RT, 14 received AZD1390+RT, 6 received ceralasertib+RT, 3 received AZD5305+RT and 2 withdrew. CONCORDE continues to recruit to the target sample size of 160 (40/arm) and welcomes further UK centres. A parallel multimodality translational program to identify biomarkers of treatment response, toxicity and the impact on the immune system are in development. Biomarkers of interest include plasma toxicity markers, immune cell profiling, radiomics and ctDNA. Clinical trial information: 10142971. Research Sponsor: Cancer Research UK; AstraZeneca.

TPS8120 **Poster Session**

Neoadjuvant toripalimab plus chemotherapy for resectable stage II-IIIB non-squamous non-small cell lung cancer with EGFR mutations: A multi-center, multi-cohort, exploratory study.

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Background: Neoadjuvant immunotherapy has been widely applied in the treatment of resectable stage II-IIIB NSCLC patients without driver gene mutation. However, as for the EGFR-positive patients, the therapeutic effect of neoadjuvant treatment, either TKI or chemotherapy, is far from satisfied and the outcome of neoadjuvant immunotherapy plus chemotherapy in these patients remains an unanswered but crucial question. Herein, we conducted a phase 2 prospective trial (NCT05962021). **Methods:** This is a multicenter, multi-cohort prospective phase 2 study in the treatment-naïve patients with resectable stage II-IIIB (N2) (AJCC 8th edition) non-squamous NSCLC harboring EGFR mutations (19DEL or L858R). Enrolled patients will be divided into two cohorts according to EGFR status and receive neoadjuvant toripalimab (240mg, q3w) plus platinum-based doublet chemotherapy (pemetrexed 500mg/m^2 plus carboplatin AUC 5, q3w) for 3 cycles. Surgery will be performed after completion of neoadjuvant therapy based on the multidisciplinary discussion, while local radiotherapy will be considered if the patient cannot undergo surgery due to disease progression. Key inclusion criteria: non-squamous NSCLC, resectable stage II-IIIB (N2), EGFR mutations (19DEL or L858R), age≥18 years, ECOG PS 0-1 and adequate cardiopulmonary function. Exclusion criteria: prior systemic anticancer treatment, contraindication to immunotherapy, active autoimmune disease. Adequate pre-treatment tissue samples are required for RT-PCR or next-generation sequencing to determine the EGFR mutation status and PD-L1 expression immunohistochemical detection. The primary study endpoint is complete pathological response (pCR) rate, per blinded independent pathologist review. Simon's optimal two-stage design will be used to test the null hypothesis of pCR rate ≤5% and alternative hypothesis of pCR rate ≥15%, and 5 or more pCRs among 56 patients per arm are needed for the primary endpoint to be met. Secondary endpoints include major pathological response (MPR) rate, pCR/MPR rate in different EGFR mutation subgroups (19DEL or L858R) and different PD-L1 expression subgroups (TPS $<$ 1% and ≥ 1%), event-free survival and safety and tolerability. Peripheral blood, stool and tissue samples will be obtained longitudinally at baseline, during perioperation and at follow-ups for exploratory analysis. Clinical trial information: NCT05962021. Research Sponsor: Shanghai Junshi Biosciences.

TPS8121 **Poster Session**

VELOCITY-Lung substudy-03: A phase 2 study of neoadjuvant domvanalimab (dom)+zimberelimab (zim)+chemotherapy (chemo) or zim+chemo followed by adjuvant dom+zim or zim in patients with resectable stage II-III non-small cell lung cancer (NSCLC).

