LBA8000 **Oral Abstract Session**

Overall survival with neoadjuvant nivolumab (NIVO) + chemotherapy (chemo) in patients with resectable NSCLC in CheckMate 816.

Patrick M. Forde, Jonathan Spicer, Mariano Provencio, Tetsuya Mitsudomi, Mark M. Awad, Changli Wang, Shun Lu, Enriqueta Felip, Stephen Broderick, Scott Swanson, Julie R. Brahmer, Keith Kerr, Tudor-Eliade Ciuleanu, Fumihiro Tanaka, Gene B. Saylors, Keneng Chen, Lily Wang, Quyen Duong, Nicolas Girard; Trinity St. James's Cancer Institute, Trinity College Dublin, Dublin, Ireland; McGill University Health Centre, Montreal, QC, Canada; Hospital Universitario Puerta de Hierro, Madrid, Spain; Kindai University Faculty of Medicine, Ohno-Higashi, Osaka-Sayama, Japan; Memorial Sloan Kettering Cancer Center, New York, NY; Tianjin Lung Cancer Center, Tianjin Medical University Cancer Institute & Hospital, Tianjin, China; Shanghai Lung Cancer Center, Shanghai Chest Hospital, Shanghai Jiao Tong University, Shanghai, China; Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology, Universitat Autònoma de Barcelona, Barcelona, Spain; The Bloomberg–Kimmel Institute for Cancer Immunotherapy, The Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins Medicine, Baltimore, MD; Brigham and Women's Hospital, Boston, MA; Aberdeen Royal Infirmary, Aberdeen, United Kingdom; Institutul Oncologic Prof Dr Ion Chiricuţă and University of Medicine and Pharmacy Iuliu Haţieganu, Cluj-Napoca, Romania; University of Occupational and Environmental Health, Kitakyushu, Japan; Charleston Oncology, Charleston, SC; State Key Laboratory of Molecular Oncology, Peking University Cancer Hospital & Institute, Beijing, China; Bristol Myers Squibb, Princeton, NJ; Institut du Thorax Curie-Montsouris, Institut Curie, Paris, France

8001 Oral Abstract Session

Neoadjuvant (neoadj) osimertinib (osi) ± chemotherapy (CT) vs CT alone in resectable (R) epidermal growth factor receptor-mutated (EGFRm) NSCLC: NeoADAURA.

Jamie E. Chaft, Walter Weder, Jianxing He, Keneng Chen, Maximilian Hochmair, Jin-Yuan Shih, Sung Yong Lee, Kang-Yun Lee, Nguyen Nhung, Somcharoen Saeteng, Carlos Henrique Andrade Teixeira, Carles Escriu, Alex Martinez-Marti, Collin M. Blakely, Yasushi Yatabe, Sanja Dacic, Xiangning Huang, Yuri Rukazenkov, Anupriya Dayal, Masahiro Tsuboi; Thoracic Oncology Service, Memorial Sloan Kettering Cancer Center, New York, NY; Department of Medicine, Weill Cornell Medical College, New York, NY; Department of Thoracic Surgery, University of Zurich, Thoracic Surgery, Clinic Bethanien, Zurich, Switzerland; Department of Thoracic Surgery and Oncology, The First Affiliated Hospital of Guangzhou Medical University, China State Key Laboratory of Respiratory Disease & National Clinical Research Centre for Respiratory Disease, Guangzhou, China; State Key Laboratory of Molecular Oncology, Beijing Key Laboratory of Carcinogenesis and Translational Research, The First Department of Thoracic Surgery, Peking University Cancer Hospital, Beijing, China; Karl Landsteiner Institute of Lung Research and Pulmonary Oncology, Klinik Floridsdorf, Vienna, Austria; Department of Respiratory and Critical Care Medicine, Klinik Floridsdorf, Vienna Healthcare Group, Vienna, Austria; Department of Internal Medicine, National Taiwan University Hospital, Taipei City, Taiwan; Division of Pulmonary Medicine, Department of Internal Medicine, Korea University Guro Hospital, Seoul, Korea, Republic of; Division of Pulmonary Medicine, Department of Internal Medicine, Shuang-Ho Hospital, Taipei Medical University, Taipei, Taiwan; Vietnam National Lung Hospital, Faculty of Medicine, UMP, VNU, Hanoi, Viet Nam; Department of Surgery, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand; Clinical Oncology Department, Hospital Alemão Oswaldo Cruz, São Paulo, Brazil; Department of Molecular and Clinical Cancer Medicine, University of Liverpool, Liverpool, UK; Department of Medical Oncology, Clatterbridge Cancer Centre NHS Foundation Trust, Liverpool, United Kingdom; Department of Medical Oncology, Vall d'Hebron Institute of Oncology (VHIO), Vall d'Hebron University Hospital, Barcelona, Spain; University of California, San Francisco, Helen Diller Comprehensive Cancer Center, University of California, San Francisco, CA; Department of Diagnostic Pathology, National Cancer Center, Tokyo, Japan; Department of Pathology, Yale School of Medicine, New Haven, CT; Biometrics, Late-stage Development, Oncology R&D, AstraZeneca, Cambridge, United Kingdom; Late-Stage Development, Oncology R&D, AstraZeneca, Cambridge, United Kingdom; Late-Stage Development, Oncology R&D, AstraZeneca, Gaithersburg, MD; Department of Thoracic Surgery and Oncology, National Cancer Center Hospital East, Kashiwa, Japan

Background: Based on the Ph 3 ADAURA study, adjuvant (adj) treatment (Tx) with osi, a 3rd-generation, EGFR-TKI, is SoC for resected EGFRm stage (stg) IB–IIIA NSCLC (AJCC 7th ed). Neoadj Tx may improve surgical and long-term outcomes. NeoADAURA (NCT04351555) is a global, Ph 3, randomized, controlled, 3-arm study assessing outcomes with neoadj osi ± CT vs CT alone, in EGFRm R-NSCLC. **Methods:** Eligible pts: aged ≥18 yrs; WHO PS ≤1; EGFRm (Ex19del/L858R) stg II–IIIB (AJCC 8th ed) R-NSCLC. Pts were stratified (stg II vs III; non-Asian vs Chinese vs other Asian; Ex19del vs L858R) and randomized 1:1:1 to neoadj osi 80 mg QD (≥9 wks) + CT (cis/carboplatin + pemetrexed; 3 cycles, Q3W), osi monotherapy (mono) 80 mg QD (≥9 wks) or placebo (PBO) QD + CT (3 cycles, Q3W). Osi/PBO + CT: double blind; osi mono: open label, sponsor blind. Adj osi was offered to all pts who completed surgery (Sx). Primary endpoint: major pathological response (MPR) by blinded central pathology review. Secondary endpoints included pathological complete response (pCR), event-free survival (EFS), and safety. Data cut-off: Oct 15, 2024. **Results:** Overall, 358 pts were randomized: osi + CT n=121/osi mono n=117/PBO + CT n=120; baseline characteristics were generally balanced across the respective arms (stg II: 49%/50%/51%; non-Asian: 27%/26%/25%; Ex19del: 50%/51%/51%). After neoadj Tx, 92%/97%/89% of pts underwent Sx in the osi + CT/osi mono/PBO + CT arms. Osi + CT (MPR rate 26%) and osi mono (25%) showed statistically significant improvement in MPR vs PBO + CT (2%): odds ratios were 19.8 ($p<0.0001$) and 19.3 ($p<0.0001$), respectively. Interim EFS (15% maturity) trended in favor of osi + CT and osi mono vs PBO + CT (Table); ≥80% of pts in each arm received adj osi. In the neoadj period, grade ≥3 all-cause AEs and AEs leading to discontinuation of any Tx occurred in 36%/13%/33% and 9%/3%/5% of pts, respectively, for osi + CT/osi mono/PBO + CT. No pts died within 30 days of Sx. **Conclusions:** Neoadj osi with or without CT showed statistically significant improvement in the MPR rate over CT alone. EFS data were immature and trended in favor of the osi containing arms. There were no new safety concerns. Neoadj osi ± CT should be considered when planning Tx for pts with EGFRm stg II–IIIB R-NSCLC. Clinical trial information: NCT04351555. Research Sponsor: AstraZeneca.

	Osi + CT (n=121)	Osi mono (n=117)	PBO + CT (n=120)
MPR rate, % (95% CI)	26 (18, 34)	25 (17, 34)	2 (<1, 6)
Difference vs PBO + CT, % (95% CI)	24 (15, 32)	23 (15, 32)	–
Odds ratio vs PBO + CT (adjusted 100×[1−alpha]% CI)	19.8 (4.6, 85.3[a])	19.3 (1.7, 217.4[b])	–
p-value	<0.0001	<0.0001	–
pCR rate, % (95% CI)	4 (1, 9)	9 (4, 15)	0 (0, 3)
12-mo EFS rate, % (95% CI)	93 (87, 97)	95 (89, 98)	83 (75, 89)
EFS hazard ratio vs PBO + CT (CI)	0.50 (0.17, 1.41[c])	0.73 (0.40, 1.35[d])	–
p-value	0.0382[e]	–	–
Median EFS follow-up, mos (range)[f]	16 (0–42)	18 (2–42)	19 (2–42)

[a]95.002% CI; [b]99.9% CI; [c]99.8% CI; [d]95% CI; [e]p-value ≤0.002 required for statistical significance at interim analysis; [f]censored pts.

8002 Oral Abstract Session

Lung cancer diagnosis rates (LCDR) in lung cancer screening (LCS) and incidental pulmonary nodule (IPN) cohorts in the Mississippi Delta.

Wei Liao, Matthew Paul Smeltzer, Jordan Goss, Talat Qureshi, Sara Johnson, Amanda Harris, Kourtney Dortch, Carrie Fehnel, Osarenren Ogbeide, Meredith Ray, Raymond U. Osarogiagbon; Baptist Cancer Center, Multidisciplinary Thoracic Oncology Program, Memphis, TN; University of Memphis, School of Public Health, Memphis, TN

Background: The LCDR in the CT screened cohort in the National Lung Screening Trial (NLST) was 1.1% over a median of 6.5 years follow up. We evaluated the LCDR in a regional US community. **Methods:** Prospective cohort study of patients in LCS and IPN programs in 22 facilities across a 125 county service area population. We compared LCDR over 3 years in LCS stratified by Lung-RADS (L-R) score (1 to 4X), IPN by nodule size (≤6, >6-15, >15-20, >20-30 mm) on initial CT scans. Comparisons used Chi-square tests, Wilcoxon tests, and Cox regression models with Hazard Ratios (HR) for lung cancer diagnosis adjusted for age, sex, race, and insurance. **Results:** From 2015 to 2023, 7121 persons were enrolled in LCS – 5447 (76%) L-R 1/2, 823 (12%) L-R 3, 452 (6%) L-R 4A, 205(3%) L-R 4B, and 114(2%) L-R 4X; and 22,455 in IPN - 8141 (36%) ≤6mm, 11177 (50%) >6-15 mm, 1596 (7%) >15-20 mm, 1535 (7%) >20-30 mm. Over this period, 334 (4.7%) and 1016 (4.5%) were diagnosed with lung cancer in LCS and IPN cohorts, respectively, including 91 (2%), 40 (5%), 60 (13%), 68 (33%), and 66 (58%) L-R 1-4X and 69 (1%), 421 (4%), 224 (14%) and 302 (20%) of IPN cohort in ascending order of nodule size. The cumulative LCDR at 36 months were: 5% (95% CI 4.4 – 5.6) in LCS- 1.9% (1.5-2.4), 5.0% (3.4-7.0), 14%(10-18), 33%(27-40), and 60% (49-68) for L-R 1 to 4X, respectively; and 4.4% (4.1 – 4.7)- 0.66% (0.49-0.88), 3.5% (3.2-3.9), 14% (12-16) and 20% (18-22) for the respective IPN cohorts. With L-R 1/2 as reference, aHR for lung cancer diagnosis was 2.9 (2.0 - 4.1, p<0.0001), 7.6 (5.4 - 10.6, p<0.0001), 24.1 (17.4 - 33.4, p<0.0001), and 66.3 (47.7 - 92.3, p<0.0001) for L-R 3, 4A, 4B & 4X in LCS cohort. With nodule >6-15 as reference, aHR was 0.2 (0.2 - 0.3, p<0.0001), 4.2(3.6 - 4.9, p<0.0001) and 5.7 (4.9 - 6.7, p<0.0001) in IPN cohort. **Conclusions:** LCDR of this Mississippi Delta LCS and IPN cohort was greater than 4-fold the NLST. The NLST significantly underestimates the potential impact of LCS in this population. Research Sponsor: Baptist Memorial Health Care Foundation; 15BD03.

	LCS						IPN				
	1-2 N = 5447	3 N = 823	4A N = 452	4B N = 205	4X N = 114	P	0-6mm N = 8147	6-15 N = 11177	15-20 N = 1596	20-30 N = 1535	P
Lung Cancer*	91 (2)	40 (5)	60 (13)	68 (33)	66 (58)	<0.0001	69(1)	421(4)	224 (14)	302(20)	<0.0001
Age Median (Q1 - Q3)	65 (60-70)	65 (60-70)	67 (61-71)	67 (63-73)	67 (63-72)	<0.0001	62 (51-72)	64 (52-74)	66 (53-75)	68 (57-77)	<0.0001
Female*	2795 (51)	400 (49)	218 (48)	107 (52)	57 (50)	0.4709	4777(59)	6191 (55)	884 (55)	788 (51)	0.0005
Black*	1005 (19)	157 (19)	87 (19)	37 (18)	25 (22)	0.972	2376(29)	3126 (28)	479 (30)	443 (29)	0.0713
Commercial insurance*	2168 (40)	297 (36)	142 (31)	58 (28)	30 (26)	0.0005	3612(44)	4544 (41)	596 (37)	515 (34)	0.0005
Never smoked*	13 (0.2)	3 (0.4)	0	0	0	0.4628	3662(45)	4537 (41)	549 (34)	474 (31)	0.0005
Adenocarcinoma**	31 (34)	15 (38)	29 (48)	31 (46)	44 (67)	0.075	24(35)	222 (53)	130 (58)	164 (54)	0.0235
Clinical stage I/II**	58 (64)	26 (65)	48 (80)	49 (72)	40 (61)	0.3168	29(42)	255 (61)	141 (63)	183 (61)	0.14

*N (%).
**Denominator is # of lung cancer patients.

8003 Oral Abstract Session

SWOG/NRG S1914: Randomized phase III trial of induction/consolidation atezolizumab + SBRT versus SBRT alone in high risk, early-stage NSCLC.

Charles B. Simone II, Megan Eileen Daly, Mary Weber Redman, Ming-Hui Hsieh, Jhanelle E. Gray, Paul Joseph Hesketh, Chen Hu, Arta Monir Monjazeb, Conor Ernst Steuer, Apar Kishor Ganti, Rojano Kashani, Jessica R. Bauman, Josephine Louella Feliciano, James Moon, Jieling Miao, Kimberly Ku, Adedayo A. Onitilo, Karen Kelly, Jeffrey D. Bradley; New York Proton Center and Memorial Sloan Kettering Cancer Center, New York City, NY; Department of Radiation Oncology, University of California Davis Comprehensive Cancer Center, Sacramento, CA; Fred Hutchinson Cancer Center, Seattle, WA; SWOG Statistical Center, Seattle, WA; H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL; Lahey Hospital and Medical Center, Burlington, MA; NRG Oncology Statistics and Data Management Center, Philadelphia, PA; UC Davis Health System, Sacramento, CA; Emory University, Atlanta, GA; University of Nebraska Medical Center, Omaha, NE; University Hospitals Seidman Cancer Center and Case Western Reserve University, Cleveland, OH; Fox Chase Cancer Center, Philadelphia, PA; Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD; SWOG Statistics and Data Management Center, Fred Hutchinson Cancer Center, Seattle, WA; Fred Hutchinson Cancer Research Center, Seattle, WA; Illinois CancerCare, Peoria, IL; Wisconsin NCORP, Marshfield, WI; UC Davis Comprehensive Cancer Center, Sacramento, CA; University of Pennsylvania, Abramson Cancer Center, Philadelphia, PA

Background: Stereotactic body radiation therapy (SBRT) is the standard of care (SoC) for early stage, medically inoperable non-small cell lung cancer (NSCLC). While rates of in-field control exceed 90%, regional and distant control after SBRT remain suboptimal. A prior phase II randomized trial suggested a benefit to adding immunotherapy (PMID 37478883). SWOG/NRG S1914 (NCT#04214262) is a randomized phase III trial evaluating neoadjuvant, concurrent and adjuvant atezolizumab plus SBRT for early-stage NSCLC vs SoC. **Methods:** Eligible patients (pts) had T1-3N0M0 NSCLC ≤7cm, were medically inoperable or declined surgery, and had ≥1 risk factor for increased recurrence: tumor diameter ≥2 cm, ≥6.2, moderately/poorly/undifferentiated histology. Randomization was to SoC SBRT (S [3-8 fractions, biologically effective dose ≥100 Gy]) or neoadjuvant, concurrent and adjuvant atezolizumab (AS [1200 mg IV Q3 week, 8 cycles]) with SBRT initiated with cycle 3, stratifying by tumor location (central vs peripheral), size (<4 cm vs ≥4cm) and ECOG performance status (PS, 0-1 vs 2). The primary objective was to compare overall survival (OS) between the arms. Secondary objectives included comparisons of progression free survival (PFS), failure patterns, toxicity and quality of life (QoL). OS and PFS were compared using a 1-sided stratified log-rank test at the 2.5% level, confidence intervals (CI) are 95%. The accrual goal was 432 eligible pts. **Results:** From 8/13/20 - 9/6/24, 417 pts were randomized, 403 met eligibility [201 to S, 202 to AS]. Accrual closed at the first interim analysis for futility based on OS and PFS per design. Median follow-up for pts still alive was 12 (range: 0.03-49) months. Median age was 73 (41-91) years and 89% had PS 0-1. Median tumor diameter was 2.3 cm. No protocol treatment was received for 6 pts on S and 8 on AS. With 49 deaths, OS was not different between the arms (HR (CI): 1.15(0.65-2.01), p=0.63; 2-year OS: 82% S vs 80% AS). With 88 events, PFS was not better with AS (HR (CI): 1.35(0.89-2.06), p=0.16); 2-year PFS was 71% on S vs 60% on AS. Regional (2% vs 3%) and distant (4% vs 5%) failures were not different; there were more local failures with AS (13% vs 7%). Among former (53%)/never (3%) smokers, AS had worse OS and PFS than S (HR(CI): 2.50 (1.11-5.59), p=0.03); HR(CI): 2.16(1.15-4.04), p=0.01), respectively. Grade (G) ≥3 adverse event (AE) rates were 12% on AS (N=21 G3, 1 G4, 1 G5 respiratory failure) vs 2% on S (N=3 G3, 1 G4). **Conclusions:** In the first reported phase III trial to assess immunotherapy (IO) added to SBRT in early-stage NSCLC, IO failed to improve survival. More G ≥3 adverse events were reported with AS. Central review of local recurrence events is ongoing. Additional investigation into subgroups, PD-L1 status, QoL and blood/tissue are pending to determine whether there are subsets who can benefit from this combination and shed further insights into these findings. Clinical trial information: NCT04214262. Research Sponsor: NIH/NCI grants U10CA180888, U10CA180819, U10CA180820, U10CA180821, U10CA180868; Genentech Pharmaceutical/Biotech Company.

LBA8004 **Oral Abstract Session**

R-ALPS: A randomized, double-blind, placebo-controlled, multicenter phase III clinical trial of TQB2450 with or without anlotinib as maintenance treatment in patients with locally advanced and unresectable (stage III) NSCLC without progression following concurrent or sequential chemoradiotherapy.

Ming Chen, Yongling Ji, Long Chen, Qingsong Pang, Ou Jiang, Hong Ge, Yufeng Cheng, Rongrong Zhou, Xiangjiao Meng, Xuhong Min, Hui Wang, Haihua Yang, Yue Xie, Anping Zheng, Jie Li, Bing Xia, Desheng Hu, Xi Zhang, Yong Chen, Wenhui Li; State Key Laboratory of Oncology in South China, Sun Yat-sen University Cancer Center, Guangzhou, China; Zhejiang Cancer Hospital, Hangzhou, China; Guangxi Medical University Affiliated Tumor Hospital, Nanning, China; Department of Radiation Oncology, Tianjin Medical University Cancer Institute & Hospital, Tianjin, Tianjin, China; The Second People's Hospital of Neijiang City, Neijiang, China; Department of Radiation Oncology, The Affiliated Cancer Hospital of Zhengzhou University, Zhengzhou, China; Department of Radiation Oncology, Qilu Hospital of Shandong University, Jinan, Shandong, China; Department of Oncology, Xiangya Hospital, Central South University, Changsha, China; Thoracic Radiation Oncology Ward IV, Shandong Provincial Cancer Hospital, Jinan, China; Oncology Radiotherapy Department, Anhui Chest Hospital, Hefei, China; Hunan Cancer Hospital and the Affiliated Cancer Hospital of Xiangya School of Medicine, Central South University, Changsha, China; Taizhou Hospital of Zhejiang Province, Taizhou, China; Chongqing Cancer Hospital, Chongqing, China; Department of Radiation Oncology, Anyang Cancer Hospital, Anyang, China; City Cancer Hospital, Anyang, China; Department of Radiation Oncology, Shanxi Cancer Hospital, Taiyuan, China; Hangzhou Cancer Hospital, Hangzhou, China; Hubei Cancer Hospital, Wuhan, China; Xiangya Third Hospital of Central South University, Oncology Department, Changsha, China; Department of Radiation Oncology, The First Affiliated Hospital, Sun Yat-sen University, Guangzhou, China; Radiotherapy Department, Yunnan Provincial Cancer Hospital, Kunming, China

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2025, issue of the *Journal of Clinical Oncology*.

LBA8005 **Oral Abstract Session**

Randomized phase II trial investigating whether atezolizumab after chemo-radiotherapy (CRT) prolongs survival in limited stage (LS) small cell lung cancer (SCLC).

Bjorn Henning Gronberg, Marianne Aanerud, Daphne W. Dumoulin, Jan Nyman, Tine Schytte, Maria Moksnes Bjaanæs, Kirill Neumann, Georgios Tsakonas, Elisabeth Anna Kastelijn, Nina Helbekkmo, Seppo W. Langer, Sacha Rothschild, Christina Appenzeller, Jos Stigt, Tine McCulloch, Hanne Sorger, Marie Søfteland Sandvei, Kristin Toftaker Killingberg, Trude Camilla Frøseth, Tarje Onsøien Halvorsen; Department of Clinical and Molecular Medicine, NTNU, Norwegian University of Science and Technology and Department of Oncology, St. Olavs Hospital, Trondheim, Norway; Haukeland University Hospital, Department of Thoracic Medicine, Bergen, Norway; Department of Pulmonary Medicine, Erasmus MC Cancer Institute, University Medical Center, Rotterdam, Netherlands; Sahlgrenska University Hospital, Göteborg, Sweden; Department of Oncology, Odense University Hospital, Odense, Denmark; Oslo University Hospital, Department of Oncology, Oslo, Norway; Department of Pulmonology, Akershus University Hospital, Lørenskog, Norway; Department of Oncology, Karolinska University Hospital, Stockholm, Sweden; Department of Pulmonology, Sint Antonius Hospital, Utrecht, Netherlands; University Hospital of North Norway, Department of Pulmonology, Tromsø, Norway; Department of Oncology, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark; Cantonal Hospital Baden, Center Oncology / Hematology, Department Internal Medicine, Baden, Switzerland and University of Basel, Basel, Switzerland, Basel, Switzerland; Kantonsspital St. Gallen, Sankt Gallen, Switzerland; Department of Respiratory Medicine, Isala Hospital, Zwolle, Netherlands; Aalborg University Hospital, Aalborg, Denmark; Department of Medicine, Levanger Hospital, Levanger, Norway

Lurbinectedin (lurbi) + atezolizumab (atezo) as first-line (1L) maintenance treatment (tx) in patients (pts) with extensive-stage small cell lung cancer (ES-SCLC): Primary results of the phase 3 IMforte trial.

Luis G. Paz-Ares, Hossein Borghaei, Stephen V. Liu, Solange Peters, Roy S. Herbst, Katarzyna Magdalena Stencel, Margarita Majem, Grzegorz Czyżewicz, Reyes Bernabe Caro, Ki Hyeong Lee, Melissa Lynne Johnson, Nuri Karadurmus, Christian Grohe, Vaikunth Cuchelkar, Vilma Graupner, Monika Dulloo Kaul, Ya-Chen Lin, Debasis Chakrabarti, Kamalnayan Bhatt, Martin Reck; Hospital Universitario 12 de Octubre, H12O-CNIO Lung Cancer Unit, Universidad Complutense and Ciberonc, Madrid, Spain; Fox Chase Cancer Center/Temple Health, Philadelphia, PA; Georgetown University, Washington, DC; University Hospital CHUV, Lausanne, Switzerland; Yale Cancer Center, Yale School of Medicine, New Haven, CT; Wielkopolska Center of Pulmonology and Thoracic Surgery of Eugenia and Janusz Zeyland, Poznan, Poland; Department of Medical Oncology, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain; The John Paul II Specialist Hospital, Cracow, Poland; Hospital Universitario Virgen del Rocio, Seville, Spain; Department of Internal Medicine, Chungbuk National University Hospital, Chungbuk National University School of Medicine, Cheongju-Si, South Korea; Tennessee Oncology, Nashville, TN; University of Health Sciences Gülhane Education and Research Hospital, Medical Oncology, Ankara, Turkey; Klinik für Pneumologie, Evangelische Lungenklinik Berlin, Berlin, Germany; Genentech, South San Francisco, CA; Roche, Basel, Switzerland; Genentech Inc, South San Francisco, CA; Genentech, Inc., South San Francisco, CA; Jazz Pharmaceuticals, Dublin, Ireland; Jazz Pharmaceuticals plc, Dublin, Ireland; Thoracic Oncology Department, LungenClinic Grosshansdorf, Grosshansdorf, Germany

Background: Despite improved efficacy when adding 1L PD-(L)1 inhibitors to platinum-based chemotherapy for ES-SCLC, long-term survival remains limited. We report primary results from the global open-label, randomized, Phase 3 IMforte study (NCT05091567) of 1L maintenance tx with lurbi + atezo vs atezo in pts with ES-SCLC. **Methods:** Tx-naive pts with ES-SCLC received standard induction tx with atezo, carboplatin, and etoposide for four 21-day cycles (q3w). After induction, eligible pts without disease progression (PD) were randomized 1:1 to receive maintenance tx q3w with lurbi (3.2 mg/m^2 IV; with G-CSF prophylaxis) + atezo (1200 mg IV) or atezo alone until PD, unacceptable toxicity, or withdrawal. Pts were stratified by liver metastases at induction baseline (BL; yes/no), receipt of prophylactic cranial irradiation before randomization (yes/no), ECOG PS (0/1) and LDH (≤ULN/ > ULN) at maintenance BL. Crossover was not allowed. Primary endpoints were independent review facility (IRF)–assessed PFS per RECIST v1.1 and OS assessed from randomization into the maintenance phase. **Results:** Of 660 enrolled pts, 483 were randomized to receive lurbi + atezo (n = 242) or atezo (n = 241). BL characteristics were generally balanced between arms. With a median 15.0-mo follow-up (data cutoff: Jul 29, 2024), IRF-PFS was significantly improved with lurbi + atezo vs atezo (stratified HR, 0.54 [95% CI: 0.43, 0.67]; $P< 0.0001$; Table). A significant OS benefit was seen with lurbi + atezo vs atezo (stratified HR, 0.73 [95% CI: 0.57, 0.95]; $P= 0.0174$). Median maintenance tx duration was 4.1 mo with lurbi and 4.2 mo with atezo in the lurbi + atezo arm (n = 242) and 2.1 mo in the atezo arm (n = 240). In the lurbi + atezo and atezo arms, respectively, treatment-related AEs (TRAEs) occurred in 83.5% vs 40.0% of pts, G3/4 TRAEs in 25.6% vs 5.8% and G5 TRAEs in 0.8% (2 pts; sepsis, febrile neutropenia) vs 0.4% (1 pt; sepsis); AEs led to tx discontinuation in 6.2% vs 3.3%. **Conclusions:** IMforte met both primary endpoints of IRF-PFS and OS, demonstrating a clinically meaningful benefit with 1L maintenance tx with lurbi + atezo vs atezo in pts with ES-SCLC. Lurbi + atezo was generally well tolerated, with no new or unexpected safety signals. IMforte is the first global Phase 3 study to show PFS and OS improvement with 1L maintenance tx for ES-SCLC and supports maintenance lurbi + atezo as a new option for pts with this aggressive disease. Clinical trial information: NCT05091567. Research Sponsor: Genentech, Inc.

Efficacy from randomization into maintenance phase	Lurbi + atezo (n=242)	Atezo(n=241)
IRF-PFS		
Event, n (%)	174 (71.9)	202 (83.8)
Median (95% CI), mo	5.4 (4.2, 5.8)	2.1 (1.6, 2.7)
Stratified HR (95% CI)	0.54 (0.43, 0.67); $P<0.0001$[a]; $\alpha=0.001$[b]	
OS		
Event, n (%)	113 (46.7)	136 (56.4)
Median (95% CI), mo	13.2 (11.9, 16.4)	10.6 (9.5, 12.2)
Stratified HR (95% CI)	0.73 (0.57, 0.95); $P=0.0174$[a]; $\alpha=0.0313$[b]	

[a]Stratified log-rank.
[b]2-sided boundary.

8007 Oral Abstract Session

A phase 2 dose expansion study of ZG006, a trispecific T cell engager targeting CD3/DLL3/DLL3, as monotherapy in patients with advanced small cell lung cancer.

Xinghao Ai, Yun Yan Zhang, Tongmei Zhang, Tienan Yi, Mingjun Li, Wenxiu Yao, Liang Han, Longhua Sun, Anwen Liu, Qi Mei, Guang Han, Zhen Zhang, Yinyin Li, Lu Li, Li Zheng, Yong Fang, Yongzhong Luo, Jason Jisheng Wu, Shun Lu; Shanghai Chest Hospital, Shanghai, China; The Affiliated Cancer Hospital of Harbin Medical University, Harbin, China; Beijing Chest Hospital, Capital Medical University, Beijing, China; Xiangyang Central Hospital, Xiangyang, China; Department of Medical Oncology, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, China; Sichuan Cancer Hospital, Chengdu, China; Xuzhou Central Hospital, Xuzhou, China; Department of Respiratory Medicine, First Affiliated Hospital of Nanchang University, Nanchang, China; The Second Affiliated Hospital of Nanchang University, Nanchang, China; Department of Oncology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, China; Hubei Cancer Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China; Nanyang First People's Hospital, Nanyang, China; Department of Oncology, Shenyang Chest Hospital, Shenyang, China; West China Hospital of Sichuan University, Chengdu, China; Sir Run Run Shaw Hospital, Zhejiang University School of Medicine, Hangzhou, China; Hunan Cancer Hospital & The Affiliated Cancer Hospital of Xiangya School of Medicine, Central South University, Changsha, China; Suzhou Zelgen Biopharmaceuticals Co., Ltd., Suzhou, China; Shanghai Chest Hospital, School of Medicine, Shan, Shanghai, China

Background: ZG006 is a trispecific T cell engager (Tri-TE) targeting Delta-like ligand 3 (DLL3) and CD3, designed to bridge tumor cells and T cells by binding to two distinct DLL3 epitopes on tumor cells and CD3 on T cells, thereby mediating T cell-specific killing of DLL3-expressing tumor cells such as small cell lung cancer (SCLC). Here, we report the results from the phase 2 dose expansion study of ZG006 for the treatment of patients (pts) with advanced SCLC. **Methods:** This is a randomization, multi-center, open-label phase 2 study of ZG006 as monotherapy in SCLC pts failed to at least 2 prior lines of standard systemic treatments. Based on ZG006 phase 1 study results, both 10 mg and 30 mg Q2W dose levels with a priming dose of 1 mg are being evaluated in this phase 2 dose optimization study, 60 pts are to be randomized at a ratio of 1:1 to receive ZG006. The primary endpoint was objective response rate (ORR) according to RECIST1.1. DLL3 expression was not required but retrospectively evaluated by IHC. **Results:** As of Dec. 31, 2024, a total of 40 SCLC pts were randomized (19 on 10 mg, 21 on 30 mg) and received≥1 dose of ZG006. Median age was 57.5 (range: 48-73) years. Of the 40 pts, 31 (77.5%) were males and 27 (67.5%) had smoking history; all had received ≥2 prior line treatments and 45.0% ≥3 lines; majority (72.5%) had prior anti-PD-(L)1 treatments. Baseline metastatic sites of liver and brain accounted 52.5% (21/40) and 20.0% (8/40), respectively. Among 27 (13 at 10 mg, 14 at 30 mg) efficacy-evaluable SCLC pts who had at least one post-baseline tumor scan, 18 (5 confirmed, others pending confirmed) achieved partial response (7 at 10 mg, 11 at 30 mg). Overall, the ORR was 66.7% and the DCR was 92.6%. For the 10 mg group, ORR was 53.8% and DCR was 84.6%; for the 30 mg group, ORR was 78.6% and DCR was 100.0%. DoR and PFS, not yet matured and will be updated with additional follow-up time. Among the all combined 27 pts, 21 (77.8%) pts had low (N = 17) or medium (N = 4) DLL3 expression at baseline, and they demonstrated reasonably great anti-tumor efficacy with 15 PRs and 71.4% ORR. Treatment-related adverse events (TRAEs) occurred in 35 pts (87.5%); most commonly (≥20%): pyrexia (57.5%), cytokine release syndrome (CRS, 47.5%), vomiting (27.5%), rash (25.0%), decreased appetite (25.0%), aspartate aminotransferase increased (22.5%), white blood cell count decreased (22.5%) and platelet count decreased (22.5%). Only five pts (12.5%) experienced grade 3/4 TRAEs including one grade 3 CRS, and no pts experienced TRAEs leading to treatment discontinuation or death. Five pts (12.5%) experienced serious TRAEs. No significant difference was observed in the safety profile between these two dose groups. **Conclusions:** ZG006 exhibited promising efficacy and acceptable safety in SCLC pts receiving ≥2 lines of prior treatment, even in pts with low DLL3 expression. The enrollment of ZG006-002 study is ongoing. Clinical trial information: NCT06283719. Research Sponsor: None.

LBA8008 **Oral Abstract Session**

Tarlatamab versus chemotherapy (CTx) as second-line (2L) treatment for small cell lung cancer (SCLC): Primary analysis of Ph3 DeLLphi-304.

Charles M. Rudin, Giannis Socrates Mountzios, Longhua Sun, Byoung Chul Cho, Umut Demirci, Sofia Baka, Mahmut Gumus, Antonio Lugini, Tudor-Eliade Ciuleanu, Myung-Ju Ahn, Pedro Rocha, Bo Zhu, Fiona Helen Blackhall, Tatsuya Yoshida, Taofeek K. Owonikoko, Luis G. Paz-Ares, Shuang Huang, Diana Maria Gauto, Gonzalo Recondo, Martin Schuler; Fiona and Stanley Druckenmiller Center for Lung Cancer Research, Memorial Sloan Kettering Cancer Center, New York City, NY; Fourth Department of Medical Oncology and Clinical Trials Unit, Henry Dunant Hospital Center, Athens, Greece; The First Affiliated Hospital of Nanchang University, Nanchang, China; Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, South Korea; Memorial Ankara Hospital, Ankara, Turkey; Interbalkan European Medical Center, Thessaloniki, Greece; Medical Oncology Unit, Istanbul Medeniyet University Hospital, Istanbul, Turkey; Azienda Ospedaliera (AO) San Giovanni Addolorata Hospital, Rome, Italy; Institutul Oncologic Prof Dr Ion Chiricuță and University of Medicine and Pharmacy Iuliu Hațieganu, Cluj-Napoca, Romania; Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea; Vall d'Hebron University Hospital, Barcelona, Spain; The Second Affiliated Hospital of Army Medical University, PLA, Chongqing, China; The Christie NHS Foundation Trust and University of Manchester, Manchester, United Kingdom; National Cancer Center Hospital, Tokyo, Japan; University of Maryland Marlene and Stewart Greenebaum Comprehensive Cancer Center, Baltimore, MD; Hospital Universitario 12 de Octubre, CNIO-H120 Lung Cancer Unit, Ciberonc and Universidad Complutense, Madrid, Spain; Amgen Inc., Thousand Oaks, CA; University Hospital Essen, West German Cancer Center, Essen, Germany

8009 Rapid Oral Abstract Session

Association of post-surgical MRD status with neoadjuvant ctDNA dynamics, genomic mutations, and clinical outcomes in patients with resectable NSCLC (R-NSCLC) from the phase 3 AEGEAN trial.

Martin Reck, Davina Gale, Zhou Zhu, David H. Harpole, Janis M. Taube, Tetsuya Mitsudomi, Dinh Van Luong, Maximilian Hochmair, Kang-Yun Lee, Yoshitsugu Horio, Laszlo Urban, Hiroaki Akamatsu, Bivas Biswas, Lorenzo Antonuzzo, Zsuzsanna Szalai, Ross Stewart, Zhongwu Lai, Darren Hodgson, Tamer M. Fouad, John Heymach; Lung Clinic Grosshansdorf, Airway Research Center North, German Center for Lung Research, Grosshansdorf, Germany; AstraZeneca, Cambridge, United Kingdom; AstraZeneca, Gaithersburg, MD; Department of Surgery, Duke University Medical Center, Durham, NC; Bloomberg–Kimmel Institute for Cancer Immunotherapy, Johns Hopkins Kimmel Cancer Center, Baltimore, MD; Division of Thoracic Surgery, Department of Surgery, Kindai University Faculty of Medicine, Osaka-Sayama, Japan; Vietnam National Lung Hospital, Hanoi, Viet Nam; Department of Respiratory and Critical Care Medicine, Karl Landsteiner Institute for Lung Research and Pulmonary Oncology, Klinik Floridsdorf, Vienna, Austria; Department of Internal Medicine, Shuang Ho Hospital, Taipei Medical University, New Taipei City, Taiwan; Department of Thoracic Oncology, Aichi Cancer Center Hospital, Nagoya, Japan; Mátraháza University and Teaching Hospital, Mátraháza, Hungary; Internal Medicine III, Wakayama Medical University, Wakayama-Shi, Japan; Tata Medical Center, Kolkata, West Bengal, India; Clinical Oncology Unit, Careggi University Hospital, Florence, Italy, and Department of Experimental and Clinical Medicine, University of Florence, Florence, Italy; Department of Pulmonology, Aladar Petz University Teaching Hospital, Győr, Hungary; AstraZeneca, Waltham, MA; AstraZeneca, New York, NY; Department of Thoracic/Head and Neck Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: In AEGEAN, perioperative durvalumab (D) + neoadj CT significantly improved the primary endpoints of event-free survival (EFS) and pathological complete response (pCR) vs neoadj CT alone in pts with R-NSCLC. Prior analyses of AEGEAN suggest that pts without ctDNA clearance during neoadj Tx or with molecular residual disease (MRD; i.e. ctDNA detected) at a landmark timepoint after Sx (adj C1D1) had worse outcomes. Using data from all biomarker-evaluable pts, we report exploratory analyses for associations of post-Sx MRD status with pt characteristics, neoadj ctDNA dynamics, pathological response, genomic mutations and outcomes. **Methods:** AEGEAN is a double-blind PBO-controlled study (NCT03800134). Adults with Tx-naïve R-NSCLC (stage II–IIIB[N2]) and ECOG PS 0/1 were randomized 1:1 to receive neoadj platinum-based CT + D or PBO IV (Q3W, 4 cycles) before Sx followed by D or PBO IV (Q4W, 12 cycles) after Sx. Efficacy was assessed in the mITT population, which excluded pts with known *EGFR*/*ALK* aberrations. ctDNA analysis was performed on plasma collected before each neoadj Tx cycle, Sx, and adj C1, C3/4 and C10/11 using pt-specific tumor-informed assays. Whole exome sequencing analysis of diagnostic tumor biopsies was performed to identify mutations associated with MRD status at the post-Sx landmark. **Results:** Among MRD-evaluable pts, 10% (17/168) were MRD-positive (D, n=10; PBO, n=7) and 90% (151/168) were MRD-negative (D, n=78; PBO, n=73) at the landmark timepoint (median 6.9 wk post-Sx). 88% [15/17] of MRD-positive pts were initially diagnosed with stage III disease. In the D arm, the majority of MRD-positive pts (9/10) also had ctDNA detected at the pre-Sx visit. No MRD-positive pts in the D arm had pCR or major pathological response. As expected, overall disease-free survival (DFS) rates at 12 mo were worse in MRD-positive (14.3%; 95% CI, 2.4–36.3) vs MRD-negative pts (89.3%; 95% CI, 82.6–93.5). In both arms, MRD-positive pts had worse DFS outcomes vs MRD-negative pts (D: HR, 21.28; 95% CI, 7.70–58.83; PBO: HR, 14.29; 95% CI, 4.94–41.36) with DFS trends favoring the D vs PBO arm, particularly in pts with no ctDNA detected (MRD-negative: HR, 0.56; 95% CI, 0.26–1.20; MRD-positive: HR, 0.78; 95% CI, 0.26–2.36). Mutated genes associated with MRD-positive status in the D arm included *KEAP1* and *KMT2C*; despite small pt numbers, EFS benefit in the D vs PBO arm was not evident in pts with the mutations (m) (*KEAP1*m: HR, 1.39; 95% CI, 0.29–6.77; *KMT2C*m: HR, 2.03; 95% CI, 0.70–5.91). In contrast, EFS benefit was evident in pts with wild type (wt) (*KEAP1*wt: HR, 0.54; 95% CI, 0.36–0.79; *KMT2C*wt: HR, 0.52; 95% CI, 0.35–0.78). **Conclusions:** Exploratory analyses based on post-Sx MRD status and genomic analysis identified a small high-risk subgroup of pts with markedly worse prognosis with potentially reduced benefit from the AEGEAN regimen. Clinical trial information: NCT03800134. Research Sponsor: AstraZeneca.

LBA8010 **Rapid Oral Abstract Session**

Perioperative nivolumab (NIVO) vs placebo (PBO) in patients (pts) with resectable NSCLC: Updated survival and biomarker analyses from CheckMate 77T.

Tina Cascone, Mark M. Awad, Jonathan Spicer, Jie He, Shun Lu, Fumihiro Tanaka, Robin Cornelissen, Lubos B. Petruzelka, Hiroyuki Ito, Ludmila De Oliveira Koch, Lin Wu, Sabine Bohnet, Cinthya Coronado Erdmann, Stephanie Meadows-Shropshire, Jaclyn Neely, Amy Hung, Padma Sathyanarayana, Sumeena Bhatia, Mariano Provencio; The University of Texas MD Anderson Cancer Center, Houston, TX; Memorial Sloan Kettering Cancer Center, New York, NY; McGill University Health Centre, Montreal, QC, Canada; National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China; Shanghai Lung Cancer Center, Shanghai Chest Hospital, Shanghai Jiao Tong University, Shanghai, China; University of Occupational and Environmental Health, Kitakyushu, Japan; Erasmus MC Cancer Institute, Rotterdam, Netherlands; Charles University, Prague, Czech Republic; Kanagawa Cancer Center, Yokohama, Japan; Hospital Israelita Albert Einstein, Sao Paulo, Brazil; Hunan Cancer Hospital, Changsha, China; University Medical Center Schleswig-Holstein, Lübeck, Germany; Bristol Myers Squibb, Boudry, Switzerland; Bristol Myers Squibb, Princeton, NJ; Hospital Universitario Puerta de Hierro, Madrid, Spain

8011 Rapid Oral Abstract Session

ctDNA-based MRD detection in unresectable NSCLC undergoing curatively intended chemoradiotherapy and durvalumab.

Henrik Horndalsveen, Vilde Drageset Haakensen, Tesfaye Madebo, Bjorn Henning Gronberg, Tarje Onsøien Halvorsen, Jussi Koivunen, Kersti Oselin, Saulius Cicenas, Nina Helbekkmo, Marianne Aanerud, Jarkko Ahvonen, Maria Silvoniemi, Maria Moksnes Bjaanæs, Britina Kjuul Danielsen, Mari Børve, Tonje Sofie Dalen, Åsa Kristina Öjlert, Aslaug Helland; Oslo University Hospital, Department of Oncology and Department of Cancer Genetics, Oslo, Norway; Stavanger University Hospital, Stavanger, Norway; Department of Clinical and Molecular Medicine, NTNU, Norwegian University of Science and Technology, Trondheim, Norway and Department of Oncology, St. Olavs Hospital, Trondheim University Hospital, Trondheim, Norway; Department of Clinical and Molecular Medicine, NTNU, Norwegian University of Science and Technology and Department of Oncology, St. Olavs Hospital, Trondheim, Norway; Oulu University Hospital, University of Oulu and MRC Oulu, Oulu, Finland; North Estonia Medical Centre, Tallinn, Estonia; National Cancer Center, Affiliate of Vilnius University Hospital Santaros Klinikos, Vilnius, Lithuania; University Hospital of North Norway, Department of Pulmonology, Tromsø, Norway; Haukeland University Hospital, Department of Thoracic Medicine, Bergen, Norway; Tampere University Hospital, Tays Cancer Center, Department of Oncology, Tampere, Finland; Turku University Hospital (TYKS), Turku, Finland; Oslo University Hospital, Department of Oncology, Oslo, Norway; Oslo University Hospital, Department of Cancer Genetics, Oslo, Norway; University of Oslo, Clinical Medicine, Oslo, Norway

Background: Durvalumab consolidation after chemoradiotherapy (CRT) has improved clinical outcomes in patients with unresectable stage III non-small cell lung cancer (NSCLC). Despite durvalumab treatment, a substantial proportion of patients relapse, while up to 20% achieve long-term survival without durvalumab. Circulating tumor DNA (ctDNA)-based minimal residual disease (MRD) detection has shown promise as a tool for risk-adaptive and personalized treatment strategies in resectable NSCLC but is still underexplored as a biomarker in patients with stage III NSCLC treated with CRT and consolidative durvalumab. **Methods:** The DART study is a multicenter phase II clinical trial enrolling 86 patients with unresectable stage III NSCLC. All patients received two cycles of platinum-doublet chemotherapy concomitant with radiotherapy to a total dose of 60–66 Gy, followed by durvalumab. We prospectively collected serial plasma samples from all patients at baseline(before CRT), at the initiation of durvalumab (one month post-CRT), and at predefined timepoints during durvalumab treatment. Plasma samples were analyzed using a novel tumor-agnostic ctDNA MRD assay (MEDICOVER Genetics), tailored to each patient's cancer biomarker profile. This hybrid capture-based assay leverages genomic information in cell-free DNA from selected coding regions in 293 genes to classify plasma samples as positive ("ctDNA detected") or negative ("ctDNA not detected"). Here, we present results of the first MRD analysis conducted in the trial, involving a total of 138 plasma samples from 20 patients who completed all scheduled blood draws. **Results:** The baseline ctDNA detection rate was 91.8% in the entire study population and 73.7% in the 20 patients with completed longitudinal MRD analyses. Detectable ctDNA at baseline varied according to stage and histology and was not associated with PFS. Nine patients had detectable ctDNA in at least one plasma sample during the first four months after CRT, which was significantly associated with shorter progression-free survival (PFS) (HR: 4.7; 95% CI: 1.6–13.1; p = 0.004). When assessing specific timepoints, patients with detectable ctDNA four months post-CRT had shorter PFS compared to patients without detectable ctDNA at this timepoint (HR: 3.77; 95% CI: 1.32–10.74; p = 0.013). In contrast, detectable ctDNAone month post-CRT was not associated with shorter PFS (HR: 2.23; 95% CI: 0.78–6.36; p = 0.13). Preliminary overall survival data indicate that detectable ctDNA during the first four months post-CRT significantly increased the odds of death within 24 months (OR: 16.48; 95% CI: 1.29–1000.51; p = 0.017). **Conclusions:** Detection of ctDNA during consolidative durvalumab after CRT using a novel tumor-agnostic MRD assay was associated with inferior outcomes, demonstrating the potential of ctDNA as a biomarker to identify high-risk patients for tailored interventions. Clinical trial information: NCT04392505. Research Sponsor: Helse Sør-Øst RHF; AstraZeneca; Medicover Genetics.