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Background: Management of resectable NSCLC involves surgery with perioperative systemic therapy. Immune checkpoint inhibitors (CPIs) and targeted therapies are now used in the perioperative setting, leading to improved survival outcomes. The combination of dom (anti–T-cell immunoglobulin and ITIM domain [TIGIT]) and zim (anti–programmed death protein 1 [PD-1]) has shown promising antitumor activity with a manageable safety profile in metastatic NSCLC and may provide an opportunity to improve clinical outcomes in the perioperative setting in early-stage, resectable NSCLC. Substudy-03 of the VELOCITY-Lung platform study is evaluating novel perioperative treatment combinations in patients with newly diagnosed, resectable, stage II-III NSCLC. **Methods:** VELOCITY-Lung (NCT05633667) is an open-label, multicenter, phase 2 platform study with 3 ongoing substudies targeting the different NSCLC patient populations. Key eligibility criteria for Substudy-03 include age $\geq$ 18 years, histologically/cytologically confirmed stage II, IIIA, IIIB (T[3-4]N2) (per AJCC 8th ed.) squamous or nonsquamous NSCLC considered resectable with curative intent, no prior systemic or CPI therapy or radiotherapy, ECOG PS 0-1, any PD-1 ligand (PD-L1) status, and no actionable *EGFR* or *ALK* genomic alterations in patients with nonsquamous NSCLC. Randomization in Substudy-03 will be stratified by disease stage (II vs III) and baseline PD-L1 expression status ($\geq$ 50% vs $<$ 50%). Current treatment groups in the neoadjuvant phase of the preliminary stage are: (A) dom+zim+platinum (Pt)-based chemo or (B) zim+Pt-based chemo for a maximum of 3 cycles; this will be followed by definitive surgery within 6 weeks of completing neoadjuvant treatment. Adjuvant treatment will include: (A) dom+zim or (B) zim and will begin within 12 weeks of surgery. Patients will continue to receive adjuvant treatment until disease recurrence, death, or unacceptable toxicity or to a maximum of 14 cycles. Dosing will be as follows: zim 360 mg intravenously (IV) once every 3 weeks (Q3W) and dom 1200 mg IV once Q3W (up to 3 cycles in the neoadjuvant phase and up to 14 cycles in the adjuvant phase). Pt-based chemo will be based on patient tumor histology (squamous vs nonsquamous). The primary endpoint is pathological complete response rate, defined as the percentage of patients with no residual invasive cancer in resected lung specimens and lymph nodes, assessed by local pathology review. Secondary endpoints include major pathological response rate (percentage of patients with $\leq$ 10% residual tumor in lung and lymph nodes at surgery), event-free survival, overall survival, and safety. Approximately 31 patients will be enrolled into each treatment group of the preliminary phase. The study is currently recruiting. Clinical trial information: NCT05633667. Research Sponsor: Gilead Sciences, Inc.

TPS8122 Poster Session

Phase II study of induction platinum doublet in combination with nivolumab followed by surgery or concurrent chemotherapy-nivolumab-radiation in unresectable stage IIIA-C non-small cell lung cancer (NSCLC).

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Background: For patients (pts) with stage IIIA-IIIC NSCLC, though standard of care chemo-radiation (XRT) followed by 1 year of durvalumab has improved 5 year overall survival (OS), fewer than 50% survive 5 years. In this study, we adopted the established neoadjuvant chemotherapy (chemo) plus nivolumab (nivo) CheckMate-816 regimens for resectable stage I(>4cm)-IIIA yielding an increased complete pathologic response (pCR) rate and event free survival compared to chemo alone, as induction therapy in unresectable stage IIIA-IIIC NSCLC. The intent is to use induction chemo-nivo to treat pts traditionally considered unresectable (multi-station N2 or N3 disease) in order to downstage them enough to permit surgical resection. The study is structured to change (1) the immune checkpoint inhibitor (ICI) regimen to induction rather than consolidation which enables the chance to observe the systemic therapy's efficacy, treat micro-metastatic disease earlier, and may decrease the morbidity of the ablative therapies (2) the ICI containing regimen by increasing from single agent ICI to combination chemo plus nivo which may improve systemic efficacy (3) the duration of treatment with pre and post ablative ICI containing therapy.Induction also provides a platform for studying tumor biology with the chance to discover surrogate markers of response and resistance to the induction regimen matched against response ahead of the definitive therapy.
Methods: This is an investigator initiated trial for pts with newly diagnosed clinical stage IIIA-IIIC EGFR/ALK/ROS1 WT, SQ and NSQ NSCLC with PS 0-1. Pts must be able to tolerate surgery and have a primary tumor which is technically resectable with an N stage IIIA > 2 or more lymph node (LN) stations positive. Pts are treated with the same platinum doublet plus nivo regimens used in CheckMate-816 for 3 cycles followed by repeat CT and repeat biopsy of all LN stations biopsied at baseline and LN stations which at baseline had a high suspicion of harboring disease and which look technically unresectable. If the cancer is down-staged to a single LN station-N2, or is N1 or N0, the pt is offered surgery with an option of post-operative XRT. If not sufficiently down-staged, pts are treated with definitive chemo-nivo-XRT. All pts receive 1 year of consolidation nivo. The primary outcome is response to the induction regimen by repeat CT scan. Secondary outcomes include the rate of converting non-surgical stage III(A-C) to surgically resectable disease, pCR rate, extent of post-induction XRT field decrease, 2-year progression free survival, OS, quality of life, and exploratory outcomes include markers of resistance and response, and remote symptom monitoring. Enrolment will be 37 pts. The study is accruing with a plan to open at a second site. Clinical trial information: NCT06003075. Research Sponsor: Bristol Myers Squibb.