8012 Rapid Oral Abstract Session

The preliminary results of a randomized phase II trial evaluating induction toripalimab plus chemotherapy followed by concurrent chemoradiotherapy and consolidation toripalimab in bulky unresectable stage III non-small-cell lung cancer (InTRist).

Yu Wang, Jianyang Wang, Lei Deng, Tao Zhang, Wenyang Liu, Yuqi Wu, Yongbo Xiang, Zhijie Wang, Nan Bi; Department of Radiation Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China; State Key Laboratory of Molecular Oncology, Department of Medical Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

Background: Unresectable stage III NSCLC patients with large tumor volumes remain challenging. Our previous retrospective study has showed promising results of induction chemo-immunotherapy before definitive chemoradiotherapy (CRT) for these patients. Here we report preliminary results of the randomized phase II study on this regimen. **Methods:** This InTRist study is a randomized, single-center, phase 2 trial, enrolling patients with unresectable stage III NSCLC with bulky diseases, and without *EGFR/ALK* alterations. Bulky diseases were defined as primary tumor ≥5 cm in greatest dimension or metastatic lymph nodes ≥2 cm in shortest diameter. Eligible patients were 1:1 randomly assigned to receive induction toripalimab (240 mg every 3 weeks) plus platinum-based doublet chemotherapy for 2 cycles (toripalimab group) versus induction chemotherapy alone for 2 cycles (chemo group) followed by concurrent CRT (60 Gy radiotherapy plus concurrent platinum-based chemotherapy). All patients without disease progression or grade ≥2 pneumonitis after CRT received consolidation toripalimab (240 mg every 3 weeks) for up to 12 months. Randomization was stratified according to histologic type. The primary endpoint was progression-free survival (PFS) from randomization. This trial is registered with ClinicalTrials.gov, NCT05888402. **Results:** BetweenJanuary 20th, 2023 and October 8th, 2024, 52 patients were randomized to induction toripalimab (n = 27) or chemo (n = 25) groups. By the data cutoff date (January 15th, 2025), the median follow-up was 13.1 months. Induction toripalimab plus chemotherapy exhibited significantly longer PFS compared to chemotherapy alone (median not reached [NR] vs NR; hazard ratio 0.25 [95% CI, 0.07-0.90], *P*=0.034). The 12-month PFS rate was 89.4% (95% CI, 76.0%-100%) in the toripalimab group and 57.8% (95% CI, 40.7%-81.9%) in the chemo group. Objective response rate after induction therapy was 77.8% (21/27) for the toripalimab group and 40.0% (10/25) for the chemo group (median tumor reduction 32% vs 21%). Grade 2 pneumonitis occurred in 26.9% (14/52) of all patients, with 18.5% (5/27) in the toripalimab group and 36.0% (9/25) in the chemo group. Grade 3 pneumonitis occurred in 7.7% (4/52) of all patients, with 11.1% (3/27) in the toripalimab group compared to 4.0% (1/25) in the chemo group. No grade 4-5 pneumonitis. **Conclusions:** Induction toripalimab plus chemotherapy, followed by concurrent CRT and consolidation toripalimab, demonstrated potentially improved short-term efficacy and manageable toxicity for patients with bulky unresectable stage III NSCLC. Further follow-up is necessary to confirm these results. Clinical trial information: NCT05888402. Research Sponsor: Chinese Academy of Medical Sciences (CAMS) Innovation Fund for Medical Sciences; 2024-I2M-C&T-B-065.

8013 Rapid Oral Abstract Session

Safety and efficacy of lurbinectedin plus atezolizumab as second-line treatment for advanced small-cell lung cancer: Results of the 2SMALL phase 1/2 study (NCT04253145).

Santiago Ponce Aix, Alejandro Navarro, Maria Eugenia Olmedo Garcia, Laura Mezquita, Margarita Majem, David Vicente, Reyes Bernabé, Alba Moratiel Pellitero, Manuel Cobo, Javier De Castro, Silverio Ros, Marta Lopez Brea, Rosario Garcia Campelo, Javier Baena, Helena Bote, Mercedes Herrera, Pedro Rocha, Jon Zugazagoitia, Enriqueta Felip, Luis G. Paz-Ares; Hospital Universitario 12 de Octubre and Oncosur Foundation, Madrid, Spain; Hospital Clinic de Barcelona, Barcelona, Spain; Departamento de Oncología Médica, Hospital Ramon Y Cajal, Madrid, Spain; Hospital Clinic of Barcelona, Barcelona, Spain; Santa Creu i Sant Pau, Barcelona, Spain; Hospital Universitario Virgen Macarena, Seville, Spain; Hospital Universitario Virgen del Rocío, Seville, Spain; Hospital Clinico Lozano Blesa, Zaragoza, Spain; Hospital civil (Hospital Regional Universitario de Málaga), Málaga, Spain; Hospital La Paz, Madrid, Spain; Virgen de la Arrixaca University Hospital, Murcia, Spain; Hospital Universitario Marqués de Valdecilla, Santander, Spain; University Hospital A Coruna HRS4R Universia gal, A Coruña, Spain; Hospital Universitario 12 de Octubre, Madrid, Spain; Hospital Universitario 12 De Octubre, Madrid, Spain; Medical Oncology Department, Vall d'Hebron University Hospital and Vall d'Hebron Institute of Oncology, Barcelona, Spain; Vall d'Hebron University Hospital, Barcelona, Spain; Hospital Universitario 12 de Octubre, Universidad Complutense de Madrid, Madrid, Spain

Background: Small-cell lung cancer (SCLC) is an aggressive malignancy, accounting for 13% of all lung cancers, with a 5-year survival rate below 12%. Relapsed SCLC remains a major therapeutic challenge, underscoring the need for innovative second-line treatments. The combination of lurbinectedin (LUR) plus atezolizumab (ATZ) has shown synergy in immuno-competent models, and clinical feasibility in a phase I trial. Here we evaluate the efficacy and safety of the regimen as second line treatment for SCLC patients. **Methods:** This prospective, open-label, multicenter study enrolled patients with ECOG PS 0-1, measurable disease by RECIST 1.1, and progression after one prior platinum-based chemotherapy alone (cohort 1 - C1) or combined with PD-1/ PD-L1 blockade (cohort 2 - C2). Key inclusion criteria included a chemotherapy-free interval (CTFI) of ≥30 days, adequate organ function. Treated brain metastases previously managed with radiotherapy were permitted. Patients received LUR (3.2 mg/m^2 i.v. 1 hour infusion) following ATZ (1200 mg i.v. 30–60 minutes infusion) on day 1, every 3 weeks. Primary G-CSF prophylaxis was administered for 5 days. The primary endpoint was overall response rate (ORR) per RECIST v1.1. Secondary endpoints included progression-free survival (PFS), overall survival (OS), and safety. **Results:** Between June 2022 and March 2024, 218 patients were screened, and 151 were enrolled: 68 in C1 and 83 in C2. The median age was 64 years (range: 45–79), with 58% being male. Most patients (73%) had an ECOG 1, and 60.92% had a CTFI of ≥90 days. Efficacy results are summarized in Table 1. The combination was well-tolerated, with no unexpected safety signals. Treatment-emergent adverse events (TEAEs) were reported in 91% of patients. Grade ≥3 hematological toxicities included neutropenia (C1: 16.18%; C2: 7.23%), febrile neutropenia (C1: 2.94%; C2: 2.41%) and thrombocytopenia (C1: 8.82%; C2: 1.20%). Treatment- emergent deaths occurred in 7 patients (C1: 4; C2: 3). **Conclusions:** The combination of LUR and ATZ showed promising efficacy in patients with relapsed SCLC regardless of prior exposure to immunotherapy, including those with resistance to platinum. The associated safety profile is manageable. The regimen is being evaluated in a phase III trial in the maintenance setting (IMforte trial NCT05091567). Clinical trial information: NCT04253145. Research Sponsor: None.

	Cohort 1 (n=68)	Cohort 2 (n=83)	CTFI<90 (n=59)	CTFI≥90 (n=92)
Overall Response, % (95% CI)	44.12 (32.27-56.63)	37.35 (27.18-48.7)	35.59 (23.87-49.20)	43.48 (33.30-54.20)
CR, n (%)	3 (4.41%)	1 (1.20%)	0 (0.00%)	4 (4.35%)
PR, n (%)	27 (39.71%)	30 (36.14%)	21 (35.59%)	36 (39.13%)
SD, n (%)	21 (30.88%)	25 (30.12%)	20 (33.90%)	26 (28.26%)
Median PFS (months), n (95%CI)	4.90 (3.87-7.27)	4.43 (3.27-5.17)	4.77 (3.27-5.90)	4.63 (3.60-6.13)
Median OS (months), n (95%CI)	11 (9.37-15.07)	9.53 (7.90-12.87)	10.10 (8.17-11.97)	11 (8.67-15.07)

Clinical and molecular characteristics of early progressors (EPs) and long-term progression-free survivors (LTPs) from the phase 3 ADRIATIC trial of consolidation durvalumab (D) vs placebo (P) after concurrent chemoradiotherapy (cCRT) in limited-stage small-cell lung cancer (LS-SCLC).

David Allen Barbie, Mingchao Xie, Maria Broggi, Ying Cheng, David R. Spigel, Byoung Chul Cho, Jian Fang, Yuanbin Chen, Yoshitaka Zenke, Ki Hyeong Lee, Qiming Wang, Alejandro Navarro, Eva Lotte Buchmeier, Mustafa Özgüroğlu, Christine L. Hann, Jocelyn Chen, Wei-Chu Victoria Lai, Yashaswi Shrestha, Suresh Senan; Lowe Center for Thoracic Oncology, Dana-Farber Cancer Institute, Boston, MA; AstraZeneca, Waltham, MA; AstraZeneca, Gaithersburg, MD; Department of Thoracic Oncology, Jilin Cancer Hospital, Changchun, China; Sarah Cannon Research Institute Oncology Partners, Nashville, TN; Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, South Korea; Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Department II of Thoracic Oncology, Peking University Cancer Hospital & Institute, Beijing, China; Cancer & Hematology Centers of Western Michigan, Grand Rapids, MI; National Cancer Center Hospital Japan East, Kashiwa, Japan; Chungbuk National University Hospital, Cheongju, Korea, Republic of; The Affiliated Cancer Hospital of Zhengzhou University & Henan Cancer Hospital, Zhengzhou, China; Hospital Vall d'Hebron and Vall d'Hebron Institute of Oncology, Barcelona, Spain; Hospitals of the City of Cologne gGmbH, Cologne, Germany; Istanbul University Cerrahpasa, Cerrahpasa Faculty of Medicine, Istanbul, Turkey; Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins School of Medicine, Baltimore, MD; AstraZeneca, Mississauga, ON, Canada; AstraZeneca, New York, NY; Amsterdam University Medical Centers, Vrije Universiteit Amsterdam, Cancer Center Amsterdam, Amsterdam, Netherlands

Background: At the first planned interim analysis of ADRIATIC, consolidation D significantly improved the dual primary endpoints of overall and progression-free survival (PFS) vs P in patients (pts) with LS-SCLC and no progression after cCRT. We assess clinical characteristics, patterns of progression, and associated molecular biomarkers in EPs (pts with PFS <6 mos) and LTPs (PFS or censored after >12 mos) in the D and P arms. **Methods:** Pts with stage I–III LS-SCLC, WHO performance status (PS) 0/1, and no progression after cCRT were randomized to D (n=264), D + tremelimumab (n=200; arm still blinded), or P (n=266) for up to 24 months. Pre-cCRT tumor samples were collected at screening and immune-related biomarkers (CD8, MHC I, PD-L1, T-cell inflamed signature [TIS], *CD8A*, and STING pathway) were assessed by immunohistochemistry or RNA sequencing for their role in response to immunotherapy (IO). **Results:** At data cutoff (15 Jan 2024), 83 (31.4%) and 113 (42.8%) pts in the D arm and 97 (36.5%) and 100 (37.6%) in the P arm were EPs and LTPs, respectively. For EPs and LTPs, respectively: 67.5% and 61.1% in the D arm and 74.2% and 72.0% in the P arm were male; 44.6% and 54.9% in the D arm and 51.5% and 48.0% in the P arm had WHO PS 0; and 90.4% and 89.4% in the D arm and 91.8% and 89.0% in the P arm were current/former smokers. Among EPs, 47.0% vs 45.4% had extrathoracic (ET) only progression, 43.4% vs 43.3% had intrathoracic (IT) only progression, and 6.0% vs 1.0% died without progression in the D vs P arms, respectively. Among LTPs, 16.8% and 25.0% of pts in the D and P arms had progression events, which were mostly IT (D: 14.2%; P: 16.0%). Similar rates of PD-L1+ tumors were observed in EPs and LTPs in both arms (Table). Trends for higher TIS and STING pathway expression were seen in LTPs vs EPs in the D arm but not the P arm. CD8 density, and *CD8A* and MHC I expressions were lower in EPs vs LTPs in both arms, regardless of D vs P (Table). **Conclusions:** Exploratory analyses suggest similar rates of IT and ET progression with D and P in EPs, but mostly IT progression in LTPs. Compared with EPs, LTPs were generally characterized by a pre-cCRT tumor microenvironment more conducive to fostering an IO response, with higher antigen presentation and cytotoxic marker expression potentially enhancing D's mechanism of action. Clinical trial information: NCT03703297. Research Sponsor: AstraZeneca.

	D, EPs	P, EPs	D, LTPs	P, LTPs
PD-L1 TC or IC ≥1%, n (%)	25 (52.1)	32 (55.2)	40 (56.3)	42 (61.8)
MHC I n, median TC score* (%)	42, 65.0	46, 75.0	66, 77.5	56, 80.0
CD8 density n, median cells/mm^2	39, 46.7	43, 50.7	57, 94.2	53, 78.7
RNASeq BEP, n	17	27	29	24
***CD8A* expression†**	1.1	1.1	1.3	1.7
TIS value†	2.3	3.1	3.2	3.4
STING signature value†	0.28	1.4	0.90	1.4

*% MHC I-positive TCs in the total tumor area.
†Median.
BEP, biomarker-evaluable population; TC, tumor cell; IC, immune cell.

8015 Rapid Oral Abstract Session

Alectinib as neoadjuvant treatment in potentially resectable stage III ALK-positive NSCLC: Final analysis of ALNEO phase II trial (GOIRC-01-2020-ML42316).

Alessandro Leonetti, Luca Boni, Letizia Gnetti, Diego Luigi Cortinovis, Giulia Pasello, Francesca Mazzoni, Alessandra Bearz, Francesco Gelsomino, Francesco Passiglia, Sara Pilotto, Giulio Metro, Angelo Delmonte, Fabiana Letizia Cecere, Federica Bertolini, Luca Toschi, Hector Soto Parra, Serena Ricciardi, Emilio Bria, Michele Tognetto, Marcello Tiseo; University Hospital of Parma, Parma, Italy; Clinical Epidemiology Unit, IRCCS Ospedale Policlinico San Martino, Genoa, Italy; Pathology Unit, University Hospital of Parma, Parma, Italy; SC Oncologia medica Fondazione IRCCS San Gerardo dei Tintori, Università degli Studi Milano-Bicocca, Milan, Italy; Department of Surgery, Oncology and Gastroenterology, University of Padova Medical School; Medical Oncology 2, Veneto Institute of Oncology IOV-IRCCS, Padua, Italy; Medical Oncology Unit, Careggi University Hospital, Florence, Italy; Department of Medical Oncology, CRO-IRCCS National Cancer Institute Aviano, Aviano, Italy; Medical Oncology, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy; Department of Oncology, University of Turin, San Luigi Hospital, Orbassano, Italy; Section of Oncology, Department of Engineering for Innovative Medicine, University of Verona, Verona, Italy; Division of Medical Oncology, Santa Maria della Misericordia Hospital, University of Perugia, Perugia, Italy; Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori "Dino Amadori" (IRST), Meldola, Meldola, Italy; Regina Elena National Cancer Institute, IRCCS, Rome, Italy; Department of Oncology, Modena University Hospital, Modena, Italy; Medical Oncology, IRCCS Humanitas Research Hospital, Rozzano, Italy; Medical Oncology, Policlinico Vittorio Emanuele, Catania, Italy; Pneumo-Oncology Unit, San Camillo-Forlanini Hospital, Rome, Italy; UOSD Oncologia Toraco-Polmonare, Comprehensive Cancer Center, Fondazione Policlinico Universitario Agostino Gemelli IRCCS; Medical Oncology, Department of Translational Medicine and Surgery, Università Cattolica del Sacro Cuore, Rome, Italy; Gruppo Oncologico Italiano di Ricerca Clinica, GOIRC, Parma, Italy; Department of Medicine and Surgery, University of Parma; Medical Oncology Unit, University Hospital of Parma; Gruppo Oncologico Italiano di Ricerca Clinica, GOIRC, Parma, Italy

Background: Stage III Non-Small Cell Lung Cancer (NSCLC) is a heterogeneous group of tumors with a wide spectrum of clinical presentations and no single definitive therapeutic approach. The role of neoadjuvant alectinib in stage III ALK-positive NSCLC is still unclear. Here, we present the final analysis of the phase II, open-label, single-arm, multicenter study aimed at investigating the activity and safety of alectinib in potentially resectable locally advanced stage III ALK-positive NSCLC patients (ALNEO trial, EUDRACT number 2020-003432-25). **Methods:** Treatment-naïve patients with potentially resectable stage III ALK-positive NSCLC, ECOG PS≤1 were registered to receive neoadjuvant alectinib for 2 cycles (8 weeks) followed by surgery and adjuvant alectinib for 24 cycles (96 weeks). The primary endpoint was major pathological response (MPR) by Blinded Independent Central Review (BICR). Secondary endpoints included pathological complete response (pCR) by BICR, objective response (OR), event-free survival (EFS), disease-free survival (DFS), overall survival (OS) and adverse events (AEs). According to the Simon's design (P0=20%, P1=40%), 18 and 33 patients were required for the first and second stage, respectively. **Results:** A total of 33 patients were registered in 20 Italian Oncology Centers from May 2021 to July 2024. Median age was 62 years (Interquartile Range [IQR], 49–74 years), 23 (70%) patients were female and 17 (52%) were never smokers. Clinical stage according to the 8th AJCC TNM was IIIA in 21 (64%) and IIIB in 12 (36%) patients. The most represented stage was T3N2 (n=8, 24%), followed by T1aN2 (n=4, 12%), T2aN2 (n=4, 12%), T4N0 (n=4, 12%) and T4N2 (n=4, 12%). All the patients completed the neoadjuvant phase and 28 (85%) underwent surgery, which consisted of lobectomy in 21 (64%), pneumonectomy in 3 (9%) and other surgery in 4 (12%) patients. Among patients who completed surgery, R0 was achieved in 24 (86%) patients. According to the BICR, MPR was documented in 15 (46%, 90% Confidence Interval [CI]: 31%–61%) patients and pCR in 4 (12%, 95% CI: 3%–28%) patients. Overall, an OR was observed in 22 (67%) patients. Adjuvant treatment was started in 26 (79%) patients with a median interval from surgery of 5.1 weeks (IQR, 3.6–6.0 weeks). After a median follow-up of 15.2 months (IQR, 6.8–27.8 months), 31 (94%) patients were alive and 5 (19%) patients completed the adjuvant treatment. Median EFS and OS were not reached. A total of 6 (18%) patients experienced disease progression/recurrence. Grade≥3 AEs occurred in 3 (9%) and 2 (8%) patients during neoadjuvant and adjuvant phase, respectively. **Conclusions:** ALNEO study met its primary endpoint, suggesting alectinib as a feasible peri-operative option in resectable locally advanced stage III ALK-positive NSCLC patients. The study was partially supported by Roche S.p.A. Clinical trial information: NCT05015010. Research Sponsor: Roche S.p.A.

8016 Rapid Oral Abstract Session

Efficacy and safety of nivolumab plus ipilimumab for patients with pre-treated type B3 thymoma and thymic carcinoma: Results from the EORTC-ETOP NIVOTHYM phase II trial.

Nicolas Girard, Benjamin Besse, Michaël Duruisseaux, Laurent Greillier, Thierry Berghmans, Nuria Pardo, Sanjay Popat, Radj Gervais, Santiago Ponce Aix, Annelies Janssens, Sjaak Burgers, Joachim Aerts, Julien Mazieres, Yvonne J. Summers, Anne-Claire Toffart, Anne-sophie Govaerts, Eleni Xenophontos, Luc Boone, Solange Peters; Institut du Thorax Curie Montsouris, Institut Curie, Paris, and UVSQ, Paris Saclay University, Versailles, France; Department of Medical Oncology, Gustave Roussy, Paris Saclay University, Paris, France; URCOT, Hôpital Louis Pradel, Hospices Civils de Lyon Cancer Institute, Lyon, France; APHM, Hôpital Nord, Service d'Oncologie Multidisciplinaire & Innovations Thérapeutiques, Marseille, France; Institut Jules Bordet, Hôpital Universitaire de Bruxelles, Brussels, Belgium; Medical Oncology, Vall d´Hebron University Hospital/Vall d´Hebron Institute of Oncology (VHIO), Barcelona, Spain; The Royal Marsden NHS Foundation Trust, London, United Kingdom; Pneumology, Centre Francois Baclesse, Caen, France; Département d'Innovation Thérapeutique et Essais Précoces, Gustave Roussy; Hospital Universitario 12 de Octubre; Fundación OncoSur, Madrid, Spain; Antwerp University Hospital, Edegem, Belgium; The Netherlands Cancer Institute, Amsterdam, Netherlands; Erasmus University Medical Center, Rotterdam, Netherlands; CHU de Toulouse, Université Paul Sabatier, Toulouse, France; Christie NHS Foundation Trust, Manchester, United Kingdom; Pulmonary Unit, Grenoble-Alpes University Hospital, Grenoble, France; EORTC Headquarters, Brussels, Belgium; EORTC HQ, Sint-Lambrechts-Woluwe, Belgium; EORTC Headquaters, Brussels, Belgium; Lausanne University Hospital, Lausanne, Switzerland

Background: Thymic malignancies represent a therapeutic challenge in the advanced, metastatic setting, with limited options after the failure of platinum-based chemotherapy. **Methods:** NIVOTHYM is a multicenter phase II, 2-cohort, single-arm trial evaluating the use of nivolumab (N)+/-ipilimumab (I) in patients ≥18yo, with advanced/relapsed type B3 thymoma or thymic carcinoma (TC), after previous exposure to platinum-based chemotherapy.Primary endpoint wasProgression-Free Survival (PFS) rate at 6 months based on RECIST1.1 per independent radiological review. We report the results of cohort 2 with patients who received N 240 mg Q2W and I 1mg/kg Q6W. **Results:** From Feb 2021 to Jan 2023, 56 patients – 8 (14%) with type B3 thymoma, 48 (86%) with TC - were enrolled in 15 centers/5 countries, of which 37 (66%) men/19 (34%) women. Median age was 64 years. 23 (41%) patients had had surgery. After a median follow-up of 16.0 months, 50 patients had discontinued N+I for: progression in 36 (72%) pts, treatment-related adverse events (TRAEs) in 11 (22%) pts, completion in 2 (4%) pts, and pt decision for 1 pt (2%). Maximal grade of adverse events was 1/2 in 29 (52%) patients, and 3/4 in 27 (48%) patients. Grade ≥3 TRAEs occurred in 16 (29%) pts: myocarditis (2 pts), colitis (4 pts), infusion-related reaction/allergy (2 pts), skin rash (2 pts), heart failure, immune-related hepatitis, arthritis, myositis, hypophysitis, Gougerot Sjogren syndrome, pharyngitis, fatigue, fever, infusion-related reaction (1 pt each); there was no grade 5 TRAE. PFS rate at 6 months was 21.6%. Objective Response and Disease Control Rates were 17.7% and 60.8%, respectively. Median PFS and Overall Survival were 3.2 (95%CI 2.1-3.6) and 22.0 (95%CI 16.6-NR) months, respectively; median duration of response was 7.1 (95%CI 1.4-17.0) months, and 8 (14%) pts received treatment for ≥12 months. **Conclusions:** N+I demonstrated limited efficacy in advanced thymic tumors, as prespecified PFS rate at 6 months of 40% was not reached, compared to the previously reported cohort 1 of this trial with N as single-agent. Numerically more patients experienced grade ≥3 TRAEs, while efficacy endpoints were not numerically higher. Clinical trial information: NCT03134118. Research Sponsor: None.

8017 Rapid Oral Abstract Session

Integrin $\alpha_V\beta_3$-targeted imaging for identification of lung cancer and mapping of lymph-node metastases: A prospective, multicenter, self-controlled phase 3 trial (TRIIL study).

Zhaohui Zhu, Shaoli Song, Xuemei Wang, Shi Gao, Xiaoli Lan, Zhi Yang, Jun Xin, Xiangsong Zhang, Xiaohong Ou, Jianjun Liu, Sijin Li, Naixin Liang, Huimin Sui, Guozhu Hou, Rongxi Wang, Hannan Gao, Haojun Chen, Hongda Chen, Fan Wang; Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China; Fudan University Shanghai Cancer Center, Shanghai, China; The Affiliated Hospital of Inner Mongolia Medical University, Hohhot, China; China-Japan Union Hospital of Jilin University, Changchun, China; Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China; Peking University Cancer Hospital, Beijing, China; Shengjing Hospital of China Medical University, Shengyang, China; The First Affiliated Hospital, Sun Yat-sen University, Guangzhou, China; West China Hospital of Sichuan University, Chengdu, China; Renji Hospital of Shanghai Jiao Tong University, Shanghai, China; The First Hospital of Shanxi Medical University, Taiyuan, China; Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China; Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China; Institute of Biophysics, Chinese Academy of Sciences, Beijing, China; The First Affiliated Hospital of Xiamen University, Xiamen, Fujian, China; Peking Union Medical College Hospital, Beijing, China; Peking University, Beijing, China

Background: Integrin $\alpha_V\beta_3$ mediates tumor formation, invasion, metastasis and angiogenesis. ^{99m}Tc-3PRGD2, a first-in-class radiopharmaceutical targeting integrin $\alpha_V\beta_3$, was advanced into a phase 3 clinical trial for evaluation of lung cancer via single photon emission computed tomography (SPECT)/computed tomography (CT), with mapping the lymph-node metastases as the primary objective. **Methods:** A prospective, multicenter, phase 3 trial of ^{99m}Tc-3PRGD2 SPECT/CT enrolled 409 patients with solid lung lesions $\geq 1.5\times1.0$ cm in high suspicion of lung cancer (TRIIL; ClinicalTrials.gov identifier: NCT04233476; chinadrugtrials.org.cn identifier: CTR20191465). A self-controlled design was used for a head-to-head comparison with the conventional metabolic imaging via F-18 fluorodeoxyglucose (^{18}F-FDG) positron emission tomography (PET)/CT. The primary outcome was to define the superiority of diagnostic specificity of ^{99m}Tc-3PRGD2 SPECT/CT over that of ^{18}F-FDG PET/CT in assessment of lymph-node metastases of lung cancer. The secondary outcomes included the other diagnostic values and safety. **Results:** No severe adverse event was observed in 407 patients with complete safety data. In 268 patients with pathological diagnosis of the lung tumors, no significant difference was found between ^{99m}Tc-3PRGD2 SPECT/CT and ^{18}F-FDG PET/CT for detection of lung malignancies (sensitivity, 96% vs 98%, P = 0.083). In 259 patients with pathological diagnosis of 1601 lymph-node stations, ^{99m}Tc-3PRGD2 SPECT/CT demonstrated superiority over ^{18}F-FDG PET/CT in the diagnostic specificity (74% vs 50%, $P < 0.001$) and accuracy (70% vs 55%, $P < 0.001$) for mapping the lymph-node metastases station-by-station, with a relatively lower sensitivity (55% vs 75%, $P < 0.001$) mainly due to spatial resolution limitation of the current SPECT systems. In a semi-quantitative analysis of the tumor-to-background ratios in each method, the areas under the receiver operating characteristic curves were 0.69 for ^{99m}Tc-3PRGD2 SPECT/CT and 0.63 for ^{18}F-FDG PET/CT (P = 0.13), respectively, for discriminating lymph-node stations with and without metastasis. In a case-by-case analysis, the integrin $\alpha_V\beta_3$-targeting ^{99m}Tc-3PRGD2 SPECT/CT corrected the false-positive diagnosis of ^{18}F-FDG PET/CT in 344 lymph-node stations from 152 (59%) of the 259 patients, providing more accurate evaluation of lymph-node metastasis in 116 (45%) patients, whereas ^{18}F-FDG PET/CT held better diagnosis of the lymph-node involvement only in 40 (15%) patients. **Conclusions:** This trial substantiates the advantages of the integrin imaging for mapping the lymph-node metastases of lung cancer, and paves the way for ^{99m}Tc-3PRGD2 SPECT/CT to be evolved into a universally accessible and cost-efficient technique for tumor diagnosis and staging, and further towards precise therapy. Clinical trial information: NCT04233476. Research Sponsor: None.

Assessment of survival benefit with immunotherapy in combination with adjuvant chemoradiation in pathologic stage II-IIIB non-small cell lung cancer.

Natasha Venugopal, Jorge Raul Vazquez Urrutia, Junjia Zhu, Asato Hashinokuchi, Shinkichi Takamori, Takefumi Komiya; Penn State Health Milton S. Hershey Medical Center, Hershey, PA; Department of Public Health Sciences, Penn State Health Milton S. Hershey Medical Center, Hershey, PA; Department of Surgery and Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan; Department of Thoracic and Breast Surgery, Oita University Faculty of Medicine, Yufu, Japan; Penn State Cancer Institute, Hershey, PA

Background: Since the Food and Drug Administration (FDA) approvals in 2021 and 2023, atezolizumab and pembrolizumab, respectively, became standard management for curatively resected stage II-III non-small cell lung cancer (NSCLC) based on improved disease-free survival. Because these studies excluded the planned use of adjuvant radiation therapy, survival benefit of adding immune checkpoint inhibitor (ICI) in those who are treated with adjuvant chemoradiation (CT+RT) have never been assessed. **Methods:** Using National Cancer Database (NCDB), we identified 8,235 cases that were completely resected, pathologic stage II-IIIB NSCLC per AJCC 8th edition and survived for at least 1 month without neoadjuvant CT or RT. Due to the timing of FDA approval and availability, only cases diagnosed in 2021 were investigated. They have been assigned into groups based on types of adjuvant treatments. Kaplan-Meier methods and multi-variable Cox regression models were used for survival analysis. Propensity Score Matching (PSM) was performed to compare groups (adjuvant CT+RT+ICI vs CT+RT). A p-value of <0.05 was considered statistically significant. **Results:** Consistent with previous clinical trials, addition of ICI to adjuvant CT improved overall survival (OS) (2-year OS 90.1% vs 86.0%, Univariate and Multivariate HRs 0.72 and 0.66, p=0.0024 and 0.0003, respectively). However, no OS benefit was seen in those who received adjuvant CT+RT (2-year OS 77.8% vs 76.1%, Univariate and Multivariate HRs 0.83 and 0.85, p=0.3677 and 0.4369, respectively). PSM analysis showed similar results (2-year OS 77.8% vs 79.6%, Univariate and Multivariate HRs 0.91 and 0.87, p=0.7143 and 0.5868, respectively). **Conclusions:** Our retrospective real-world analysis suggests that adjuvant ICI do not improve survival outcome when combined with adjuvant CT+RT. This result appears to mirror recent negative trials using concurrent use of ICI with CT+RT in unresectable stage III NSCLC (PACIFIC2) and limited-stage SCLC (NRG-LU005). Further investigations are warranted. Research Sponsor: None.

Overall survival of p-stage II-IIIB NSCLC treated with designated therapy regimens.

Groups	Adjuvant CT+ICI	Adjuvant CT	Adjuvant CT+RT+ICI	Adjuvant CT+RT
N	3,549	878	132	375
2-year OS (month)	90.1%	86.0%	77.8%	76.1%
Univariate HR (95%CI)	0.72 (0.57-0.89)		0.83 (0.55-1.23)	
p-value (Log-rank)	0.0034		0.3744	

Real world characteristics of stages II-III NSCLC patients (pts) who initiate neo-adjuvant chemo-immunotherapy (NACT-I) and do not undergo surgical resection.

Jair Bar, Giuseppe Domenico Maiocco, Kaushal Parikh, Talia Shentzer Kutiel, Walid Shalata, Sivan Shamai, Mor Moskovitz, Chul Kim, Muskan Agarwal, Alfredo Addeo, Arianna Marinello, Damien Urban, Stanislav Bahlai, Dina Laznik, Idan Tsadok, Hadas Gantz Sorotsky; Jusidman Cancer Center, Sheba Medical Center, Ramat Gan, Israel; Mayo Clinic, Rochester, MN; Oncology Department, Rambam Health Care Campus, Haifa, Israel; Soroka Medical Center, Beer Sheva, Israel; Tel Aviv Sourasky Medical Center, Tel Aviv, Israel; Davidoff Cancer Center, Beilinson Medical Center, Petah Tikva, Israel; Georgetown University, Washington, DC; MedStar Georgetown University Hospital, Washington, DC; Oncology Department, University Hospital Geneva Switzerland, Geneva, Switzerland; Gustave Roussy Cancer Center, Villejuif, France; Hadassah Medical Center, Jerusalem, Israel

Background: Neoadjuvant and perioperative chemo-immunotherapy studies report 15%-20% of pts initiating NACT-I do not undergo surgical resection. **Methods:** Real-world data of pts who initiated NACT-I was collected retrospectively for January 1st 2022 till September 30th 2024. Pts and treatment details, reason for not undergoing resection (as assessed by the clinicians) and later treatments and outcomes were recorded. Total number of pts who initiated NACT-I in this period was identified from each center's records. Missing data was not imputed. **Results:** Data was collected from 10 centers in 4 countries (USA, Israel, Switzerland, France). Out of 330 pts that started NACT-I 43 pts (13%; range 4-33% in different centers) did not undergo surgical resection. Of these 43 pts, 34.9% became unresectable due to disease progression (PD). 20.9% in retrospect were non-resectable and did not regress as expected. 11.6% in retrospect were non-operable. 11.6% suffered toxicity and became unfit for surgery. 7% of pts refused surgery, 14% were not resected for other reasons (Table). Of the non-resected pts, 9.3% died prior to any second-line treatment. As a second line, 44.2% of the non-resected pts were treated with chemo-radiation, 14% with radiation alone, 7% chemotherapy and immunotherapy, 4.7% immunotherapy alone and 2.3% chemotherapy alone. 7% received palliative radiation followed by chemo or immunotherapy, 7% had follow-up alone. **Conclusions:** The rate of no surgical resection in this real-world multi-national cohort was 13%, in line with the rate in reported studies. Most un-resected pts underwent appropriate staging. Most were male, with high rate of T3/T4. Survival rate at 12 months was 73.7%. The most common causes for no surgery were PD or being upfront unresectable. The patients with the worst outcome were those who experienced PD during NACT-I. Research Sponsor: None.

	N (% out of 43 non-resected)	Male (%)	Age (median)	PET Done prior to any therapy (%)	Brain MRI staging (%)	Documented MDT decision of NACT-I (%)	Documented surgeon evaluation prior to NACT-I decision (%)	T3-4 (%)	N2a/b (9th V TNM; %)	Survival rate at 12 month (95% CI)
	43 (100.0)	69.8	71	95.3	95.0*	96.6*	86.2*	69.8	40.5	73.7% (50.5-87.2%)
PD	15 (34.9)	80.0	67	93.3	100.0*	100.0*	92.3*	80.0	40.0	68.2% (14.2-89.7%)
In retrospect not resectable	9 (20.9)	55.6	69	100.0	100.0	100.0*	50.0*	77.8	33.3	76.2% (33.2-93.5%)
In retrospect not operable	5 (11.6)	80.0	71	100.0	60.0	100.0*	33.3*	40.0	20.0	100.0% (100.0-100.0%)
Toxicity	5 (11.6)	80.0	72	100.0	100.0	100.0*	100.0*	80.0	80.0	80.0% (20.4-96.9%)
Patient refusal	3 (7.0)	0.0	72	100.0	100.0	100.0	100.0	66.7	33.3	100% (100.0-100.0%)
Other **	6 (14.0)	83.3	75	83.3	100.0*	75.0*	100.0	50.0	40.0*	50.0% (11.1-80.4%)

Percentages relate to the total of each row, besides 1st column relating to total of 43.
*% of available data.
**Death (n=3), intra-operative decision (n=2), additional malignancy (n=1).

8021 Poster Session

Adjuvant icotinib of 12 months versus observation as adjuvant therapy for completely resected EGFR-mutated stage IB non-small-cell lung cancer: 5-year update from CORIN (GASTO1003).

Si Yu Wang, Hao Jiang, Wei Ou, Bao-Xiao Wang, Teng-Fei Zhu, Zeng-Hao Chang, Xin-Xin Hu; Shenshan Medical Center, Sun Yat-sen Memorial Hospital, Shanwei, China; Sun Yat-sen University Cancer Center, Guangzhou, China; Sun Yat-sen Memorial Hospital, Guangzhou, China

Background: In the phase II CORIN trial,adjuvant therapy of icotinib for 1-year shows prolonged disease-free survival (DFS) and acceptable toxicity in patients with completely resected epidermal growth factor receptor (EGFR)-mutated stage IB non-small-cell lung cancer (NSCLC). Here, we report the 5-year survival update from this study. **Methods:** In the phase II, open-label, randomized CORIN trial, patients with completely resected, EGFR-mutated, stage IB (7th TNM staging) NSCLC without adjuvant chemotherapy according to physician and patient choice were randomly assigned in a 1:1 ratio to receive icotinib (125mg, three times daily, 12 months) or undergo observation. Therapy continued until disease recurrence or intolerable toxicity. The primary endpoint was DFS. Secondary endpoints included overall survival (OS) and toxicity. **Results:** Of 128 enrolled patients, 63 received icotinib and 65 underwent observation. At the December 20 2024 database lock, the median follow-up was 65.0 (95% confidence interval [CI], 58.4-71.5) months. A total of 30 recurrence events had occurred, including 9 in the icotinib arm and 21 in the observation arm. Icotinib for 1 year continued to improve DFS versus observation, with the 5-year DFS of 88.5% and 67.7%, respectively (log-rank P=0.012, hazard ratio [HR], 0.38; 95%CI: 0.18-0.83). Icotinib showed a marginal OS improvement versus observation (log-rank P=0.045, HR, 0.15; 95%CI: 0.02-1.27). The 5-year OS was 98.3% in the icotinib group and 90.5% in the observation group. No new safety signals were observed at this update. Additional efficacy outcomes will be presented. **Conclusions:** In this 5-year update analysis from CORIN, adjuvant icotinib continues to demonstrate durable DFS benefit versus observation in resected EGFR-mutated stage IB NSCLC, with a manageable safety profile. Icotinib sustained OS separation versus observation over time and demonstrated a marginal OS benefit, which is limited by the small sample size and wide CIs. Adjuvant icotinib for 1 year provides a treatment option for these patients. Clinical trial information: NCT02264210. Research Sponsor: None.

IMpower010: Genomic profiling and clinical outcomes with adjuvant atezolizumab in early-stage non-small cell lung cancer (eNSCLC).

Heather A. Wakelee, Enriqueta Felip, Caicun Zhou, Eric Vallieres, Martin Reck, Nasser K. Altorki, Achim Rittmeyer, Tibor Csőszi, Ihor O. Vynnychenko, Antonio Chella, Velimir Gayevskiy, Wei Zou, Barbara Jenifer Gitlitz, Marcus Ballinger, Elizabeth Bennett, Barzin Y. Nabet, Minu K. Srivastava; Stanford University School of Medicine/Stanford Cancer Institute, Stanford, CA; Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; Tongji University Affiliated Shanghai Pulmonary Hospital, Shanghai, China; Swedish Cancer Institute, Seattle, WA; LungenClinic Grosshansdorf, German Center for Lung Research, Grosshansdorf, Germany; NewYork-Presbyterian Hospital, Weill Cornell Medicine, New York, NY; LKI Lungenfachklinik Immenhausen, Immenhausen, Germany; Oncology Department, Jász-Nagykun-Szolnok County Hospital, Szolnok, Hungary; Sumy State University, Sumy, Ukraine; Pneumology Unit, Azienda Ospedaliero Universitaria Pisana, Pisa, Italy; Genentech, Inc., South San Francisco, CA; Genentech Inc., South San Francisco, CA

Background: In metastatic NSCLC (mNSCLC), genomic alterations (MUT) are well studied and have led to the development of efficacious new drugs. However, the association of MUT in the adjuvant setting in eNSCLC is not as well understood. Here, we describe an exploratory, retrospective analysis of genomic profiling by whole exome sequencing and clinical association in IMpower010. **Methods:** Whole exome sequencing was done on baseline tumor samples and germline DNA from whole blood from the biomarker-evaluable population (n=623). Multiple MUT were identified in the full population, including by histology. Disease-free survival (DFS) and overall survival (OS) were assessed in the most common gene subgroups. **Results:** The distribution of MUT and co-occurrence patterns were similar to expected non-squamous and squamous patterns in mNSCLC, except for lower prevalence of *STK11* (17%) and *KEAP1* (12%) MUT. In non-squamous disease, *STK11*, *EGFR*, and *KEAP1* MUT were associated with increased prevalence in PD-L1–negative tumors, and *TP53* MUT with PD-L1–positive tumors (adjusted $P<0.1$). *KRAS* MUT were associated with Stage II; *STK11* MUT were associated with Stage I more than with Stages II and III (adjusted $P<0.1$). Increased enrichment of *KRAS*, *STK11*, *KEAP1*, and *TP53* MUT was seen in those with previous or current smoking status, and *EGFR* MUT were enriched in those who never smoked (adjusted $P<0.1$). In non-squamous disease, *STK11* MUT were a poor prognostic for OS but not DFS, whereas *KEAP1* MUT were not significantly associated with poor prognosis for DFS or OS (Table). Neither *STK11* or *KEAP1* MUT were significantly associated with differential atezolizumab vs best supportive care DFS or OS benefit (interaction $P>0.05$). **Conclusions:** This analysis represents the largest dataset evaluating the genomic profile of patients with eNSCLC who were treated with cancer immunotherapy. The prevalences of *STK11* and *KEAP1* MUT were lower than in mNSCLC and were enriched for PD-L1–negative in non-squamous NSCLC. Unlike in mNSCLC, patients with tumors that harbored *KEAP1* MUT did not have poor prognosis in IMpower010. Data are hypothesis generating and require validation in independent eNSCLC datasets with larger numbers. Clinical trial information: NCT02486718. Research Sponsor: Genentech, Inc.; Medical writing assistance for this abstract was provided by Nimisha H. Bhoola, PhD, of Nucleus Global, an Inizio Company, and funded by F. Hoffmann-La Roche Ltd.

***STK11* and *KEAP1* associations with DFS and OS in combined arms (non-squamous).**

		***STK11* MUT**	***STK11* WT**	***KEAP1* MUT**	***KEAP1* WT**
	n	71	342	49	364
DFS	Median, mo	43.1	41.8	45.3	41.8
	HR (95% CI)	1.03 (0.73, 1.46)		0.91 (0.60, 1.39)	
OS	Median, mo	NR	NR	NR	NR
	HR (95% CI)	1.66 (1.10, 2.52)		1.08 (0.63, 1.85)	

CI, confidence interval; mo, month; NR, not reached; WT, wild type.

8023 Poster Session

Evaluating the role of consolidative chest radiotherapy after chemo-immunotherapy in extensive-stage small cell lung cancer: A retrospective study.

Jorge Raul Vazquez Urrutia, Natasha Venugopal, Junjia Zhu, Joseph Miccio, Mitch Machtay, Takefumi Komiya; Penn State Health Milton S. Hershey Medical Center, Hershey, PA; Department of Public Health Sciences, Penn State Health Milton S. Hershey Medical Center, Hershey, PA; Penn State Hershey Medical Center, Hershey, PA; Penn State Milton S. Hershey Medical Center, Hershey, PA; Penn State Cancer Institute, Hershey, PA

Background: Consolidative chest radiotherapy (XRT) after chemoimmunotherapy may provide benefits in extensive-stage small cell lung cancer (ES-SCLC) due to the condition's high sensitivity to radiation. Current guidelines suggest chest XRT for ES-SCLC patients who respond to chemotherapy, given its association with improved 2-year overall survival (OS), and reduced progression and recurrence rates. However, its role in the era of chemo-immunotherapy in ES-SCLC remains unclear. **Methods:** Data from the National Cancer Database (NCDB) for ES-SCLC patients diagnosed between 2017 and 2020 were analyzed (n=24,676). Cases included those treated with multi-agent chemotherapy, with data for T, N, and M status, and chest XRT. Exclusion criteria included survival <30 days, limited-stage SCLC cases, and missing key data elements. The primary outcome was OS from diagnosis, analyzed using Kaplan-Meier and multivariate Cox regression models. Propensity Score Matching (PSM) was performed to compare outcomes in ES-SCLC patients receiving chest XRT after immunotherapy versus immunotherapy alone, adjusting for T, N, and M status, institution, sex, and CD score. A p-value of <0.05 was considered statistically significant. **Results:** The study stratified patients in two groups: 10,437 immunotherapy receivers and 14,239 not receiving immunotherapy. The proportion of chest XRT receivers was similar across both groups (13% vs. 14%, p=0.17). Receipt of XRT was significantly associated with younger age (<70), female sex, T3-4 stage, N2-N3, and M1a status; (p<0.05). Chest XRT was associated with a significant increase median OS in both groups: immunotherapy (13.1 months vs. 9.8 months; p<0.001) and non-immunotherapy (11.6 months vs. 8.4 months; p<0.001). XRT was an independent predictor of better OS in both groups after controlling for other covariates (HR 0.72 and 0.66; p<0.001). PSM analysis of 1,399 patients receiving XRT and 1,399 receiving immunotherapy alone confirmed the OS benefit of XRT after immunotherapy (13.1 months vs. 9.4 months; HR 0.63, p<0.001) with a 3-year survival of 16% (95%CI: 13.7-18.3%) vs 7% (95% CI: 5.3-8.7%), respectively. **Conclusions:** Our analysis shows that consolidative chest XRT is associated with improved overall survival in patients with ES-SCLC, especially when combined with chemoimmunotherapy. These findings are hypothesis-generating and support ongoing randomized studies evaluating consolidative radiotherapy in the chemoimmunotherapy era. Research Sponsor: None.