TPS8123 **Poster Session**

A randomized phase II trial of atezolizumab with or without tiragolumab before and after definitive chemoradiation for unresectable stage III non-small cell lung cancer (NSCLC; AFT-57).

Helen J. Ross, David E. Kozono, Michael D Mix, James John Urbanic, Terence Marques Williams, Taylor O'Donnell, Ilze Bara, Katja Schulze, Xiaofei F. Wang, Garth D. Nelson, Tom Stinchcombe; Rush University Cancer Center, Chicago, IL; Brigham and Women's Hospital/Dana-Farber Cancer Institute, Boston, MA; SUNY Upstate Medical Center, Syracuse, NY; University of California, San Diego, Ideker Laboratory, Encinitas, CA; City of Hope National Medical Center, Duarte, CA; Alliance Foundation Trials, Boston, MA; Genentech Inc, South San Francisco, CA; Genentech, South San Francisco, CA; Duke University Medical Center, Durham, NC; Mayo Clinic, Rochester, MN; Duke Cancer Institute, Durham, NC

Background: A minority of patients with unresectable stage III non-small cell lung cancer (NSCLC) may be cured by chemoradiotherapy (CRT). Adjuvant checkpoint inhibition through PD-L1 blockade after CRT improved survival compared to placebo in the PACIFIC trial (median progression-free survival (mPFS) 16.9 vs 5.6 months (mo), median overall survival (mOS) 47.5 vs 29.1 mo), but overall survival at 5 years remains below 50% (Spigel D, et al J Clin Oncol 2022, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9015199/. Only patients completing CRT without progression and with good performance status were eligible for this approach. Neoadjuvant checkpoint inhibition would allow more patients the opportunity to benefit from immunotherapy and may attenuate tumor-related immunosuppression via depletion of regulatory T cells and clonal expansion of effector T cells, thereby improving tumor immunogenicity. Neoadjuvant atezolizumab had favorable outcomes compared to historic PACIFIC data in the phase II single arm trial, AFT-16 (mPFS 30 mo and mOS not reached). Whether combination immunotherapy therapy before CRT will improve outcomes in this setting is the question posed in the AFT-57 trial. **Methods:** This phase II randomized Alliance Foundation Trials study (AFT-57) will evaluate safety and efficacy of atezolizumab with or without the anti-TIGIT monoclonal antibody, tiragolumab, before and after definitive CRT with concurrent atezolizumab. The primary endpoint is PFS in the two experimental arms with a goal to select the most promising regimen for further study. AFT-57 will randomly assign 158 patients with stage III NSCLC (AJCC v8), Eastern Cooperative Oncology Group performance status 0-1, no active autoimmune disease and no underlying organ dysfunction to 2 cycles of neoadjuvant atezolizumab (1200 mg intravenously [IV] every 21 days) with or without tiragolumab (600 mg IV). Non-progressing patients will receive carboplatin and paclitaxel weekly with atezolizumab 1200 mg IV every 21 days concurrent with 60 Gray involved field thoracic radiation in 30 daily fractions (Monday - Friday) followed by atezolizumab with or without tiragolumab on the same schedule as the neoadjuvant doses, with a plan to complete one year of therapy. A pilot cohort of 20 patients for whom tiragolumab will be combined with atezolizumab during chemoradiotherapy is planned toward the end of accrual. Correlative science includes tissue and blood-based immune-related biomarkers at baseline and during therapy. This trial utilizes the Alliance Participant Engagement Portal, a patient-facing site designed to provide information and resources to Alliance clinical trial participants. The trial was activated on 12/7/23 with the first patient screened 1/19/24. Clinical trial information: NCT05798663. Research Sponsor: Alliance Foundation.

TPS8124 **Poster Session**

Phase 2 study to evaluate the novel mitochondrial PRX3 inhibitor, RSO-021, as an intrapleural monotherapy and in combination with IV paclitaxel in patients with malignant pleural effusion due to mesothelioma or another advanced solid tumor.

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Background: Tumor cells generate elevated levels of reactive oxygen species (ROS), leading to increased expression and activity of critical ROS scavenging pathways. Peroxiredoxin 3 (PRX3) is the principal peroxide scavenging enzyme in mitochondria. RSO–021 is a novel small molecule PRX3 inhibitor that inactivates PRX3 through direct covalent adduction of active site cysteine residues, in turn inducing oxidative stress that is incompatible with tumor cell survival. Preclinical studies of RSO-021 show that it selectively inhibits mitochondrial PRX3 in vitro and is highly effective in a variety of tumor models, including mesothelioma and many solid tumors. RSO-021 has completed phase 1 evaluation in patients with advanced mesothelioma or solid tumors with predominant pleural disease and malignant pleural effusions. The phase 1 data supported weekly intrapleural dosing of RSO-021 at the 90 mg dose level, with acceptable safety and early signals of efficacy. Some patients were able to receive >30 weeks of treatment. Pre- and post-dose primary prophylaxis for local inflammatory reactions to intrapleural injection was instituted during dose escalation, using corticosteroids, NSAIDS and paracetamol. It also became clear that RSO-021 should not be administered to patients with a dry pleural tap, due to risk of extravasation. **Methods:** The objectives of this open-label, multi-center, 4-arm phase 2 study (MITOPE) are to confirm the efficacy, safety, tolerability, and pharmacology of weekly intrapleural RSO-021 administration. Exploratory endpoints include target engagement as well as biomarkers of response and inflammation. The study explores 2 different RSO-021 doses (90 mg/wk and 45 mg/wk) per FDA Project Optimus, both as monotherapy and in combination with IV paclitaxel 175 mg/m^2 every 3 weeks at until progression or limiting toxicity. Each arm at each dose has a 2-stage Simon design (12-21 patients) requiring 1 response to trigger stage 2 (null/target response rate 3%/20% and type I/type II error 0.05/0.8) for a maximum of 168 patients in the trial. Three of the 4 study arms are investigating the antitumor activity of RSO-021 monotherapy (arms 1-3) and the fourth is assessing the paclitaxel combination. Eligibility (by arm) requires: newly diagnosed treatment-naïve mesothelioma with pleural effusion; mesothelioma with pleural effusion that progressed on ≥1 standard of care (SoC) regimen; solid tumor with predominant pleural/lung disease and effusion that progressed on ≥1 SoC regimen; and breast, epithelial ovarian or non-small cell lung cancer with predominant pleural/lung disease and effusion that progressed on ≥1 SoC regimen. The first patient was treated in 4Q2023 and the trial is actively recruiting to all 4 arms at 9 UK sites. Additional sites are planned. Clinical trial information: NCT05278975. Research Sponsor: RS Oncology.

TPS8125 **Poster Session**

Neoadjuvant immunotherapy in sarcomatoid mesothelioma (Alliance A082101).

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Background: Sarcomatoid mesothelioma is the most aggressive form of pleural mesothelioma and is associated with the worst prognosis of the histologic variants of this disease. In the Checkmate 743 clinical trial the patients with sarcomatoid mesothelioma who received ipilimumab and nivolumab had survival outcomes that were similar to those of patients with epithelioid mesothelioma. In comparison, the patients with sarcomatoid mesothelioma who received chemotherapy had the worst outcomes in this trial, highlighting the known limited efficacy of chemotherapy against this histologic variant. Checkmate 743 demonstrated that ipilimumab and nivolumab is a new standard of care for non-epithelioid mesothelioma. Surgery typically has not been offered to this group of patients given their historically poor outcomes. With the significant survival gains seen patients with sarcomatoid mesothelioma treated with immunotherapy, we hypothesized that surgery may extend the benefits seen with immunotherapy. **Methods:** Alliance for Clinical Trials in Oncology A082101 is a prospective, phase 2 nonrandomized clinical trial for patients with sarcomatoid mesothelioma. The co-primary objectives are to determine the percentage of patients with potentially resectable sarcomatoid mesothelioma able to proceed with surgery after neoadjuvant ipilimumab and nivolumab, and the progression-free survival (PFS) at 12 months (12-month PFS) after the initiation of ipilimumab and nivolumab. For sample size determination, we assumed that if the true rate of surgery is 75% or greater, it would indicate that neoadjuvant immunotherapy is feasible to be given prior to surgery. On the other hand, if the true rate of surgery is 50% or less it would indicate that neoadjuvant immunotherapy is not worthy of further investigation. Twenty-six (26) eligible patients will be needed to receive neoadjuvant immunotherapy. If 16 or fewer of the 26 eligible patients proceed to surgery, it will be concluded that the experimental therapy is not worthy of further investigation. Otherwise, it will be concluded that the experimental therapy is worthy of further investigation. Safety monitoring will be done through a 6-week run-in for the first 10 patients to assess for pre-operative and post-operative toxicities and complications. Sequential boundaries will be used to monitor severe toxicity and complication rates. Accrual will be halted if excessive numbers of severe toxicity and complications in pre-operative and post-operative phases are seen. The accrual and safety data will be summarized in reports for semiannual reviews by Alliance Data and Safety Monitoring Board. Tumor and blood-based biomarkers will be included as exploratory biomarkers. Support: U10CA180821, U10CA180882, U24 CA196171; https://acknowledgments.alliancefound.org. Clinical trial information: NCT05647265. Research Sponsor: National Cancer Institute; U10CA180821; National Cancer Institute; U10CA180882; National Cancer Institute; U24CA196171.