Multivariable Cox regression analyses for overall survival in ES-SCLC.

Factor	Immunotherapy +	Immunotherapy -
	HR (95% CI)	HR (95% CI)
Chest XRT (Yes/No)	0.72 (0.68-0.77)	0.67 (0.64-0.71)
p-value	P<0.0001	P<0.0001

ES, extensive stage; SCLC, small cell lung cancer; HR, hazard ratio; CI, confidence interval; Ref, reference; CD, Charlson-Deyo; XRT, radiation.

Ensartinib as postoperative adjuvant therapy in patients with ALK-positive non-small cell lung cancer (NSCLC): A registered, retrospective, real-world study.

Lin Wang, Jing Zhang, Sihua Wang, Siyuan Dong, Xiaoming Qiu, Lei Zhao, Zhongyuan Yin, Kong-Jia Luo, Changfa Qu, Xiangning Fu, Baogang Liu, Junfeng Wang, Yang Xue, Sai Zhang, Liang Yu, Renhua Guo, Jialong Guo, Ruilin Song, Lanjun Zhang, Yuankai Shi; National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing Key Laboratory of Clinical Study on Anticancer Molecular Targeted Drugs, Beijing, China; Department of Thoracic Surgery, the Chinese People's Liberation Army General Hospital, Beijing, China; Department of Thoracic Surgery, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China; Department of Thoracic Surgery, The First Hospital of China Medical University, Shenyang, China; Department of Lung Cancer Center, West China Hospital, Sichuan University, Chengdu, China; Department of Thoracic Surgery, The First Affiliated Hospital of Dalian Medical University, Dalian, China; Department of Thoracic Surgery, Sun Yat-sen University Cancer Center, Guangzhou, China; Department of Thoracic Surgery, Harbin Medical University Cancer Hospital, Harbin, China; Department of Thoracic Surgery, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China; Department of Thoracic Surgery, Sichuan Provincial People's Hospital, Chengdu, China; Department of Thoracic Surgery, The Second Affiliated Hospital of Zhejiang University, Hangzhou, China; Department of General Thoracic Surgery, The General Hospital of Ningxia Medical University, Yinchuan, China; Department of Oncology, Jiangsu Provincial People's Hospital, Nanjing, China; Department of Thoracic, Cardiac, and Great Vessel Surgery, Shiyan Taihe Hospital, Shiyan, China; China Pharmaceutical Innovation Promotion Association, Beijing, China

Background: Ensartinib has been approved as ALK-positive locally advanced/metastatic NSCLC, but its role in adjuvant therapy remains unknown. This real-world study aimed to evaluate the efficacy and safety of ensartinib as adjuvant therapy in ALK-positive NSCLC. **Methods:** Data were retrospectively collected from "Ensacove Patient Assistance Program" held by Betta pharmaceutical company. The patients who were ≥18 years-old and had completely resected, histologically confirmed stage I-III NSCLC as classified according to the eighth edition of AJCC/UICC, were documented ALK-positive, and had at least one post-baseline CT scan. The primary endpoint is 2-year disease-free survival (DFS) rate. Secondary endpoints include DFS, safety and OS. **Results:** From November 19, 2020, to May 31, 2024, a total of 296 patients were screened. 222 patients were enrolled. The median age was 55 years-old. 128 females. 98 (44.1%) were stage I, 42 (18.9%) were stage II, 82 (36.9%) were stage III. 98.2% were lung adenocarcinoma. Thirty-two patients (14.4%) received postoperative chemotherapy. The median duration of ensartinib treatment was 25.3 (95% confidence intervals [CI], 3.1-47.2) months. At the data-cutoff date of December 29, 2024, median follow-up time was 23.5 months (95% CI, 21.7-26.2). The median DFS was immature. The 2-year DFS rate was 92.1% (95% CI, 86.6%-95.5%) for all patients, and 89.3% (95% CI, 77.9%-95.0%), 100.0% (95% CI, NR-NR) and 91.0% (95% CI, 80.6%-95.9%) for patients with stage I, stage II, and stage III, respectively. 16 patients had disease recurrence or death, including 7 patients with local recurrence and 9 patients with distant metastasis. The OS data was immature with only 2 deaths occurred. The treatment-related adverse events (TRAEs) of any grade occurred in 169 patients (76.1%), and 11 patients (5.0%) experienced ≥grade 3 TRAEs. The most common TRAEs were rash (60.8%). Serious TRAEs were 8 (3.6%) patients. TRAEs led to dose reductions, dose interruptions and permanent discontinuation were 21.2%, 9.0% and 3.2% of the patients, respectively. No deaths due to TRAEs were reported. **Conclusions:** To our knowledge, this real-world study has the largest sample size on postoperative adjuvant therapy with ALK inhibitors. In this real-world setting, ensartinib demonstrated encouraging efficacy and well-tolerated safety profile among stage IA1-IIIB ALK-positive NSCLC, providing a potential adjuvant therapy option in this patient population. Research Sponsor: None.

8025 Poster Session

Molecular profiling of neoadjuvant immunochemotherapy and identification of residual cancer cells in pCR NSCLC: A single-cell analysis of CTONG 1804 clinical trial.

SiYang Maggie Liu, Song Dong, Si-Yang Liu, Xue-Ning Yang, Ri-qiang Liao, Ben-Yuan Jiang, Xiao-song Ben, Jun-Tao Lin, Hong-Hong Yan, Lixu Yan, Qiang Nie, HaiYan Tu, Bin-Chao Wang, Jinji Yang, Qing Zhou, Wei-Chi Luo, Chen Huang, Jiayan Wu, Wenzhao Zhong, Yi-Long Lung Cancer Wu; Guangdong Lung Cancer Institute, Guangdong Provincial People's Hospital (Guangdong Academy of Medical Sciences), Southern Medical University, Guangzhou, China; Guangdong Lung Cancer Institute, Guangzhou, Guangdong, China; Guangdong Lung Cancer Institute, Guangdong Provincial People's Hospital (Guangdong Academy of Medical Sciences), Southern Medical University, Guangzhou, Guangdong, China; Guangdong Provincial People's Hospital (Guangdong Academy of Medical Sciences), Southern Medical University, Guangzhou, China; Department of Pathology, Guangdong Provincial People's Hospital (Guangdong Academy of Medical Sciences), Southern Medical University, Guangzhou, Guangdong, China; Guangdong Lung Cancer Institute, Guangdong Provincial People's Hospital (Guangdong Academy of Medical Sciences), Southern Medical University, Guangzhou, Guangdong, China; Kanghui Biotech Co. LTD, Beijing, China

Background: Previously, we reported the clinical findings of stage-one enrollment from a phase II trial of neoadjuvant immunochemotherapy (IO) in untreated patients with resectable non-small cell lung cancer (NSCLC) (CTONG1804, NCT04015778). Recently, two-stage enrollment has been completed. This trial provided an opportunity to investigate the correlation of pathological response and early immune microenvironment during neoadjuvant IO. **Methods:** We conducted single-cell RNA sequencing (scRNA-seq) on fresh tumor tissue of 21 patients at pre- and post-IO treatment. Multi-omics sequencing was also used in this exploratory study, that included bulk RNA sequencing and tumor-informed MRD sequencing. **Results:** The pathological complete response (pCR) rate was 42.9% (9/21). Unexpectedly, a total of 143 cancer cells with genome alterations were identified in six (6/9=66.7%) patients with pCR. Only one pCR patient presented MRD positive within one month after surgery, who had the highest number of cancer cells. These residual cancer cells exhibited reduced proliferative capacity and diminished stem cell-like features but retained epithelial-mesenchymal transition (EMT) markers, suggesting metastatic potential and drug resistance. Elevated antigen presentation pathways, particularly involving CD74-MHC class II, were observed in pCR cancer cells, alongside a significant reduction in tumor neoantigen burden. When comparing the immune cells of different pathological response, we found that conventional dendritic cell type 2 (cDC2) emerged as a critical antigen-presenting cell subtype in pCR patients, enhancing T-cell activation and promoting immune response. Reduced CD4-Treg3 populations correlated with improved treatment outcomes, while CD8-MAIT cells exhibited functional plasticity, transitioning from tumor-promoting to tumor-rejecting phenotypes post-therapy. **Conclusions:** Our study highlights the persistence of residual cancer cells even in pCR patients and identifies key immune cell subsets, such as cDC2 and CD8-MAIT cells, that play pivotal roles in modulating anti-tumor response. These findings provide valuable insights into the mechanisms of immune activation and suppression in NSCLC and suggest potential biomarkers and therapeutic targets for optimizing neoadjuvant immunochemotherapy. Clinical trial information: NCT04015778. Research Sponsor: None.

Molecular profiling and survival in oncogene-addicted resected stage IIIAN2 non-small cell lung cancer (NSCLC): A study from the Lung ART IFCT 0503 trial.

Victor Albarran-Artahona, Benjamin Besse, Ludovic Lacroix, Wael Zrafi, Diego Díaz-Jiménez, Maria Rosa Ghigna, Guillaume Granier, Nathalie Cozic, Emilie Bouvier-Morel, Julien Adam, Cecile Le Pechoux, Antonin Levy; Department of Cancer Medicine, Gustave Roussy, Villejuif, France; Gustave Roussy, Villejuif, France; Department of Medical Biology and Pathology, Gustave Roussy, Villejuif, France; Department of Biostatistics and Bioinformatics, Gustave Roussy, Villejuif, France; Department of Biology and medical pathology, Gustave Roussy, Villejuif, France; Service de Pathologie, Centre Hospitalier Henri-Duffaut, Avignon, France; Biostatistics Unit, Gustave Roussy, Villejuif, France; Bureau de Biostatistique et d'Epidémiologie, Gustave Roussy, Villejuif, France; Department of Anatomopathology, Marie-Lannelongue Hospital, Le Plessis-Robinson, France; Department of Radiation Oncology, Gustave Roussy, Villejuif, France

Background: Molecular profiling is standard-of-care in metastatic NSCLC and increasingly important in earlier stages as personalized approaches arise. The role of adjuvant radiotherapy (ART) in oncogene-addicted, fully-resected stage IIIAN2 NSCLC remains undefined. **Methods:** The LungART trial (NCT00410683) randomized 501 patients (pts) with resected stage IIIAN2 NSCLC (AJCC 7th ed.) to ART or observation. No disease-free survival (DFS) benefit was found for ART. For consenting pts, a tumor block was collected. A histological central review was performed in all cases. Molecular profiling was conducted by Whole transcriptome sequencing (WTS; mRNA capture with Agilent exome lit and Illumina NovaSeq 6000 S4 Reagent Kit v1.5-300 cycles paired sequencing) to identify relevant alterations, with findings treated as per standard procedures. **Results:** 282 pts had available samples, from which 50% received ART. 90% were current or former smokers. Baseline characteristics were well balanced (table 1). After review, 79% of pts were classified as non-squamous cell carcinoma. *TP53* was the most common mutation (mut) identified (46%). Targetable mutations included *KRAS* p.G12C (8.8%), *EGFR*-sensitizing -exon 19 in-frame deletion and L858R mut- (3.5%), and *BRAF* p.V600 (1.4%). Non p.G12C *KRAS* mut were found in 28 pts, while atypical *EGFR* mut including exon 20 insertion, and non V600 *BRAF* were identified in 3.1% and 2.8% of pts, respectively. A *ERBB2* exon 20 insertion mut was identified in one case. *STK11* and *KEAP1* mutation were identified in 5.3% and 3.5% of pts, respectively. No translocations were detected. In the *STK11* mut subgroup, a significant difference in DFS (p=0.032) and OS (p=0.0043) was observed. No differences in outcomes were observed for other major molecular alterations nor between treatment arms, including *TP53* (p=1.0 and 0.86 for DFS and OS, respectively). **Conclusions:** Our study did not found a significant outcomes difference among major oncogenic-driven alterations, probably due to population characteristics and small representation of oncogene addicted subgroups. Our findings confirm *STK11* as a poor prognostic factor in resected stage IIIAN2 NSCLC. Of note, *TP53* did not show any impact on survival. Further studies are needed to confirm these observations and explore its implications. Research Sponsor: None.

Baseline characteristics.

Characteristic	ART N=141	Observation N=139
Age	61 (54-68)	61 (55-66)
Gender		
Female	44 (31%)	42 (30%)
Male	97 (69%)	97 (70%)
Neoadj. ChT	22 (16%)	23 (17%)
Adj. ChT	120 (85%)	120 (86%)
Smoking		
Current	16 (11%)	14 (10%)
Former	110 (78%)	112 (81%)
Never	15 (11%)	13 (9.4%)
Major molecular alterations		
TP53	67 (47%)	65 (46%)
***KRAS* p.G12C**	16 (11%)	9 (6.4%)
***KRAS* non-p.G12C**	14 (9.9%)	14 (10%)
***EGFR* sensitizing**	4 (2.8%)	6 (4.3%)
***EGFR* (others)**	3 (2.1%)	6 (4.3%)
STK11	6 (4.3%)	9 (6.5%)
KEAP1	6 (4.3%)	4 (2.9%)
***BRAF* p.v600**	0 (0%)	3 (2.1%)
***BRAF* non-p.V600**	6 (4.2%)	3 (2.1%)

LBA8027 **Poster Session**

An international, multicenter, prospective randomized trial of adjuvant chemotherapy for stage Ia-IIa non-small cell lung cancer identified as high-risk by a 14-gene molecular assay.

David R. Spigel, Virginie Westeel, Ian Churchill Anderson, Laurent Greillier, Florian Guisier, Olivier Bylicki, Firas Benyamine Badin, Gaelle Rousseau-Bussac, Clotilde Deldycke, Frank Griesinger, Adam Bograd, Wangjian Zhong, Matthew A. Gubens, John Crowley, Heiko von der Leyen, Gavitt Alida Woodard, Johannes Ruediger Kratz, David Jablons, Michael Mann; Sarah Cannon Research Institute Oncology Partners, Nashville, TN; CHU Besançon, Hôpital J. MINJOZ, Service de Pneumologie, Besançon, France; Providence Medical Center, Santa Rosa, CA; Assistance Publique Hôpitaux de Marseille (AP-HM), Marseille, France; Hospital Center University De Rouen (CHU Rouen), Rouen, France; HIA Sainte Anne, Toulon, France; Baptist Healthcare System, Inc., Lexington, KY; Centre Hospitalier Intercommunal De Creteil, Créteil, France; Hôpital de la Milétrie - Centre Hospitalier Universitaire de Poitiers, Poitiers, France; Pius-Hospital Oldenburg, Oldenburg, Germany; Swedish Cancer Institute, Seattle, WA; Baptist Health Lagrange, Prospect, KY; University of California, San Francisco, San Francisco, CA; Cancer Research and Biostatistics (CRAB), Seattle, WA; Conreso, Hanover, Germany; Yale School of Medicine, New Haven, CT

8028 Poster Session

A panel of four protein tumor markers for effective and affordable lung cancer early detection by artificial intelligence.

Mao Mao, Bing Wei, Wenjian Wang, Peng shuai Geng, Wei Wu, Yu chen Ding, Dandan Zhu, Yao Shuo Cheng, Qiu rong Zhao, Yi Luan, Shiyong Li; Research & Development, SeekIn Inc, San Diego, CA; Henan Cancer Hospital, The Affiliated Cancer Hospital of Zhengzhou University, Zhengzhou, China; Guangdong Provincial Key Laboratory of Malignant Tumor Epigenetics and Gene Regulation, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, Guangzhou, China. Department of Thoracic Surgery, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, Guangzhou, China; Clinical Laboratories, Shenyou Bio, Zhengzhou, China; Research & Development, SeekIn Inc., Shenzhen, China; Sun Yat-sen Memorial Hospital, Guangzhou, China

Background: Lung cancer is the most common and deadly malignancy worldwide. While low-dose computed tomography (LDCT) reduces mortality in high-risk populations, its high false-positive rate and the required specialized infrastructure and radiologists limit its application. This study assesses LungCanSeek, a novel blood-based protein test for lung cancer early detection. **Methods:** This study enrolled 1,814 participants (1,095 lung cancer, 719 non-cancer) from three independent cohorts. Blood samples were analyzed for four protein tumor markers (PTMs) using Roche cobas. Artificial intelligence (AI) algorithms were developed for lung cancer detection and subtype classification (lung adenocarcinoma (LUAD), lung squamous cell carcinoma (LUSC), and small cell lung cancer (SCLC)). A two-step lung cancer screening approach was modeled, using LungCanSeek for initial screening, followed by LDCT for LungCanSeek's positive cases. **Results:** LungCanSeek showed 83.5% sensitivity, 90.3% specificity, and 86.2% accuracy overall. Sensitivities of LUAD, LUSC, and SCLC were 83.3%, 81.4%, and 91.9%. Sensitivity increased with clinical stage in non-small cell lung cancer (NSCLC): 59.5% (I), 69.8% (II), 86.5% (III), and 91.3% (IV). Sensitivities of limited- and extensive-stage SCLC were 91.3% and 93.0%. The subtype classification accuracy was 77.4%. Compared with the other blood-based lung cancer early detection tests like OncImmune's EarlyCDT-Lung (41.0% sensitivity, 91.0% specificity) and DELFI's FirstLook-Lung (84.1% sensitivity, 50.9% specificity), LungCanSeek's performance was superior. LDCT had 93.1% sensitivity and 76.5% specificity in NLST study. A screening was modeled for 9 million high-risk adults, based on the number of 15 million eligible individuals in the USA in 2024 at a 60% rate, with a 1.2% lung cancer incidence. While LungCanSeek reduced false positives by 2.4-fold to 862,524 compared to 2,089,620 with LDCT, the two-step approach further lowered false positives by 10.3-fold to just 202,693. Additionally, LDCT's total cost was $2,493 million, exceeding LungCanSeek's $720 million by 3.5-fold and two-step's $978.5 million by 2.5-fold. **Conclusions:** LungCanSeek is a non-invasive, easy to perform, cost-effective (reagent cost $15) and robust test for lung cancer early detection. It also provides accurate subtype prediction that may guide patients' clinical management and monitor subtype switching during treatment. The two-step approach not only effectively reduces LDCT's high false positives but also yields substantial economic benefits, making it a cost-effective strategy for population-wide lung cancer screening. Research Sponsor: None.

8029 Poster Session

Genomic characterization of STAS in stage 1 EGFR-mutated NSCLC and prognostic implications.

Stephanie Pei Li Saw, Mengyuan Pang, Clare Patteri, Angela M. Takano, Ngak Leng Sim, Jia Chi Yeo, Gillianne Lai, Darren Wan-Teck Lim, Ravindran Kanesvaran, Mei-Kim Ang, Quan Sing Ng, Amit Jain, Wan Ling Tan, Aaron C. Tan, Wei Chong Tan, Amanda Oon Lim Seet, Boon-Hean Ong, Tony Kiat Hon Lim, Anders Skanderup, Daniel Shao-Weng Tan; Division of Medical Oncology, National Cancer Centre Singapore, Singapore, Singapore; Genome Institute of Singapore, Singapore, Singapore; Department of Pathology, Singapore General Hospital, Singapore, Singapore; Division of Medical Oncology, National Cancer Centre Singapore, Singapore, Singapore, Singapore; National Heart Centre Singapore, Singapore, Singapore

Background: Spread through air spaces (STAS) is a poor prognostic factor and was recently introduced as a histologic descriptor in the TNM edition 9 for stage 1 lung cancer. While STAS-positivity (STAS+) is known to be associated with adenocarcinoma, the molecular epidemiology and determinants of STAS+ specific to epidermal growth factor receptor-mutated lung cancer (EGFRm) and prognostic implications remain unknown. **Methods:** Consecutive patients from National Cancer Centre Singapore diagnosed with AJCC8 stage 1 lung adenocarcinoma with minimum 3 years follow up post-surgery and known EGFR and STAS status (+ or -) were included. Fresh frozen tumour and normal samples were subject to whole exome sequencing (WES) at 400X and 100X coverage respectively, with 50 million paired-end reads for RNA-seq per sample. PD-L1 expression by immunohistochemistry was scored using SP263. Wilcoxon and Fisher's exact tests were used for association analysis and Kaplan Meier method for survival. **Results:** Between 1/1/16-31/12/21, 300 patients were included (203 EGFRm; 97 EGFR-wildtype (EGFRwt)). While the incidence of STAS+ was similar between EGFRm and EGFRwt (49.8% versus (vs) 56.7%, p=0.316), 5-year disease-free survival (DFS) was significantly worse for STAS+ vs STAS- EGFRm (67.8% vs 93.2%, p=0.005) but not EGFRwt (78.9% vs 82.0%, p=0.6). Comparing STAS+ and STAS- EGFRm, there was no significant difference in the proportion of never-smokers (77.2% vs 76.4%, p=0.248) and females (52.5% vs 60.8%, p=0.292). Distribution of EGFR mutation subtype was also similar (ex19del 43.6% vs 41.2%; L858R 37.6% vs 44.1%; others 18.8% vs 14.7%, p=0.576). Lymphovascular invasion (LVI) (20.8% vs 3.9%, $p<0.001$) and high histological grade (32.7% vs 4.0%, $p<0.001$) were significantly more common in STAS+ vs STAS- EGFRm. Among EGFRm, 193 patients had available WES and RNA-seq. Incidence of TP53 co-mutations (60.7% vs 43.2%, p=0.020) and whole genome doubling (WGD) (34% vs 17%, p=0.013) was significantly more common among STAS+ than STAS- tumours. No other significant differences in co-mutations or copy number alterations were observed. The proportion of PD-L1 expression ≥1% (42.3% vs 21.2%, p=0.011) and non-TRU transcriptomic subtype (55.9% vs 22.2%, $p<0.001$) were also significantly higher in STAS+ compared to STAS- tumours. Controlling for stage (1A vs 1B), age, smoking status, gender, histological grade and LVI, STAS+ remained an independent predictor of inferior DFS in stage 1 EGFRm (hazard ratio: 4.0, 95% confidence interval: 1.1-15.2, p=0.04). **Conclusions:** Despite a similar incidence, STAS+ independently predicts for inferior DFS in patients with stage 1 EGFRm but not EGFRwt. STAS+ stage 1 EGFRm demonstrate a higher frequency of *TP53* co-mutations, WGD, non-TRU subtype and PD-L1≥1% as compared to STAS- stage 1 EGFRm. Our findings highlight the molecular determinants of STAS+ and support STAS as a risk stratification factor for stage 1 EGFRm. Research Sponsor: National Medical Research Council of Singapore.

8030 Poster Session

Genomic and immunophenotypic landscape of early-stage pulmonary carcinoid tumors.

Song Xu, Dingzhi Huang, ChunXia Su, Ning Zhou, Lingling Zu, Jingya Wang, Xiongfei Li, Haixiang Yu; Tianjin Medical University General Hospital, Tianjin, China; Department of Thoracic Oncology, Tianjin Key Laboratory of Cancer Prevention and Therapy, Tianjin Medical University Cancer Institute and Hospital, National Clinical Research Center for Cancer, Tianjin's Clinical Research Center for Cancer, Tianjin, China; Oncology Department, Shanghai Pulmonary Hospital, Shanghai, China; Tianjin Medical University Cancer Institute and Hospital, Tianjin, China; Shanghai Chest Hospital, Shanghai, China; China-Japan Union Hospital of Jilin University, Changchun, China

Background: Pulmonary carcinoids (PCs), which encompass atypical carcinoids (ACs) and typical carcinoids (TCs), represent a rare category of lung cancer characterized by low to moderate malignancy. However, there is a limited understanding of the genomic and immune characteristics associated with PCs on a global scale. **Methods:** This study included a cohort of 126 surgically resectable Chinese PC patients, comprising 44 ACs and 82 TCs. Next-generation sequencing utilizing a 578-gene panel was conducted on 90 of PC patients, followed by the calculation of tumor mutation burden (TMB). Additionally, immunohistochemical staining for PD-L1 (n=108) and CD8 (n=94) was carried out to investigate the characteristics of the tumor microenvironment in PCs. **Results:** The most frequently altered genes in early-stage PCs were identified as *EGFR* (n=16, 18%), *KMT2C* (n=11, 12%), *LRP1B* (n=10, 11%), *MEN1* (n=10, 11%), and *NOTCH2* (n=9, 10%). Dysregulation of the RTK/RAS, NOTCH, and PI3K pathways was commonly observed in these PCs. Notably, genetic alterations in TP53, ARID1A, and CUL3 were more prevalent in ACs compared to TCs. However, TMB, PD-L1 expression, and CD8+ T cell infiltration were found to be low in early-stage PCs, with no significant differences observed between ACs and TCs. We identified age, gender, TNM stage, tumor type, smoking status, TMB, and *LRP1B* mutation, as indicators of poor prognosis, and further established a molecular classification that categorizes early-stage PCs into three distinct subtypes, each associated with varying clinical outcomes. **Conclusions:** We depicted the genetic and immune landscape of early-stage PCs and subsequently proposed a molecular classification based on the status of *LRP1B* mutation and smoking history. Our research offers novel insights into the biological mechanisms of PCs which contributes to the individualized treatment for Chinese PC patients.
Research Sponsor: None.

Association of 8-gene signature with early recurrence in resected non-small cell lung cancer.

Arsalan A. Khan, Kelly M. Cagin, Savan K. Shah, Wara Naeem, Minha Ansari, Oluwamuyiwa Adebayo, Gillian Alex, Nicole M. Geissen, Michael J. Liptay, Jeffrey Allen Borgia, Christopher W. Seder; Rush University Medical Center, Chicago, IL; RUSH University Medical Center, Chicago, IL; Rush University, Chicago, IL

Background: Limited evidence exists defining a genetic signature associated with early-recurrence in patients with non-small cell lung cancers (NSCLC). This study aims to identify a genomic panel associated with early recurrence, defined as recurrence within 12 months from surgery. **Methods:** Patients with resected pT1-2aN0 NSCLC that underwent tumor RNA sequencing at a single institution from 2010-2021 were included. Exclusion criteria included neoadjuvant therapy, unknown pN status, and no recurrence. Differential gene expression (DGE) analysis was performed using DESeq2 after count normalization, identifying 50 genes with a log2 fold change > 1 or < -1 and an adjusted p-value<0.05. Recursive feature elimination (RFE) with random forests was applied to evaluate subsets of genes, utilizing repeated 10-fold cross-validation to ensure robust performance estimation. Accuracy and model stability were compared across subsets to identify the gene panel most strongly associated with early recurrence. Cross-validation was performed using a secondary RFE random forest analysis optimized for AUC, to refine the gene selection process. A multivariable logistic regression analysis was conducted to examine the association between the gene panel and early recurrence, while controlling for potential confounders. **Results:** 118 patients met study criteria, of whom 54% (64/118) were female, 82% (97/118) had adenocarcinomas, and 59% (70/118) underwent lobectomy. The median tumor size was 1.8 cm (IQR 1.5–2.6). Early recurrence was observed in 25.4% (30/118). DGE analysis involved 61.4% (27,009/43,959) of genes. After filtering for low total counts, using an FDR <0.1, 2% (530/27,009) were upregulated and 1.3% (351/27,009) downregulated in patients with early recurrence. After RFE with random forests, an 8-gene panel was selected, including *ART3*, *SLC51A*, *SNAP25*, *CCNA1*, *GRK1*, *GPR63*, *CNTNAP2*, and *TNFRSF11B* achieving an accuracy of 71.7%. The panel had an area under the curve (AUC) of 79.1, sensitivity of 93.9%, and specificity of 33.3%. On multivariable logistic regression, after adjusting for tumor size, histology, surgical procedure, pack years, and number of nodes sampled, and performance status, patients with differential expression of four or more genes within the panel were associated with early recurrence (OR: 4.11, 95% CI:1.27–13.31, p=0.02). **Conclusions:** A unique tumoral 8-gene signature is associated with early recurrence in resected early-stage NSCLC patients. Research Sponsor: None.

Univariable and multivariable logistic regression analysis examining predictors of early recurrence.

Variable	Unadjusted OR (95% CI)	*p-value*	Adjusted OR (95% CI)	*p-value*
≥ 4 of the 8 Gene Panel	**4.17 (1.46–11.88)**	**0.01**	**4.11 (1.27–13.31)**	**0.02**
Tumor Size	1.39 (0.86–2.26)	0.18	**2.22 (1.10–4.46)**	**0.03**
Histology				
Adenocarcinoma	Ref		Ref	
Squamous Cell Carcinoma	1.22 (0.42–3.49)	0.72	0.58 (0.14–2.41)	0.46
Surgical Resection				
Anatomic	Ref		Ref	
Sub-anatomic	1.82 (0.78–4.29)	0.17	1.85 (0.48–7.09)	0.37
Pack-Years	1.00 (0.99–1.02)	0.61	1.01 (0.99–1.03)	0.22
Performance Status >0	1.21 (0.52–2.77)	0.66	0.91 (0.82–1.03)	0.13
Number of nodes sampled	**0.91 (0.83-0.99)**	**0.04**	1.27 (0.45–3.54)	0.65

Study on optimizing serum-based lung cancer diagnosis using a multi-biomarker approach.

Hyejin Sung, Jinsu Lee, Sukki Cho, Sojin Jung, Sungwon Shin; Beyonddx, Gwangmyeong, South Korea; Beyonddx, Gyeonggi-Do, South Korea; Seoul National University Bundang Hospital, Seongnam, South Korea; Beyonddx, Gyeonnggi-Do, South Korea

Background: Lung cancer remains the leading cause of cancer-related mortality, largely due to the challenges in early diagnosis. Elevated levels of serum carcinoembryonic antigen (CEA), serum amyloid A (SAA), and osteopontin (OPN) have been reported in various cancers. However, the diagnostic efficiency of these biomarkers as a combined panel for lung cancer detection is not well understood. This study evaluates the diagnostic value of combining these three biomarkers for lung cancer screening. **Methods:** Serum samples from 1,429 lung cancer patients and 1,000 healthy donors were analyzed for CEA, SAA, and OPN levels to assess their diagnostic accuracy. The data were divided into three independent cohorts: a development set, a training set, and a validation set. The diagnostic performance of each individual biomarker and the combined multi-biomarker panel was evaluated. **Results:** In the discovery set, the most influential variables in the support vector machine model were OPN, SAA, CEA, in that order, while the least influential were NSE, SCC, CYFRA. The optimized multi-biomarker panel comprising SAA, CEA, and OPN, with a cut-off value of 0.61, demonstrated sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of 83.59%, 90.10%, 93.16%, and 77.29%, respectively, in the training set. Validation confirmed robust performance with sensitivity of 81.21%, specificity of 86.86%, PPV of 90.87%, and NPV of 74.15%. The multi-biomarker panel outperformed individual biomarkers across all stages of lung cancer, achieving AUC values of 0.9320 in the training set and 0.9230 in the validation set. **Conclusions:** The combined multi-biomarker panel of CEA, SAA, and OPN significantly improves diagnostic performance compared to single biomarkers. This panel represents a promising non-invasive tool for early and accurate lung cancer diagnosis. Research Sponsor: Ministry of SMEs and Startups(MSS, Korea); RS-2024-00437469.

8033 Poster Session

A novel aptamer-based non-invasive test for lung cancer: A proof-of-concept.

Line Nederby, Peter Hjorth-Hansen, Asger Givskov Jørgensen, Daniel Miotto Dupont, Ole Hilberg, Morten Hornemann Borg, Sara Witting Christensen Wen, Torben Frøstrup Hansen, Jørgen Kjems; Department of Biochemistry and Immunology, Vejle Hospital, University Hospital of Southern Denmark, Vejle, Denmark; Department of Oncology, Vejle Hospital, University Hospital of Southern Denmark, Vejle, Denmark; Interdisciplinary Nanoscience Centre (iNANO), Aarhus University, Aarhus, Denmark; AptaShape ApS, DK-8000, Denmark; Department of Internal Medicine, Vejle Hospital, University Hospital of Southern Denmark, Vejle, Denmark

Background: Lung cancer (LC) is the leading cause of cancer-related mortality, primarily due to late-stage diagnoses. Low-dose computed tomography (LDCT) screening lowers mortality rates by detecting LC at earlier stages, but the program is limited by high costs, capacity constraints, and low compliance. We describe the early-phase development of a test based on the APTASHAPE technology, designed as a cost-effective, scalable tool to pre-qualify individuals for LDCT screening. This technique uses RNA aptamers to analyze protein composition in lung cancer patients, identifying cancer-specific protein fingerprints across all stages. Variations in aptamer ratios reflect plasma protein composition, profiled through next-generation sequencing and machine learning. **Methods:** A discovery cohort of 24 LC patients (stage I+II, n=12; stage III+IV, n=12) and 24 individuals initially referred on suspicion of LC but ultimately diagnosed as non-cancer cases were analyzed. Additionally, a test cohort of 48 LC patients (stage I+II, n=24; stage III+IV, n=24) and 48 non-LC cases were analyzed. In four rounds of Systematic Evolution of Ligands by EXponential Enrichment (SELEX), a library of 10^{15} 2'-fluoro-protected RNA aptamers was incubated with a pool of plasma prepared from the LC patients in the discovery cohort to facilitate binding to the plasma proteins. Non-binders were removed, and bound aptamers were amplified by PCR. Following SELEX, linear regression identified the aptamers capturing LC-specific protein signatures. The selected aptamers were then applied to the test cohort and their ability to differentiate between LC and non-LC cases was evaluated using principal component analysis and receiver operating characteristic (ROC) curve. **Results:** In the discovery cohort, statistical analysis identified 13 aptamers whose binding to plasma proteins formed a cancer-specific fingerprint, able to discriminate participants with lung cancer from those without. We used this profile to predict LC in the test cohort and obtained an area under the curve (AUC) of 0.74 (95% confidence interval (CI) 0.62-0.87). Importantly, the discriminatory ability was equally effective for stage I+II and stage III+IV (AUC=0.71 (95% CI 0.58-0.84) and AUC=0.74 (95% CI 0.61-0.86), respectively). **Conclusions:** We present a proof-of-concept for a promising, cost-effective, and scalable technique for pre-qualifying individuals for LDCT screening. While still in the earliest stage of development, we anticipate that expanding the study population will improve the machine learning algorithm and markedly increase the AUC value. Importantly, this approach holds significant promise in detecting early-stage lung cancer -an area where blood-based technologies usually face substantial limitations. Ongoing optimizations aim to enhance its performance. Research Sponsor: None.

8034 Poster Session

Diagnostic properties of a novel ctDNA assay for lung cancer detection.

Peter Hjorth-Hansen, Cecilie Mondrup Jacobsen, Line Nederby, Morten Hornemann Borg, Ole Hilberg, Sara Witting Christensen Wen, Signe Timm, Torben Frøstrup Hansen, Rikke Fredslund Andersen; Department of Oncology, Vejle Hospital, Vejle, Denmark; Department of Biochemistry and Immunology, Vejle Hospital, University Hospital of Southern Denmark, Vejle, Denmark; Department of Internal Medicine, Vejle Hospital, University Hospital of Southern Denmark, Vejle, Denmark; Department of Oncology, Vejle Hospital, University Hospital of Southern Denmark, Vejle, Denmark; Department of Biochemistry, Vejle Hospital, University Hospital of Southern Denmark, Vejle, Denmark

Background: Lung cancer is a devastating disease, characterized by high mortality rates and limited treatment options once it progresses to advanced stages. Early detection is critical for improving survival outcomes, as curative treatments are only possible in the early stages of the disease. Developing a blood test for lung cancer detection would provide a minimally invasive, highly valuable tool for early diagnosis and could significantly enhance screening efforts. A novel digital droplet polymerase chain reaction multiplex assay was evaluated for its diagnostic accuracy in detecting hypermethylated circulating tumor DNA (ctDNA) in lung cancer in a high-risk population. **Methods:** The study enrolled 249 patients undergoing diagnostic evaluation for suspected lung cancer. Blood samples for ctDNA analysis were collected during the first hospital visit. Lung cancer diagnoses were subsequently determined through clinical workup and assessment by a multidisciplinary team (MDT). If the initial MDT assessment refuted the suspicion of lung cancer, participants were followed for at least 12 months to ensure they did not develop lung cancer in the follow up period. The assay targeted hypermethylated CpG-islands in five genes: *HOXA9, OTX1, MCIDAS, TFAP1B*, and *SP9*. ROC-analyses were performed for the five ctDNA markers alone and in combination. **Results:** The assay, using the combined model of the five markers, showed a sensitivity of 67% (95% Confidence Interval [CI]: 57–76) and a specificity of 77% (95% CI: 69–8) to discriminate cases from cancer-free controls. Positive and negative predictive values were 70% (95% CI: 60–78) and 75% (95% CI: 67–82), respectively. Sensitivity increased to 73% (95% CI: 62–83) in subgroup analysis of stages III and IV lung cancer and cancer-free controls. Notably, the assay successfully detected all 9 cases of small cell lung carcinoma (SCLC) within the cohort. Additional analysis revealed an association in stage IV participants between ctDNA and higher tumor burden, potentially explaining the improved assay performance in these advanced stages. Conversely, amongst the seven false negative stage IV cases, they all had lower tumor burden and were diagnosed with adenocarcinomas. **Conclusions:** The presence of aberrantly methylated ctDNA is a potential diagnostic biomarker for lung cancer. Further optimization of the multiplex assay might improve its overall performance making it a relevant tool for early detection of lung cancer. Importantly, this study was performed in a high-risk cohort, with a lung cancer prevalence of 43%, and hence, the assay would potentially perform better in a screening population. Research Sponsor: None.

8035 Poster Session

Actionable gene alterations in resected non-small cell lung cancer (AGA-R study).

Ilaria Attili, Gloria Pellizzari, Carla Corvaja, Luca Bertolaccini, Gianluca Spitaleri, Pamela Trillo Aliaga, Ester Del Signore, Antonio Passaro, Elena Guerini Rocco, Lorenzo Spaggiari, Filippo de Marinis; Division of Thoracic Oncology, European Institute of Oncology IRCCS, Milano, Italy; Division of Early Drug Development, European Institute of Oncology IRCCS, University of Milan, Milan, Italy; Division of Thoracic Surgery, European Institute of Oncology, Milano, Italy; Division of Thoracic Oncology, European Institute of Oncology IRCCS, Milan, Italy; European Institute of Oncology IRCCS, Milano, Italy; Division of Pathology, European Institute of Oncology IRCCS, University of Milan, Milan, Italy

Background: To date, molecular testing indication in resected non-small cell lung cancer (NSCLC) is limited to epidermal growth factor receptor (*EGFR*) mutations (mut) and anaplastic lymphoma kinase (*ALK*) rearrangements, because of demonstrated benefit and approval of adjuvant targeted therapies. The use of next generation sequencing (NGS), routinely adopted in the metastatic setting to guide treatment, is very limited in resected NSCLC. The prevalence of driver gene alterations other than *EGFR* and *ALK*, and their impact on adjuvant treatment outcomes, disease recurrence (DR) and survival remain unclear. **Methods:** We retrospectively analyzed molecular, clinical and survival data from consecutive Caucasian patients (pts) who underwent surgery for stage IA-IIIB NSCLC (AJCC 8th Edition) and had NGS performed on tumor tissue between January 2020 and December 2023 at our Institute. Primary endpoint was the prevalence of driver gene alterations in the overall cohort. Exploratory analyses were planned to evaluate DR, disease free survival (DFS) and overall survival (OS) and their relationship with the mutational status. **Results:** Overall, 216 resected NSCLC pts had NGS available. The prevalence of oncogenic driver alterations was 71%, the most common being *KRAS* (30%; 13% G12C and 17% non-G12C), followed by *EGFR* (26%; stage I: 29%), with exon 19 deletions (13%), exon 21 L858R substitution (6%), exon 20 insertion (2%), and uncommon mut (5%). Other detected alterations included *MET* exon 14 skip (6%; stage I: 8%), *BRAF* (4%; 2% V600), and *HER2* exon 20 mut (3%). Only 1% of cases had *ALK* or *RET* rearrangements. The overall prevalence of gene alterations was similar in men (69%) and women (70%), however *KRAS* and *MET* exon 14 skip were reported more frequently in men, *EGFR* in women. Among 181 pts with available follow up (median f up 14mo), n=52 DR events were observed. Median time to DR was 13.5 months (95% CI 11-16mo). Of note, among resected stage I pts with *EGFR* common mut who did not receive adjuvant TKI (n=10), 30% DR occurred. The overall highest DR rates (75%) were observed in the presence of gene fusions, exon 20 ins, and *BRAF* non-V600, followed by (50%) *KRAS* non-G12C and *HER2* mut. The lowest DR rate was observed in *MET* ex14 skip (8%) and BRAF V600 (0%). DR rate in other mut subtypes was similar to that observed in wild-type population. Median DFS was 32 months (24-NA), OS data are still not mature at data cut-off. **Conclusions:** Our study detected driver mutations in 70% of resected NSCLC, including stage I. The prevalence of *EGFR* and *MET* exon 14 skip mut in the early stage setting almost doubled the reported prevalence in the metastatic setting. Differential DR rates according to specific mut subtypes, are hypothesis-generating, and suggest the need of NGS testing to inform prognosis and personalize follow up in current clinical practice. Further investigation on tailored adjuvant treatments, also in stage I resected tumors, is supported by our results. Research Sponsor: None.

Tumor type prediction via tissue- and liquid-based comprehensive genomic profiling: High-specificity tobacco signature detection to support lung cancer diagnosis.

Soo-Ryum Yang, Anjali Rohatgi, Swetali Patel, Natalie Danziger, Julius Honecker, Jamal K. Benhamida, Dexter X. Jin, Zoe Fleischmann, Ethan Sokol, Richard Hickman, Tyler Janovitz, Douglas I. Lin, Julia A. Elvin, Lauren Ritterhouse, Douglas A. Mata, Matthew Hiemenz; Memorial Sloan Kettering Cancer Center, New York, NY; Siteman Cancer Center, Washington University School of Medicine in St. Louis, St. Louis, MO; Foundation Medicine, Inc., Cambridge, MA; Foundation Medicine, Inc., Boston, MA

Background: Cigarette smoking exposes the lungs to tobacco mutagens, producing a distinct mutational pattern with elevated tumor mutational burden and strand bias for C>A mutations, aiding identification of lung origin in cancer of unknown primary (CUP). We evaluated a tobacco signature (TSig) caller for diagnosing lung cancer on tissue (TBx) and liquid biopsies (LBx) tested via the FoundationOne CDx (F1CDx) and FoundationOne Liquid CDx (F1LCDx) comprehensive genomic profiling (CGP) assays. **Methods:** We analyzed 351,611 TBx and 68,888 LBx samples, assessing TSigs (COSMIC v2 signatures 4 and 29) in a research use only capacity in cases with ≥10 somatic non-driver variants. For LBx, ctDNA tumor fraction (TF) was estimated via aneuploidy, fragment length, and variant features. TSig caller performance and co-occurring genomic alterations were evaluated against submitted diagnoses. Concordance was assessed in paired TBx and LBx samples (TF ≥1%) collected within 90 days of one another. **Results:** In all, 20.3% (71,211/351,611) of TBx and 13.6% (9,385/68,888) of LBx specimens had sufficient somatic variants for TSig analysis, with TSigs detected in 13.1% (9,302/71,211) of TBx and 10.2% (954/9,385) of LBx cases. Of TSig+ TBx cases, 87.5% (8,140/9,302) were submitted with a primary lung cancer diagnosis, 6.2% (579/9,302) as CUP, and 6.3% (583/9,302) as non-lung cancer. For TSig+ LBx cases, 81.9% (781/954) were submitted as primary lung cancers, 6.4% (61/954) as CUP, and 11.7% (112/954) as non-lung cancer. TSig+ cases were enriched for *TP53*, *KRAS*, *STK11*, *KEAP1*, *SMARCA4*, and *MET* alterations ($P < 0.001$), consistent with their association with smoking-related lung cancer, regardless of submitted diagnosis, indicating that many cases submitted as CUP or non-lung cancer represented misdiagnosed lung cancers. Conversely, TSig− lung cancers were enriched for *EGFR*, *ALK*, *ROS1*, and *RET* alterations ($P < 0.001$), common in non-smokers. For cases with sufficient variants for TSig analysis, the TBx TSig caller had a high specificity of 97.1% but a lower sensitivity of 26.3%, with an accuracy of 66.3%, positive predictive value (PPV) of 87.5%, and negative predictive value (NPV) of 63.1%. LBx performance was comparable, with 96.7% specificity, 18.6% sensitivity, 61.8% accuracy, 81.9% PPV, and 59.5% NPV. In 272 paired TBx and LBx lung cancer samples, the positive percent agreement for TSig detection was 61.0%. **Conclusions:** TSig analysis identified misdiagnoses in 6.3% of TBx and 11.7% of LBx cases and supported lung origin in 6.3% of CUP cases. High specificity and PPV established TSig+ results as strong indicators of lung cancer, while lower sensitivity reflected the intrinsic limitation of the biomarker in detecting non-smoking-related cancers. These data highlight the utility of F1CDx and F1LCDx TSig analysis in refining lung cancer diagnosis and treatment. Research Sponsor: None.

Racial and ethnic disparities in risk of second primary lung cancer among initial lung cancer survivors in the United States.

Pragati Gole Advani, Christina R. Crabtree-Ide, Sarah Mullin, Tessa Faye Flores, Mary E. Reid, Nicolas Schlecht, Saikrishna S. Yendamuri; Roswell Park Cancer Institute, Buffalo, NY; Roswell Park Comprehensive Cancer Center, Buffalo, NY

Background: Previous studies have reported significant racial/ethnic disparities in incidence and mortality of lung cancer. However, with several studies reporting significantly increased risk of second primary lung cancer (SPLC) among these first primary lung cancer (FPLC) survivors, we sought to examine SPLC risk among FPLC survivors by race/ethnicity and age utilizing a large population-based database. **Methods:** From 17 United States population-based Surveillance, Epidemiology and End Results (SEER) program cancer registry areas, we identified 305,432≥12-month FPLC survivors diagnosed between 2000-2021. Standardized incidence ratios (SIRs) and accompanying 95% confidence intervals (CIs) quantified SPLC risk by race/ethnicity (non-Hispanic White, Black, Asian/Pacific Islander [API] and Hispanic), compared with the general population. Excess SPLC risks were calculated based on SIRs and excess absolute risks (EARs) per 10,000 person-years at risk (PYR). **Results:** Overall, we observed 13,005 SPLCs representing a 5.6-fold significantly increased risk (95% Confidence Interval [CI] =5.51-5.71) among FPLC survivors compared to the general population and an excess of 118 cases per 10,000 PYR. SPLC risk varied significantly by race/ethnicity with Hispanic FPLC survivors presenting highest risk ($SIR_{Hispanic}$=8.42; CI=7.73-9.16) followed by the API and Black patients (SIR_{API}=6.58; CI=6.11-7.07; SIR_{Black}=5.63; CI=5.32-5.96) ($P_{heterogeneity}<0.001$). Although 81% SPLC cases were reported among White FPLC survivors, the SIR compared to the other patients was relatively lower among the White (SIR_{White}=5.45; CI=5.35-5.56). Analysis by age at FPLC diagnosis reported a significantly increasing trend in SPLC risk with decreasing age ($P_{trend}<0.001$). Heterogeneity by race/ethnicity in SIRs was most pronounced in younger, particularly the adolescent and young adult (AYA) patients aged between 20 to 39 years at FPLC diagnosis. Strikingly elevated risk was observed among the Hispanic and API AYA FPLC survivors (SIRs of 49.62 and 87.17, respectively), followed by the corresponding Black and White patients (SIRs of 39.64 and 22.15, respectively) ($P_{heterogeneity}<0.001$). Similar pattern in racial/ethnic and age-related disparity was observed by latency, with higher SPLC risk among the young and minority patients within first 5 years since FPLC diagnosis. **Conclusions:** We observed substantial disparities in SPLC risk by race/ethnicity, with patients belonging to minority groups, particularly the Hispanic, and the AYA age group experiencing higher risks. Further research to understand drivers of these observed racial/ethnic and age-related heterogeneity is warranted. Similarly, tailored surveillance strategies are required to reduce disparities among FPLC survivors by accounting for these patient characteristics. Research Sponsor: None.