TPS8126 **Poster Session**

IDeate-Lung02: A phase 3, randomized, open-label study of ifinatamab deruxtecan (I-DXd) vs treatment of physician's choice (TPC) in relapsed small cell lung cancer (SCLC).

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Background: SCLC is an aggressive malignancy, and patients (pts) with extensive stage (ES)-SCLC have a relatively short median overall survival (OS), with limited treatment options beyond first-line (1L) therapy. B7 homolog 3 (B7-H3 [CD276]) is a transmembrane protein expressed in many solid tumors but with low/no expression in normal tissue. In SCLC, B7-H3 is highly expressed and associated with poor prognosis and lack of response to standard therapy. I-DXd is a B7-H3-directed antibody–drug conjugate comprising an anti-B7-H3 mAb linked to a topoisomerase I inhibitor payload (DXd) via a stable cleavable linker, designed to enhance selective tumor cell death and reduce systemic exposure. I-DXd demonstrated durable efficacy (objective response rate [ORR] 52.4%; median duration of response [DoR] 5.9 mo; median OS 12.2 mo) irrespective of B7-H3 status, with a manageable safety profile in 21 ES-SCLC pts with a median of 2 prior lines of therapy in a Phase 1/2 trial (NCT04145622). I-DXd is being investigated in an ongoing Phase 2 trial in pretreated ES-SCLC, IDeate-Lung01 (NCT05280470). We describe a Phase 3 trial comparing the efficacy and safety of I-DXd vs TPC in relapsed SCLC.
Methods: IDeate-Lung02 (NCT06203210) is a global, multicenter, randomized, open-label, Phase 3 trial in adult pts with relapsed SCLC who have received 1 prior line of platinum-based therapy and have an ECOG PS of ≤1; pts with asymptomatic brain metastases are eligible. Pts are randomized 1:1 to receive I-DXd 12 mg/kg iv every 3 wks (n = 234) or TPC (n = 234; topotecan, amrubicin, or lurbinectedin). Randomization is stratified by chemotherapy-free interval after 1L therapy (< 90 vs ≥90 days); TPC (topotecan vs amrubicin vs lurbinectedin); prior treatment with PD-(L)1 (yes vs no); and presence/history of asymptomatic brain metastases (yes vs no). Study treatment continues until disease progression, unacceptable toxicity, withdrawal of consent, death, loss to follow-up, or other reasons per protocol. Radiographic tumor assessments occur every 6 wks for 48 wks, then every 12 wks. Dual primary efficacy endpoints are ORR per RECIST v1.1 by blinded independent central review (BICR) and OS. Secondary efficacy endpoints are ORR per investigator; progression-free survival, DoR, disease control rate and time to response by BICR and investigator; and patient-reported outcomes. Safety endpoints include incidence of treatment-emergent adverse events (TEAEs), deaths, serious TEAEs, and TEAEs leading to dose modification or discontinuation. Immunogenicity of I-DXd and relationship between B7-H3 expression and clinical outcome are also secondary objectives. ORR will be analyzed using a Cochran-Mantel-Haenszel test at a 2-sided 1% alpha level, and OS will be analyzed using a log-rank test at a 2-sided 4% significance level, under a 2-look group sequential design. Clinical trial information: NCT06203210. Research Sponsor: This study is sponsored by Daiichi Sankyo, Inc.; Medical writing support was provided by BOLDSCIENCE and funded by Daiichi Sankyo, Inc.

TPS8127 Poster Session

DAREON-8: A phase I, open-label, dose escalation/expansion trial of the DLL3-targeting T-cell engager, BI 764532, combined with first-line (1L) standard of care (platinum, etoposide, and anti-PD-L1 antibody) in patients (pts) with extensive-stage small cell lung carcinoma (ES-SCLC).

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Background: Platinum/etoposide chemotherapy in combination with anti-PD-L1 antibodies is the 1L standard of care (SoC) for pts with ES-SCLC. However, most pts relapse and subsequent treatment (Tx) options are limited. Hence, outcomes are poor with a 5-year survival rate of $<$ 7%. Delta-like ligand 3 (DLL3) is a Notch receptor ligand expressed on tumor cells but not on normal cells. BI 764532 is an IgG-like T-cell engager (TcE) that binds simultaneously to CD3 on T-cells and DLL3 on tumor cells, resulting in selective, T-cell mediated tumor cell lysis. An ongoing Phase I trial of BI 764532 (NCT04429087) in pts with pretreated DLL3-positive tumors demonstrated an overall response rate of 28%, a disease control rate of 54%, and a manageable safety profile. Here, we describe DAREON-8 (NCT06077500), a Phase I open-label dose escalation/expansion trial of BI 764532 plus SoC as a 1L Tx for pts with ES-SCLC. **Methods:** Pts will be recruited from ~20 sites into this two-part trial. In Part A (dose escalation), ~30 pts will receive escalating doses of intravenous BI 764532 (target dose after step-in dosing) plus carboplatin/etoposide + atezolizumab. Dose escalation will be guided by a Bayesian logistic regression model with overdose control. Tx with BI 764532 will continue for 36 months, withdrawal or progressive disease (PD). The primary objective is to determine the maximum tolerated dose (MTD) of BI 764532 and/or the recommended dose for expansion (RDE)/ recommended Phase II dose (RP2D) for BI 764532 plus SoC. Safety, efficacy and/or PK assessments will guide the RDE/RP2D. The primary endpoint focuses on the occurrence of dose-limiting toxicities (DLTs) in the MTD evaluation period. In Part B (dose expansion), ~30 pts will receive BI 764532 at the RDE/RP2D determined in Part A for 36 months, withdrawal or PD and platinum/etoposide + either atezolizumab or durvalumab. The primary objective of Part B is to confirm the safety and tolerability of BI 764532 at the RDE/RP2D plus SoC Tx as measured by the occurrence of DLTs during the on-Tx period. Key inclusion criteria include confirmed ES-SCLC; no prior systemic treatment for ES-SCLC; and eligibility to receive platinum/ etoposide chemotherapy + anti-PD-L1 antibodies. Key exclusion criteria include previous Tx with DLL3-targeting TcEs; persistent, unresolved toxicity from previous Txs; immunodeficiency, or systemic steroid or other immunosuppressive therapy $\leq$7 days prior to first dose of BI 764532; and significant cardio/cerebrovascular disease. Clinical trial information: NCT06077500. Research Sponsor: Boehringer Ingelheim.

TPS8128 **Poster Session**

Alisertib in patients with extensive-stage small-cell lung cancer: The phase 2 ALISCA-Lung1 study.

Taofeek K. Owonikoko, Alberto Chiappori, Ryan D. Gentzler, Stephen V. Liu, Adedayo A. Onitilo, Nathan A. Pennell, Jacob Sands, Bo Wang, Beth Hillary Lowenthal, Judith D. Bebchuk, Lisa DeFazio Eli, Elaine K. Wong, Afshin Dowlati; University of Maryland Marlene and Stewart Greenebaum Comprehensive Cancer Center, Baltimore, MD; H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL; University of Virginia, Charlottesville, VA; Georgetown University, Washington, DC; Marshfield Clinic-Weston Center, Marshfield, WI; Cleveland Clinic Taussig Cancer Institute, Cleveland, OH; Dana-Farber Cancer Institute and Harvard Medical School, Boston, MA; Willamette Valley Cancer Institute and Research Center, Eugene, OR; Puma Biotechnology Inc., Laurel, MD; Puma Biotechnology, Los Angeles, CA; UH Cleveland Medical Center, Cleveland, OH

Background: Treatment options are limited for patients (pts) 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 treating 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, either c-Myc expression or mutation in *RB1*, *RBL1*, *RBL2*, or *CDK6* showed strong correlation with an improvement in both PFS and OS in the alisertib arm. **Methods:** ALISCA-Lung1(NCT06095505) is a phase 2 study to determine whether there is a biomarker-defined population of pts with extensive-stage SCLC that derives increased benefit from alisertib monotherapy. Key inclusion criteria: ≥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 to alisertib monotherapy. Biomarkers will be assessed by next-generation sequencing, mRNA expression analysis, and immunohistochemistry. Candidate biomarkers include, but are not limited to, RB1 loss of function, c-Myc expression, *TP53*mutation, AURKA expression, and SCLC molecular subtype. Secondary objectives: to determine investigator-assessed efficacy, survival, safety, and population pharmacokinetics. Eligible pts 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 pts will undergo sparse pharmacokinetic sampling. Recruitment is underway and up to 60 pts will be enrolled at ~20 centers in the USA. Findings are anticipated to identify a biomarker-defined pt population that derives the greatest clinical benefit from alisertib. Future development of alisertib in SCLC is anticipated to focus on this biomarker-defined population. Clinical trial information: NCT06095505. Research Sponsor: None.