8038 Poster Session

Longitudinal *EGFR* assessment in plasma and tissue samples in early non–small cell lung cancer (NSCLC).

Sara Torresan, Alex Martinez-Marti, Aina Arbusà Roca, Augusto Valdivia, Patricia Iranzo Gomez, Nuria Pardo, Ilaria Priano, Oriol Mirallas, Pedro Rocha, Susana Cedres Perez, Irene Sansano, Mara Cruellas, Mireia Soleda, Ana Vivancos, Enriqueta Felip; Department of Medicine (DME), University of Udine, Italy and Medical Oncology Department, Vall d'Hebron University Hospital and Vall d'Hebron Institute of Oncology, Barcelona, Spain; Medical Oncology Department, Vall d'Hebron University Hospital and Vall d'Hebron Institute of Oncology, Barcelona, Spain; Medical Oncology Department, Vall d'Hebron Institute of Oncology, Barcelona, Spain; Pathology Department, Vall d'Hebron University Hospital, Barcelona, Spain

Background: Osimertinib has become the standard adjuvant treatment for patients (pts) with surgically resected, early-stage, *EGFR*-mutated non-small cell lung cancer (NSCLC), after the results of the ADAURA trial. However, the temporal distribution of *EGFR* mutations (mut) and its relation with recurrence patterns in this population have not been established yet. Aim of the study is to describe the prevalence of circulating tumor DNA and *EGFR* mut at different timepoints in early-stage NSCLC and the correlation between their presence and prognosis. **Methods:** This is a single center study conducted at the Vall d'Hebron Institute of Oncology, including consecutive pts with surgically resected, stage I-III NSCLC harbouring *EGFR* mut from 2008 to 2024. Next Generation Sequencing (NGS) with ONCOMINE panel was performed on tissue samples, archival when surgery pre-dated the start of the study. NGS on plasma samples was performed using Guardant360 panel at timepoints: 1, 3 and 6 months after surgery and at recurrence. For pts receiving adjuvant osimertinib, additional plasma samples were collected before drug initiation and during treatment. Pts were referred for genetic consultation if NGS on tissue samples detected a *TP53* mut with a variant allele frequency (VAF) >30%, or if NGS on plasma identified *TP53* or *BRCA* mut with a VAF >20%, or a basal T790M mutation. **Results:** Currently, 70 pts were enrolled, of which 24.3% were male. Median age was 68 years, and 35.7% were former/current smokers. Pts with stage IA were 37.1%, IB 24.3%, IIA 2.9%, IIB 11.4%, IIIA 14.3%, IIIB 5.7%. All pts had an EGFR mut, 54.2% detected by NGS on surgical or pre-surgical specimens. *EGFR* mut of the other samples were detected using PCR Cobas, and NGS are ongoing. *EGFR* mut was not detected on plasma after surgery (except for 1). Most pts harboured common mut (47.1% ex19del and 45.7% exon21 L858R on COBAS, 65.6% ex19del and 34.4% exon21 L858R on ONCOMINE). Interestingly, of the 43 pts with post-surgery NGS on plasma, 41.9% had a pathogenic mutation (*TP53* 50%, *ARID1* and *BRCA1/2* 11.1% each, 5.6% each *SMAD4, MPL, TSC1, NOTCH1, JAK2, APC, FGFR1* and *KRAS*) with a median VAF of 0.25% (tissue confirmation is needed to exclude hematopoietic origin). Liquid biopsies were obtained from all pts, with at least one sample collected post-surgery at varying time points. Adjuvant/neoadjuvant chemotherapy was administered to 31.4% of pts, while 17.1% received adjuvant osimertinib (100% after adjuvant osimertinib approbation by local label if indicated) and 11.4% also received radiotherapy. Disease recurrence occurred in 22 patients (31.4%), with 8 being local recurrence. At data lock 83% of pts were alive. **Conclusions:** Evaluation of *EGFR* in early-stage NSCLC should be standard procedure. We aim to identify a pattern associated with higher risk of recurrence and worse prognosis. Dynamic monitoring of *EGFR* could aid in personalising adjuvant treatments and follow-up scheduling. Research Sponsor: None.

8039 Poster Session

Clinical utility of pathologist-directed comprehensive comparative molecular profiling for the classification of separate primary lung cancers vs. intrapulmonary metastasis.

Douglas I. Lin, Smruthy Sivakumar, Richard Sheng Poe Huang, Ole Gjoerup, Julia A. Elvin, Lauren Ritterhouse, Douglas A. Mata, Richard Hickman, Deepa Rangachari, Paul A. VanderLaan; Foundation Medicine, Inc., Cambridge, MA; Beth Israel Deaconess Medical Center, Boston, MA

Background: Lung cancers can present as multiple pulmonary tumors, representing either separate primary lung carcinomas (SPLCs) or intrapulmonary metastases (IPMs) arising from a single advanced cancer. Distinguishing SPLCs from IPMs is important for effective staging, prognosis, and treatment. Comparative molecular profiling (CMP) of paired tumors can elucidate their clonal relationship. We report real-world data on the use of CMP to distinguish SPLCs versus IPMs. **Methods:** Paired lung tumors from the same patients, submitted for FoundationOne CDx (F1CDx) comprehensive genomic profiling within a 12-month period from one another between 2014 and 2024, were centrally reviewed by a board-certified pathologist. After excluding clonal hematopoiesis and germline alterations, 1) tumors with different driver alterations were classified as SPLCs, 2) tumors with shared drivers and other alterations as IPMs, and 3) tumors with 1 common driver but different other alterations as SPLCs. The molecular landscapes of SPLCs and IMPs as defined by CMP were subsequently compared. **Results:** In all, 359 paired lung cancers were identified and analyzed using pathologist-directed CMP. Of these, 32.6% (117/359) were classified as SPLCs, 63.8% (229/359) as IPMs, and 1.1% (4/359) as misdiagnoses (i.e., not lung cancer). Among SPLC pairs, 89.7% (105/117) harbored actionable genomic alterations in one tumor but not the other. Classification of 2.5% (9/359) of pairs was inconclusive due to suboptimal sequencing quality control metrics. Misdiagnoses, based on the molecular results, included 2 metastatic HPV-associated carcinomas (supported by high-risk HPV reads), and 2 metastatic cutaneous squamous or basal cell carcinomas (supported by ultraviolet mutational signatures). Of 31 paired lung tumors with different histologies, 67.7% (21/31) were SPLCs, while 32.3% (10/31) were IPMs. Molecular landscape analysis showed that IPMs had significantly higher frequencies of *CDKN2B* (20.1% vs. 10.3%, P=0.03, OR=2.2) and *ERBB2* (6.3% vs. 0.9%, P=0.03, OR=7.8) alterations, while SPLCs were more likely to have elevated tumor mutational burden (i.e., TMB $\geq$10 Muts/Mb) (39.8% vs. 21.3%, P$<$0.0001). **Conclusions:** Pathologist-directed CMP using F1CDx facilitates the classification of multiple lung cancers as SPLCs or IMPs and may identify diagnostic errors associated with conventional histopathological examination. The higher prevalence of *ERBB2* alterations in IPMs suggests a role in their development and opportunities for targeted therapy, while the increased rate of elevated TMB in SPLCs indicates a field cancerization effect, driven by smoking or other exposures, and possible responsiveness to immunotherapy. Accurately classifying SPLCs and IPMs is important for proper staging and therapeutic planning in patients with lung cancer. Research Sponsor: None.

A window of opportunity study for preoperative brigatinib in resectable anaplastic lymphoma kinase (ALK)-positive non-small-cell lung cancer (NSCLC): WILDERNESS trial.

Chang Gon Kim, Min Hee Hong, Jaehyung Kim, Moonki Hong, Hyo Sup Shim, Mina Han, Eun Yonug Kim, Byung Jo Park, Ha Eun Kim, Young Ho Yang, Tae Hee Hong, Chang Young Lee, Hye Ryun Kim; Division of Medical Oncology, Department of Internal Medicine, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, South Korea; Department of Pathology, Yonsei University College of Medicine, Seoul, South Korea; Division of Pulmonology, Department of Internal Medicine, Severance Hospital, Yonsei University College of Medicine, Seoul, South Korea; Department of Thoracic and Cardiovascular Surgery, Severance Hospital, Yonsei University College of Medicine, Seoul, South Korea

Background: Although ALK inhibitors are approved for patients with *ALK*-positive recurrent and/or metastatic NSCLC or resected NSCLC, their role as neoadjuvant therapy in resectable NSCLC remains unclear. Here, we report the results of a window-of-opportunity study evaluating neoadjuvant brigatinib in resectable *ALK*-positive NSCLC, aiming to identify the molecular mechanisms underlying drug-tolerant persister cells in cancer (NCT05361564). **Methods:** We conducted a single-arm, open-label, phase 2 trial of neoadjuvant brigatinib in patients with resectable *ALK*-positive NSCLC. Patients received brigatinib at a dose of 180 mg once daily following a 7-day lead-in period at 90 mg. Radiologic objective response rate (ORR), major pathologic response (MPR) rate, disease-free survival (DFS), event-free survival (EFS), and overall survival (OS) were evaluated. Single-cell transcriptomic analyses were performed to characterize the tumor microenvironment according to the achievement of MPR. **Results:** All 12 enrolled patients underwent surgical resection following neoadjuvant treatment without delays or increased surgical complications. The median time interval between neoadjuvant treatment initiation and surgical resection was 45 days (range: 38-64 days). The ORR was 83.3% (10/12), and MPR (defined as ≤10% residual cancer cells in the surgical specimen) was achieved in 7 patients (58.3%). The most common adverse event was elevated creatine phosphokinase (50.0%), and one patient experienced a grade 3 adverse event (asymptomatic creatine phosphokinase elevation). Over a median follow-up period of 602 days (range: 300–826 days), three patients experienced recurrence, resulting in a 2-year EFS rate of 70.1%. Single-cell transcriptomic analysis revealed that ZNF683-positive CD8+ T cells expressing effector-related genes including Blimp-1, were significantly enriched in patients with MPR. In contrast, FOXP3-positive regulatory CD4+ T cells were enriched in patients without MPR. **Conclusions:** Neoadjuvant brigatinib was effective and safe in patients with resectable *ALK*-positive NSCLC. Single-cell transcriptomic analysis highlights the balance between effector and regulatory T cell programs as a critical determinant of pathologic response and the clearance of drug-tolerant and persister cancer cells. Clinical trial information: NCT05361564. Research Sponsor: None.

8041 Poster Session

Genomic landscape of NSCLC with no targetable driver mutation among different races: An exploratory analysis of the AACR Project GENIE Database.

Yazan Hamadneh, Osama Mustafa Younis, Anas Mohammad Zayed, Mohammad Ma'koseh, Kamal Hosni Al-rabi; University of Jordan, Amman, Jordan; The University of Jordan, Amman, Jordan; King Hussein Medical Center, Amman, Jordan; KHCC, Amman, Jordan; Department of Internal Medicine, King Hussein Cancer Center, Amman, Jordan

Background: Non-small cell lung cancer (NSCLC) is the most prevalent subtype of lung cancer, and it has been historically associated with poor prognosis. Fortunately, recent advancements in targeted therapies have significantly improved the prognosis of this disease. However, around 40% of those diagnosed with NSCLC do not harbor a targetable oncogenic driver mutation. This percentage is not consistent among all races, as those who are eastern Asian or from eastern Asian descent have higher rates of targetable drivers and a unique genomic signature that makes them distinct to others. Even though Asians have higher rates of targetable NSCLC, about 20% of Asians diagnosed with NSCLC do not harbor targetable mutations. This raises the need to study the genomics of non-targetable NSCLC in different races to understand the nature of the disease and have a more precise understanding of its behavior in different populations. **Methods:** The Association for Cancer Research Project Genomics Evidence Neoplasia Information Exchange (AACR-GENIE) cohort v17.0-public registry was queried to study patients diagnosed with non-targetable NSCLC (n = 16,866). Non-targetable NSCLC was defined as NSCLC that does not harbor targetable driver mutation for the following genes (EGFR, NTRK1/2/3, KRAS, BRAF, MET, RET, NRG1, ERBB2) The patients were divided into three racial groups: White (85.2%), Black (9.5%), and Asian (5.3%). cBioportal was used to study the genetic mutations and clinical differences between the groups. Black & White groups were merged due to the patients' disease having similar genomic features and the group was named non-Asian (94.7%). Chi-squared test was used to measure the relationship between mutation frequencies between different groups. **Results:** A higher proportion of Asian patients with non-targetable mutations were males compared to the non-Asian group (61.96% vs 47.54%,$P < 0.001$). The most significant differences were found in 4 genes: *KRAS* (Asian 21.16%, non-Asian 30.22%, $P < 0.001$), *STK11* (Asian 9.88%, non-Asian 17.58%, $P < 0.001$), *KEAP1* (Asian 13.61%, non-Asian 20.50% ,$P < 0.001$), and *TERT* (Asian 12.22%, non-Asian 7.56%, $P < 0.001$). There was a significant difference in the prevalence of *TP53* mutations (Asian 52.13%, non-Asian 56.31%, P = 0.0232). **Conclusions:** Among non-targetable driver mutations, KRAS, KEAP1, STK11 and TP53 were less frequent in the Asian group vs non-Asian, while TERT was higher in the Asian group. These differences can be explained by variation in carcinogens exposure (smoking rates) and the unique genetic profile between ethnicities. It supports the significance of ethnicity and racial background even in the era of precision medicine. Research Sponsor: None.

Trends in lung cancer epidemiology and mortality over 12 years: Socioeconomic and demographic disparities.

Ali Shahbaz Baloch, Youjin Oh, Navika Chhabra, Shweta Gupta; John H. Stroger, Jr. Hospital of Cook County, Chicago, IL

Background: Lung cancer (LC), the most common cancer worldwide, remains a significant health burden with high rate of incidence and mortality in the United States and worldwide. Studies show that Black patients are 15% less likely to obtain an early diagnosis and have lower 5-year survival compared to White patients. **Methods:** The National Inpatient Sample database (2010–2021) was analyzed to identify adult hospitalizations with LC as a primary or secondary diagnosis. Multivariate logistic regression assessed epidemiologic and mortality trends and their association with demographic factors. **Results:** A total of 1,462,998 hospitalizations were identified with LC between 2020 and 2021. Of these, 196,225 patients (13.4%, 95% CI: 13.2–13.6) received palliative care. For metastatic LC admissions (n = 574,935), 21.5% (123,577) received palliative treatment. In 2010, the mean patient age was 67.6 years, which went up to 69.1 years in 2021. The percentage of LC patients with age over 65 years increased from 62.7% to 68.3%, whereas for patients under 45 and those between 45 and 65 years old, the percentage decreased from 2.0% to 1.4%, and 35.3% to 30.3%, respectively. The percentage of women diagnosed with lung cancer increased from 47.1% to 52.3% in 12 years. From 2010-2021, overall mortality from LC decreased (OR 0.96, 95% CI: 0.95–0.96). However, mortality was found to be lower in females (OR 0.80, 95% CI: 0.78–0.82, $p < 0.001$), and higher in Blacks than Whites (OR 1.07, 95% CI: 1.02–1.17, p = 0.003), and higher in those over 65 than in those between the ages of 18 and 45 (OR 1.11, 95% CI: 0.99–1.24, p = 0.063). Mortality rates were greater among Black people across all genders. While age-related differences were not significant among females, older age was linked to higher mortality among males (OR 1.15, 95% CI: 0.99–1.34, p = 0.066). Across all ethnicities, the death rate was consistently lower for females. Only White people showed substantial variations in age-related mortality, with older patients having higher mortality. Mortality rates within the lowest income bracket were the same for any age and ethnic group. Conversely, Black people had a higher mortality rate than White people in the highest income category (OR 1.24, 95% CI: 1.08–1.41, p = 0.002). **Conclusions:** Over the years, while LC mortality has decreased overall, disparities persisted with Black patients showing higher mortality compared to Whites, even in the higher income brackets. Increased mortality was associated with older age and male gender. These findings highlight the need for targeted interventions to address racial, gender, and socioeconomic disparities and to improve the survival of the identified high-risk population, especially minorities. Research Sponsor: None.

8043 Poster Session

Safety and efficacy of radiotherapy combined with anlotinib in locally advanced non-small cell lung cancer patients intolerant to concurrent chemoradiotherapy: Preliminary result of a phase II clinical trial.

Yupei Yuan, Haiyuan Li, Tao Zhang, Lei Deng, Wenyang Liu, Wenqing Wang, Xin Wang, Jima Lv, Zongmei Zhou, Qinfu Feng, Zefen Xiao, Nan Bi, Jianyang Wang; Cancer Hospital Chinese Academy of Medical Sciences, Beijing, China; Department of Radiation Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China; Department of Radiation Oncology, National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences, Beijing, China

Background: Concurrent chemoradiotherapy (cCRT) is the standard treatment for patients with unresectable locally advanced non-small cell lung cancer (LA-NSCLC). However, parts of patients only receive sequential chemoradiotherapy (sCRT) due to various reasons. This phase II study aimed to improve the outcomes of patients receiving sCRT by combining anti-angiogenesis therapy (anlotinib) during radiotherapy course. **Methods:** Patients with unresectable LA-NSCLC intolerable to cCRT were prospectively enrolled. Induction chemotherapy with or without immunotherapy were given for 4-6 cycles. Then patients were prescribed oral 12 mg anlotinib up for 3 cycles during radiotherapy. The primary endpoint is 2-year overall survival (OS). Acute adverse events (AEs) were defined as any treatment related events from the start of radiotherapy until 3 months post-radiotherapy. The trial has been registered in ChiCTR.org as ChiCTR2200060712. **Results:** From October 2020 to January 2024, 41 patients with stage II-III NSCLC were enrolled. 11 (26.8%) patients received induction chemotherapy and 30 (73.2%) patients received induction chemotherapy combined with immunotherapy. The rate of grade 3–4 acute hematological AEs was 29.3% (12 cases). The rates of grade 3 hemoptysis were 2.4% (1 case), with no grade 4 hemoptysis reported. The incidence of grade 3–4 radiation pneumonitis was 9.8% (4/41). No grade 5 AEs occurred in all patients. The median follow-up was 16.8 (range: 7.0–50.7) months. 22 (53.7%) patients experienced recurrence, including 5 patients (12.2%) with primary-site recurrence and 7 patients (17.1%) with regional-node recurrence, 12 patients (29.3%) had distant metastases. The median progression-free survival (PFS) was 18.9 months (95%CI 14.6-23.2 months) and 1-year PFS was 77.2%. 9 patients (22.0%) died, including 3 patients who died of covid-19 pneumonia during the follow-up period, 1 patient who died of hydatid pneumonia due to long-term bed rest after cerebral infarction, and 4 patients who died of tumor-related diseases. The 1-year overall survival was 89.9%. **Conclusions:** Our data first showed the combination of thoracic radiotherapy and anti-angiogenesis therapy (anlotinib) is of safety, well controlled toxicity, and efficacy for inoperable LA-NSCNC patients who cannot tolerate cCRT. Clinical trial information: ChiCTR2200060712. Research Sponsor: Beijing Hope Run Special Fund of Cancer Foundation of China (LC2020A14); Chinese Academy of Medical Sciences (CAMS) Innovation Fund for Medical Sciences (2024-I2M-C&T-B-065).

Clinical characteristics and prognosis of pulmonary lymphoepithelioma-like carcinoma: A multicentre retrospective study.

Zan Hou, Mei Lan, Yixiang Zhu, Ruixia Ma, Shan Liu, Lei Wu, Yi Wang, Gang Wan, Baoqing Chen, Qifeng Wang; Department of Radiation Oncology, Sichuan Clinical Research Center for Cancer, Sichuan Cancer Hospital & Institute, Sichuan Cancer Center, Affiliated Cancer Hospital of University of Electronic Science and Technology of China, Chengdu, Sichuan, China; Sun Yat-sen University Cancer Center, Guangzhou, Guangdong, China; Department of Radiation Oncology, Sichuan Cancer Hospital & Institute, Sichuan Cancer Center, University of Electronic Science and Technology of China, Chengdu, Sichan, China

Background: Pulmonary lymphoepithelioma-like carcinoma (PLELC) is a rare form of squamous lung cancer, and large-scale clinical studies on its clinical features, prognosis at different stages, and outcomes following treatments are limited. **Methods:** Patients with PLELC diagnosed by pathology from January 2009 to December 2023 at Sichuan Cancer Hospital and Sun Yat-sen University Cancer Centre were retrospectively analysed. Survival curves were estimated using the Kaplan-Meier method, Log-rank tests were used to compare differences between groups, and the Bonferroni method was used to correct the p-value when two-by-two comparisons between multiple groups were involved. **Results:** A total of 1,106 PLELC patients were included in the study. Most patients were non-smokers (73.4%), and brain metastasis was rare (0.3%). Tumor-specific characteristics showed a low incidence of EGFR mutation (0.6%) but a high prevalence of PD-L1 positivity (71.6%). The median follow-up duration was 31.6 months. The two-year overall survival (OS) rates for stage I, II, III, and IV patients were 99.4%, 97.7%, 92.7%, and 70.4%, respectively, while the five-year OS rates were 94.8%, 88.7%, 70.6%, and 37.8%, respectively. No statistically significant differences in progression-free survival (PFS) or OS were observed between surgery alone and surgery combined with adjuvant therapy in stage I and II patients, or between radiochemotherapy and combined surgery-radiochemotherapy in stage IIIA and IIIB patients. However, in stage IV patients, chemotherapy combined with immunotherapy resulted in significantly better PFS and OS compared to chemotherapy alone. **Conclusions:** PLELC patients, mostly non-smokers with rare brain metastasis and high PD-L1 positivity, show favorable prognosis, but further research is needed to refine its optimal treatment strategies. Research Sponsor: None.

PFS and OS in patients with different stages.

Stage	Number of cases	Median PFS (months)	2-year PFS	95% CI	5-year PFS	95% CI	Median OS (months)	2-year OS	95% CI	5-year OS	95% CI
IA	145	108.3	94.0%	88.9%-99.1%	75.6%	63.2%-88%	Incalcu	99.1%	97.3%-100%	95.7%	90.7%-100%
IB	56	119.2	78.0%	65.3%-90.7%	65.2%	49.5%-80.9%	Incalcu	100.0%	100%-100%	93.5%	84.8%-100%
IIA	37	Incalcu	85.4%	70.1%-100%	62.9%	40.9%-85%	Incalcu	100.0%	100%-100%	96.2%	88.8%-100%
IIB	104	87.9	78.0%	68.6%-87.4%	60.0%	47.2%-72.8%	Incalcu	96.9%	93.6%-100%	85.6%	77.1%-94.1%
IIIA	213	47.9	70.6%	63.5%-77.7%	42.8%	33.9%-51.7%	161.5	97.9%	95.9%-99.9%	79.7%	72.4%-87%
IIIB	132	24.6	51.1%	41.3%-60.9%	21.3%	11.7%-30.9%	83.7	87.9%	81.6%-94.2%	65.3%	54.8%-75.8%
IIIC	73	22.0	44.0%	29.5%-58.5%	24.7%	8.4%-41%	53.5	84.9%	75.3%-94.5%	49.4%	31.8%-67%
IVA	123	12.0	29.8%	20.4%-39.2%	0.0%	0%-4.5%	50.0	79.3%	70.9%-87.7%	44.1%	30.9%-57.3%
IVB	223	9.0	16.0%	10.3%-21.7%	2.7%	0%-6%	33.6	65.4%	58.1%-72.7%	34.1%	24.3%-43.9%

Incalcu: Incalculable; CI: confidence interval.