TPS8129 **Poster Session**

A phase II trial of monalizumab in combination with durvalumab (MEDI4736) plus platinum-based chemotherapy for first-line treatment of extensive stage small cell lung cancer (MOZART): Hoosier Cancer Research Network LUN21-530 study.

Hirva Mamdani, Seongho Kim, Ryan D. Gentzler, Misty Dawn Shields, Muhammad Furqan, Kristen Pizana, Qura Abid, Shadia Ibrahim Jalal; Barbara Ann Karmanos Cancer Institute, Wayne State University, Detroit, MI; University of Virginia, Charlottesville, VA; Indiana University Simon Comprehensive Cancer Center, Indianapolis, IN; Universty of Iowa Holden Comprehensive Cancer Center, Iowa City, IA; Karmanos Cancer Institute, Detroit, MI; Indiana University Melvin and Bren Simon Comprehensive Cancer Center, Richard L Roudebush VA Medical Center, Indianapolis, IN

Background: Chemoimmunotherapy consisting of platinum, etoposide, and PD-L1 inhibitor remains 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, a monoclonal antibody targeting NKG2A, 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 cytotoxic chemotherapy, especially platinum. Post-chemotherapy NK cells display an induced expression of NKG2A compared with pre-chemotherapy patients 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-(L)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. 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. Five of the planned 30 patients have been enrolled to date. Clinical trial information: NCT05903092. Research Sponsor: AstraZeneca.

TPS8130 **Poster Session**

Tazemetostat in combination with topotecan and pembrolizumab in patients with recurrent small cell lung cancer.

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Background: Small-cell lung cancer (SCLC) is the most fatal type of lung cancer characterized by exquisite chemo-sensitivity at diagnosis and chemoresistance at relapse. Despite a highly mutated genome, patients with SCLC derive little benefit from immunotherapy. EZH2 (enhancer of zeste homolog 2) is a master epigenetic regulator of SCLC neuroendocrine cell fate and plasticity. EZH2 inhibition 1) promotes upregulation of Schlafen 11 (SLFN11) which irreversibly blocks replication in response to DNA damaging agents and 2) enhances intrinsic immune signaling, leading to constitutive MHC I recovery, sensitizing resistant SCLC models to DNA damaging chemotherapy and immunotherapy. Tazemetostat is a selective oral EZH2 inhibitor. **Methods:** This is an investigator-initiated, NCI Cancer Therapy Evaluation Program (CTEP) sponsored, phase I dose escalation and dose expansion study which will evaluate safety and tolerability of combination of tazemetostat with topotecan, a selective TOP1 inhibitor, and programmed cell death protein 1 (PD-1) inhibitor antibody pembrolizumab. Adult patients with relapsed/recurrent SCLC after at least platinum doublet (limited stage-SCLC) or chemo-immunotherapy (extensive stage-SCLC) and ECOG performance 0-1 are eligible. The regimen design involves a 7-day "run-in" of oral tazemetostat BID followed by 21-day cycles of tazemetostat (1-21 days), intravenous (IV) topotecan (day 1-5) and IV pembrolizumab (Day 1). The dose escalation cohort aims to determine safety and optimal doses of tazemetostat and topotecan (with standard dose of pembrolizumab) using a 3+3 design by assessing for dose limiting toxicities. The dose expansion cohort aims to assess safety, tolerability and preliminary efficacy of the combination in 15 additional patients with relapsed SCLC. The study involves collection of mandatory biopsies at pre-treatment and post-treatment (cycle 1) to gain insights into mechanism of action and resistance of the combination using single cell and spatial transcriptomic approaches. For more questions regarding enrollment and eligibility please contact Rasa.vilimas@nih.gov or anish.thomas@nih.gov. Clinical trial information: NCT05353439. Research Sponsor: CTEP.

TPS8131 **Poster Session**

A phase II exploratory trial of adebrelimab in combination with chemotherapy and concurrent radiotherapy as a first-line treatment for oligo-metastatic extensive-stage small-cell lung cancer.

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Background: Oligometastasis of extensive-stage small-cell lung cancer (ES-SCLC) is an intermediate state between local and extensive metastasis, characterized by reduced metastatic potential and a limited number of metastatic sites, which makes local treatment of each lesion possible. Multiple clinical studies have shown that adding local therapy to standard systemic therapy can improve the prognosis of patients with oligometastatic disease. The PD-L1 inhibitor adebrelimab combined with chemotherapy has become one of the standard regimens for first-line treatment of ES-SCLC. Based on these, we hypothesize that in patients with oligometastatic ES-SCLC at risk of early progression, the early addition of chest radiotherapy and stereotactic radiotherapy (SBRT) for metastatic lesions to first-line treatment with adebrelimab combined with chemotherapy may be expected to achieve local control, thereby improving survival benefits. **Methods:** This is a prospective, single-arm, multicenter, phase II exploratory trial. Patients will be eligible if they are 18 to 75 years of age; have histopathologically or cytologically confirmed ES-SCLC with the number of metastatic lesions of $\leq$ 5 and organ metastasis of $\leq$ 3 (i.e. oligometastases); have an ECOG PS of 0-1; and have no previous systemic treatment. The treatment period in this trial is subdivided into induction therapy, concurrent chemoradiotherapy, and consolidation and maintenance therapy. In the induction setting, patients will receive two 3-week cycles of adebrelimab (20 mg/kg on day 1), carboplatin (AUC of 5 mg/mL per min on day 1)/cisplatin (75 mg/m^2 on day 1), and etoposide (100 mg/m^2 on days 1-3). Patients who achieve partial response or stable disease after induction therapy will then receive concurrent chemoradiotherapy, of which chemotherapy regimen is the same as the induction setting. Radical IMRT radiotherapy (2.5-3 Gy/f, total dose 45-55 Gy) will be performed for the primary tumor in the chest and lymph node region, and SBRT radiotherapy will be given to metastatic lesions. Prophylactic cranial irradiation is optional. After the end of chemoradiotherapy, patients will receive 1-2 cycles of consolidation treatment with the same regimen as induction treatment, followed by adebrelimab monotherapy (20 mg/kg on day 1, q3w) as maintenance treatment until disease progression, intolerance toxicity, or up to 2 years of adebrelimab. The total cycle number of chemotherapy is 4-6. The primary endpoint is progression-free survival (PFS), and secondary endpoints are objective response rate, duration of response, overall survival (OS), 6-month and 1-year PFS rates, 1-year and 2-year OS rates, and safety. The trial is under recruitment, and a total of 62 patients are planned to be enrolled. Clinical trial information: NCT06177925. Research Sponsor: Jiangsu Hengrui Pharmaceuticals Co., Ltd.

TPS8132 **Poster Session**

JCOG2002: A randomized phase III study of thoracic radiotherapy for extensive stage small cell lung cancer.

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Background: Consolidative thoracic radiotherapy (cTRT) has shown a marginal improvement in overall survival (OS) and progression-free survival (PFS) for extensive-stage small-cell cancer (ES-SCLC). Consequently, ASTRO and NCCN guidelines conditionally recommend the use of cTRT. Despite the recent establishment of anti-PD-L1 antibody (aPD-L1) combined with platinum-doublet chemotherapy as the standard first-line treatment for ES-SCLC, the impact of cTRT in the era of immunotherapy remains uncertain. **Methods:** The JCOG2002 study, a randomized, multicenter phase 3 trial, initiated in October 2021 to assess the superiority of additional cTRT in terms of OS for ES-SCLC following induction aPD-L1 plus platinum doublet chemotherapy. Eligibility patients must meet criteria for the first registration including ES-SCLC, no prior radiation or chemotherapy history, age 20 or older, ECOG performance status 0 or 1, and adequate organ function. Induction treatment involves atezolizumab + carboplatin + etoposide or durvalumab + cisplatin / carboplatin + etoposide. Responding patients proceed to the second registration, randomization (1:1 between 30 Gy in 10 fractions of cTRT plus aPD-L1 maintenance therapy and maintenance therapy only). The cTRT targets metastatic lymph nodes in stations #1-7 and ipsilateral stations #10-12 identified at diagnosis. The adjustment factors include response to induction treatment (CR/PR versus SD), presence of brain metastasis (yes versus no), participating institutions, and aPD-L1 type (atezolizumab versus durvalumab). The primary endpoint is OS, with secondary endpoints being PFS and safety. The study aims to enroll 240 randomized patients, with 330 in the first registration, providing 80 % power at a one-sided 5 % significance level to detect a hazard ratio of 0.69 with 3-year accrual period and 1-year follow-up. As of February 6, 2024, 239 patients initiated induction treatment, and 121 have been randomized. This trial is registered at Japan Registry of Clinical Trials as jRCTs031210393 (https://jrct.niph.go.jp/detail/jRCTs031210393). Clinical trial information: jRCTs031210393. Research Sponsor: Japan Agency for Medical Research and Development; 24ck0106866h0002; National Cancer Center Research and Development Fund; 2020-J-3, 2023-J-0.