8045 Poster Session

Neoadjuvant immunotherapy and surgery in patients with stage IIIB-IIIC (N3) non-small cell lung cancer.

Wen-Yu Zhai, Xiangyang Yu, Xiaotong Guo, Hao Long, Junye Wang; Sun Yat-sen University Cancer Center, Guangzhou, Guangdong, China; National Cancer Center/National Clinical Research Center for Cancer, Cancer Hospital & Shenzhen Hospital, Shenzhen, Guangdong, China; Sun Yat-sen University Cancer Center, Guangzhou, China

Background: Stage IIIB-IIIC (N3) non-small cell lung cancer (NSCLC) is generally seen as unresectable, and Durvalumab following concurrent chemoradiotherapy (CCRT) is the standard of care for these patients. The use of immune checkpoint inhibitor (ICI) in neoadjuvant therapy has resulted in unprecedented rates of pathological response and lymph node downstaging, which has made resecting previous unresectable disease possible. However, it remains uncertain whether certain N3 patients may derive survival benefit from surgery after neoadjuvant immunotherapy. **Methods:** This multicenter retrospective study included patients with cN3 NSCLC who received inducing immunochemotherapy and completed surgery. As a comparison, patients with cN3 NSCLC who received ICI following CCRT, ICI plus CCRT, and CCRT following inducing immunochemotherapy were also included. 1:1 Propensity score matching (PSM) was implemented to balance important baseline characteristics included gender, age, smoking history, histologic type, differentiated degree, cT stage between patients with surgery and radiotherapy. Log-rank test was used to compared progression-free survival (PFS). **Results:** The median follow-up time of 82 patients with surgery and 114 patients with radiotherapy was 28.1 months and 21.8 months, respectively. In patients with surgery, 29 patients reach complete pathological response (pCR) and 53 patients reached node clearance. After PSM, 74 patients with surgery and 74 patients with radiotherapy showed balanced baseline characteristics. Before PSM, patients with surgery displayed a significant advantage in median PFS (24.6 months vs 21.3 months, p=0.040) but this advantage disappeared after PSM (31.3 months vs 30.8 months, p=0.132). In post-treatment subgroup analyses, patients reached pCR had better PFS than patients with radiotherapy (median PFS not reach vs 30.8 months, p=0.001). In addition, patients reached node clearance also had better PFS than patients with radiotherapy (median PFS not reach vs 30.8 months, p=0.010). In pre-treatment subgroup analyses, surgery did not outperform radiotherapy in male or female patients, smokers or nonsmokers, squamous or non-squamous carcinoma and poorly differentiated carcinoma. In patients with high or moderately differentiated tumors, patients with surgery had better PFS than patients with radiotherapy (median PFS not reach vs 13.2 months, p=0.001). **Conclusions:** In patients with cN3 NSCLC, surgery after neoadjuvant immunochemotherapy do not transcend ICI with CCRT in PFS. Only patients with high or moderately differentiated tumors, or reached pCR, node clearance after surgery have better PFS than patients with radiotherapy. Prospective clinical is needed to evaluate the benefit of surgery after neoadjuvant immunotherapy for cN3 NSCLC. Research Sponsor: None.

8046 Poster Session

Neoadjuvant durvalumab (D) + chemotherapy (CT) + novel anticancer agents and adjuvant D ± novel agents in resectable non-small-cell lung cancer (NSCLC): Updated outcomes from NeoCOAST-2.

Tina Cascone, Laura Bonanno, Florian Guisier, Amelia Insa, Moishe Liberman, Olivier Bylicki, Lorenzo Livi, Thomas Egenod, Romain Corre, Agata A. Bielska, Alula Yohannes, Yun He, Adam Dowson, Lara McGrath, Gozde Kar, Rakesh Kumar, Italia Grenga, Jonathan Spicer, Patrick M. Forde; Department of Thoracic/Head and Neck Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX; Istituto Oncologico Veneto, IRCCS, University of Padova, Padova, Italy; Univ Rouen Normandie, LITIS Lab QuantIF team EA4108, CHU Rouen, Department of Pneumology and Inserm CIC-CRB 1404, Rouen, France; Hospital Clínico Universitario de Valencia, Valencia, Spain; Division of Thoracic Surgery, University of Montréal and CETOC - CHUM Endoscopic Tracheobronchial and Oesophageal Center, Centre Hospitalier de l'Université de Montréal, Montreal, QC, Canada; Respiratory Medicine Department, Hôpital d'Instruction des Armées Sainte-Anne, Toulon, France and Ecole du val de Grace, Paris, France; Department of Radiation Oncology, University of Florence, Florence, Italy; Department of Thoracic Oncology, Dupuytren University Hospital, Limoges, France; Department of Pneumology, CH de Cornouaille, Quimper, France; AstraZeneca, Waltham, MA; AstraZeneca, Gaithersburg, MD; AstraZeneca, Cambridge, United Kingdom; Department of Thoracic Surgery, McGill University, Montreal, QC, Canada; Bloomberg–Kimmel Institute for Cancer Immunotherapy, Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University, Baltimore, MD

Background: Perioperative CT + immune checkpoint inhibitor therapy has improved outcomes in resectable NSCLC but most patients (pts) still do not experience pathological complete response (pCR) and long-term benefit. We report final pCR rates, ongoing circulating tumor DNA (ctDNA) findings, and updated safety data from Arms 1/2/4 of NeoCOAST-2 (NCT05061550), a phase 2 platform study evaluating neoadjuvant and adjuvant D ± novel agent-based combinations in pts with untreated Stage IIA–IIIB resectable NSCLC. **Methods:** Pts were stratified by PD-L1 expression (<1% vs ≥1%) and randomized to neoadjuvant D + platinum-doublet CT + oleclumab (anti-CD73 monoclonal antibody [mAb]) then adjuvant D + oleclumab (Arm 1), neoadjuvant D + platinum-doublet CT + monalizumab (anti-NKG2A mAb) then adjuvant D + monalizumab (Arm 2), or neoadjuvant D + single-agent platinum CT + Dato-DXd (TROP2-directed antibody-drug conjugate [ADC]) then adjuvant D (Arm 4). Neoadjuvant therapy was given Q3W for 4 cycles. Adjuvant therapy was given for up to 1 year or until disease progression. Primary endpoints were pCR rate by blinded independent pathology review and safety and tolerability. Key secondary endpoints included major pathological response (mPR) rate, ctDNA clearance, and feasibility of surgery. **Results:** As of Dec 19 2024, 202 pts were randomized (Arms 1/2/4, N=76/72/54). Among dosed pts with confirmed NSCLC, pCR and mPR rates were numerically higher in Arm 4 vs Arms 1/2 overall and in pts with a PD-L1 TPS <1% or ≥1% (Table). Rates of ctDNA clearance in the neoadjuvant period were higher in Arm 4 vs Arms 1/2, and higher in pts with pCR vs non-pCR and with mPR vs non-mPR across arms. Among dosed pts, 69/74 (93.2%) pts in Arm 1, 66/71 (93.0%) pts in Arm 2, and 51/54 (94.4%) pts in Arm 4 underwent surgery; overall, grade ≥3 treatment-related adverse events occurred in 36.5%, 40.8%, and 20.4% of pts, respectively. **Conclusions:** All arms show that novel perioperative combinations may improve pCR rates and maintain tolerability and feasibility of surgery in resectable NSCLC. The final analysis of pCR and mPR rates in Arm 4 is the first for an ADC in this setting and confirms the encouraging efficacy and manageable safety profile of D + CT + Dato-DXd. Presurgical ctDNA clearance is associated with pathological responses. Clinical trial information: NCT05061550. Research Sponsor: AstraZeneca.

	Arm 1	Arm 2	Arm 4
Overall, n (%) [95% CI]	n=74	n=70	n=54
pCR	**15 (20.3) [11.8–31.2]**	**18 (25.7) [16.0–37.6]**	**19 (35.2) [22.7–49.4]**
mPR	31 (41.9) [30.5–53.9]	35 (50.0) [37.8–62.2]	34 (63.0) [48.7–75.7]
PD-L1 TPS <1%, n (%)	n=25	n=28	n=16
pCR	**4 (16.0)**	**5 (17.9)**	**5 (31.3)**
mPR	10 (40.0)	10 (35.7)	10 (62.5)
PD-L1 TPS ≥1%, n (%)	n=49	n=42	n=38
pCR	**11 (22.4)**	**13 (31.0)**	**14 (36.8)**
mPR	21 (42.9)	25 (59.5)	24 (63.2)

Initial treatment and survival outcomes for early-stage NSCLC in Veterans: Insights from cancer cube data.

Madison Panell, Rafeh Safdar, Noor Humayun, Syed Arzoo Mehdi; Albany Medical Center Hospital, Albany, NY; Samuel S. Stratton VA Medical Center, Albany, NY; Albany Medical Center, Albany, NY; VAMC, Albany, NY

Background: Non-small cell lung cancer (NSCLC) accounts for 85% of lung cancer cases and remains the leading cause of cancer-related deaths in the United States. Early-stage NSCLC (Stage I) is potentially curable, with surgical resection as the standard of care. However, for patients who are medically inoperable or decline surgery, stereotactic ablative radiotherapy (SABR) is an alternative. Prior studies suggest that demographic factors, including age, race, and sex, may influence treatment decisions and outcomes, particularly among veterans with a high burden of comorbidities. This study examines treatment patterns and survival outcomes for veterans with Stage I NSCLC using data from the Veterans Affairs Cancer Care Cube. **Methods:** This retrospective study included veterans diagnosed with Stage I NSCLC between 2000 and 2023. Patients were categorized by initial treatment (surgery or radiation therapy) and stratified by demographics (age, race/ethnicity, gender, and ECOG status). Survival outcomes were analyzed using Kaplan-Meier curves, log-rank tests, and Cox proportional hazards models to control for confounding variables. Logistic regression identified predictors of treatment choice. Patients with incomplete data or advanced-stage disease were excluded. Statistical analyses were conducted using R and Python. **Results:** Surgery demonstrated superior survival outcomes across all demographics. • Age: Surgery offered significantly higher 5-year survival rates in younger (40–59 years, 41.77–54.32%) and older (>70 years, 42.32%) patients compared to radiation (0–24.68%). • Race: Surgery utilization was consistent across racial groups, with the highest 5-year survival in Asian patients (60.87%). Native Hawaiian/Pacific Islander (NHPI) patients had the lowest survival for both treatments, highlighting disparities in care. • Sex: Women were more likely to undergo surgery (71.79%) and had better survival outcomes than men, similar to trends seen in non-veteran populations. • ECOG Status: Surgery remained the preferred treatment across all ECOG scores, though long-term survival declined with higher ECOG scores. • Exposure Type: Agent Orange and asbestos exposure were associated with the best survival outcomes following surgery, while radiation offered limited long-term benefits regardless of exposure. **Conclusions:** Surgery consistently yields better survival outcomes than radiation therapy for veterans with early-stage NSCLC, even among subgroups with higher comorbidity burdens. Demographic and exposure-related disparities highlight the need for tailored interventions to optimize care. These findings inform clinical decision-making and emphasize the importance of equitable access to curative treatments in this vulnerable population. Research Sponsor: None.

Survival of induction aumolertinib followed by aumolertinib and concurrent radiotherapy (RT) in unresectable *EGFR*-mutated stage III NSCLC: Final analysis of the phase III ADVANCE trial and real-world data.

Nan Bi, Jianyang Wang, Wei Jiang, Xiaolong Fu, Lujun Zhao, Zhe Yang, Dong Qian, Xianglong Chen, Haihua Yang, Hui Wang, Guoyong Shan, Ming Chen, Luhua Wang; National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital & Shenzhen Hospital, Beijing, China; Department of Radiation Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China; National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital & Shenzhen Hospital , Chinese Academy of Medical Sciences and Peking Union Medical College, Shenzhen, China; Department of Radiation Oncology, Shanghai Chest Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, China; Tianjin Medical University Cancer Institute and Hospital, Tianjin, China; Shandong Provincial Hospital Affiliated to Shandong First Medical University, Jinan, China; Anhui Provincial Hospital, Hefei, China; Zhujiang Hospital, Southern Medical University, Beijing, China; Taizhou Hospital of Zhejiang Province affiliated to Wenzhou Medical University, Taizhou, China; Department of Radiation Oncology, Hunan Cancer Hospital & the Affiliated Cancer Hospital of Xiangya School of Medicine, Central South University, Changsha, China; People's Hospital of Zhengzhou, Zhengzhou, China; State Key Laboratory of Oncology in South China, Guangdong Key Laboratory of Nasopharyngeal Carcinoma Diagnosis and Therapy, Guangdong Provincial Clinical Research Center for Cancer, Sun Yat-sen University Cancer Center, Guangzhou, China; Department of Radiation Oncology, Cancer Institute (Hospital) Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

Background: The LAURA trial established concurrent chemoradiotherapy (cCRT) followed by consolidation targeted therapy as the standard for unresectable stage III EGFR-mutated non-small cell lung cancer (NSCLC). The phase III ADVANCE trial (ChiCTR2000040590) evaluated induction aumolertinib followed by aumolertinib and concurrent RT versus cCRT. **Methods:** Eligible patients (pts) aged 18-75 with unresectable stage III non-squamous NSCLC and centrally confirmed *EGFR* exon 19 deletion or L858R mutation were randomized 1:1 to receive aumolertinib+RT (experimental) or cCRT (control). The primary endpoint was progression-free survival (PFS), assessed by investigator. The accrual target was 98 pts, aiming for a hazard ratio (HR) of 0.5 (80% power, one-sided α =0.025). A real-world database (RWD; NCT04304638) from 6 trial sites was developed to validate long-term survival outcomes for pts treated with RT and third-generation EGFR TKIs. **Results:** Between March 2021 and March 2024, 43 eligible pts were randomized (24 to experimental, 19 to control) following early termination due to feasibility issues. At a median follow-up of 25.5 months (mo), the experimental group showed significantly longer PFS (34.0 vs. 7.8 mo; HR 0.15, 95% CI 0.06–0.24). Median overall survival (OS) was not reached in the experimental group but was 30.5 mo in the control (p = 0.17). The control group reported more neutropenia (52.6% vs. 16.7%, p = 0.01) and nausea (26.3% vs. 0.0%, p = 0.03), while quality of life was better in the experimental group. Among 18 experimental and 16 control pts completing RT without progression, the experimental group had significantly longer PFS (not reached vs. 12.8 mo; HR 0.05, 95% CI 0.01–0.16) and OS (HR 0.09, 95% CI 0.01–0.68). From 2012 to 2024, 125 consecutive pts were included in the RWD cohort: 31 in RT + TKI, 33 in CRT + TKI, and 61 in CRT. At a median follow-up of 32.7 mo, PFS and OS were significantly longer in RT + TKI and CRT + TKI compared to CRT (PFS: not reached vs. 36.7 vs. 9.8 mo; OS: not reached vs. not reached vs. 48.9 mo; $p < 0.001$). No significant differences in PFS and OS were observed between RT + TKI and CRT + TKI (p=0.59 and 0.80, respectively). **Conclusions:** The ADVANCE trial and RWD demonstrate that induction EGRF TKI followed by TKIs and RT delays progression and improves survival in unresectable stage III EGFR-mutated NSCLC. Clinical trial information: ChiCTR2000040590. Research Sponsor: None.

A prospective, single-arm, phase II study to evaluate the efficacy and safety of perioperative tislelizumab in resectable non-small-cell lung cancer (NSCLC).

Daqiang Sun, Meng Wang, Xin Li; Department of Thoracic Surgery, Tianjin Chest Hospital, Tianjin, China

Background: Perioperative immunotherapy has emerged as a promising strategy for the treatment of resectable non-small cell lung cancer (NSCLC). This study was designed to evaluate the efficacy and safety of a comprehensive perioperative regimen, comprising neoadjuvant tislelizumab in combination with chemotherapy, followed by surgical resection and adjuvant tislelizumab, in patients with resectable stage II-IIIB NSCLC. **Methods:** This open-label, single-arm, phase 2 trial was designed to enroll patients (pts) with resectable stage II-IIIB (N2) NSCLC (AJCC 8th edition). Participants received neoadjuvant therapy consisting of intravenous tislelizumab in combination with chemotherapy administered every 3 weeks for 2 to 4 cycles prior to surgery, and 0 to 2 cycles following surgery (totaling up to 4 cycles of perioperative therapy). This was followed by adjuvant tislelizumab monotherapy administered Q3W for 1 year. The primary endpoint of the study was the major pathological response (MPR) rate. Secondary endpoints included the pathological complete response (pCR) rate, objective response rate (ORR), event-free survival (EFS), overall survival (OS), and safety. **Results:** Between February 2023 and June 2024, a total of 30 patients were enrolled. The median age was 64 years (range: 43-77 years), with 25 males (83.3%). Twenty-eight patients (93.3%) had squamous cell carcinoma, while 2 patients (6.7%) had adenocarcinoma. In terms of disease stage, 12 patients (40%) were at stage II, and 18 patients (60%) were at stage III. For treatment, 23 patients (76.7%) received three cycles of neoadjuvant immunotherapy, and 7 patients (23.3%) received four cycles. The objective response rate (ORR) was 53.3% and surgical resection was performed in 27 patients (90%), with a complete (R0) resection rate of 96.3% (26/27). A major pathological response (MPR) was observed in 53.3% (16/30) of patients, and the pathological complete response (pCR) rate was 33.3%(10/30). With a median follow-up of 12.1 months, the median event-free survival (EFS) and overall survival (OS) data were not yet mature. In the intention-to-treat (ITT) population, the 1-year EFS rate and OS rate were 92.3% and 96.7%, respectively. During the neoadjuvant phase, the incidence of treatment-related adverse events (TRAEs) of any grade was 70%, with grade 3-4 adverse reactions occurring in 13% of patients. **Conclusions:** Perioperative tislelizumab achieved notable major pathological response (MPR) and pathological complete response (pCR) rates, while also demonstrating feasible surgical resection and manageable toxicity in patients with stage II-IIIB non-small cell lung cancer (NSCLC). The current data align with the initial findings and underscore the need for continued follow-up to further validate these outcomes. Clinical trial information: ChiCTR2300068140. Research Sponsor: None.

8050 Poster Session

Characteristics, treatment patterns, and outcomes of HIV-associated lung cancer.

Tina Roy, Ujjwal Karki, Tianzhi Tang, Anya Gupta, Kanchi Krishnamurthy, Camelia Bencheqroun, Jia Li Dong, Joan Mattle, Maryam Abdussamad, Samir Gupta, Shuo Wang, Subha Jamal, Joshua E. Reuss, Jaeil Ahn, Stephen V. Liu, Marta Catalfamo, Adil Alaoui, Chul Kim; Georgetown Lombardi Comprehensive Cancer Center, Washington, DC; Georgetown University School of Medicine, Washington, DC; Georgetown University, Washington, DC; Georgetown University Medical Center, Washington, DC

Background: Lung cancer is a leading cause of cancer-related mortality in people with HIV (PWH). Prior studies have shown worse survival in PWH with lung cancer compared to people without HIV (PWoH) with lung cancer. However, it is unclear whether this difference in survival is due to differences in tumor biology, socioeconomic factors, and/or treatment disparities. **Methods:** This is a retrospective study of PWH and lung cancer identified from 2005 - 2024 within MedStar Health serving a major urban area with a high burden of HIV. Age and race matched PWoH and lung cancer were used as a control group. Clinical, pathological, and molecular characteristics, along with social determinants of health, treatment patterns, and outcomes were collected. Factors associated with survival and receipt of stage-appropriate treatment were determined using multivariable analysis. **Results:** We analyzed 148 PWH with lung cancer and 127 PWoH with lung cancer. The median age at lung cancer diagnosis among PWH was 61.8 years, with a statistically significant trend of increasing age over the study period. PWH were disproportionately male (65%), unmarried (62%), had government provided health insurance (79%), and had more comorbidities compared to the control group. The stage at diagnosis was similar between both groups, with 68% of PWH and 66% of PWoH diagnosed at stage III and IV, and no evidence of stage migration to earlier stage observed over the study period. Similar rates of KRAS/EGFR/ALK/BRAF alterations were observed. Stage-appropriate treatment was received by 70% of PWH and 82% of PWoH ($p=0.057$). Median OS (mOS) in stages I and II was 5.8 years in PWH and 8.8 years in PWoH ($p=0.22$). Across all stages, mOS was 1.5 years in PWH and 1.9 years in PWoH ($p=0.23$); the difference in mOS was attenuated when comparing patients who received stage-appropriate treatment ($p=0.52$). Among PWH with lung cancer, factors associated with improved survival included receipt of chemotherapy (HR 0.35, $p<0.001$) and immunotherapy (HR 0.53, $p=0.042$), and higher CD4 count (>400 cells/mm3) at diagnosis ($p=0.013$). Factors that contributed to whether PWH received stage appropriate treatment were based on performance status, with an ECOG ≥ 3 significantly associated with lower likelihood of receiving treatment (OR 0.01, $p=0.003$). Among PWH, 96 were eligible for lung cancer screening per the USPSTF criteria, but only 7 patients (7.3%) were diagnosed through a screening CT scan. **Conclusions:** Decreased CD4 count, poor performance status at presentation, and advanced disease stage at diagnosis may contribute to worse outcomes in PWH with lung cancer. The lower rate of diagnosis through lung cancer screening and the potential number of eligible patients at the time of lung cancer diagnosis highlight missed opportunities for early detection in PWH. Targeted interventions to address barriers to timely diagnosis and stage-appropriate treatment could improve survival outcomes in PWH. Research Sponsor: U.S. National Institutes of Health.

8051 Poster Session

Impact of lymph node characteristics on clinical outcomes in clinical N2 non-small cell lung cancer patients treated with chemoradiotherapy: Single- vs. multiple-stations, bulky vs. non-bulky and discrete vs. infiltrative.

Yuki Kato, Hibiki Udagawa, Atsuyuki Nakanishi, Keiju Aokage, Masaki Nakamura, Hidehiro Hojo, Yu Tanaka, Tetsuya Sakai, Hiroki Izumi, Eri Sugiyama, Yoshitaka Zenke, Shigeki Umemura, Shingo Matsumoto, Kiyotaka Yoh, Koichi Goto; National Cancer Center Hospital East, Kashiwa, Japan; Department of Thoracic Surgery, National Cancer Center Hospital East, Kashiwa, Japan; Department of Thoraci surgery, National Cancer Center Hospital East, Kashiwa, Japan; Department of Radiation Oncology, National Cancer Center Hospital East, Kashiwa, Japan; Department of Thoracic Oncology, National Cancer Center Hospital East, Chiba, Japan; Department of Thoracic Oncology, National Cancer Center Hospital East, Kashiwa, Japan

Background: Stage III, N2 non-small cell lung cancer (NSCLC) is a heterogeneous disease with various patterns of lymph node metastasis. Recently, chemoradiotherapy followed by immune-checkpoint inhibitors (ICIs) and neoadjuvant chemotherapy with ICIs followed by surgery have been developed as treatment strategies for clinical N2 (cN2) NSCLC. However, the difference of clinical outcomes according to cN2 subclassification, such as single- vs. multiple-stations, non-bulky vs. bulky and discrete vs. infiltrative, in NSCLC patients treated with chemoradiotherapy are still unclear. **Methods:** The clinical outcomes in cN2 NSCLC patients who received chemoradiotherapy at our institution were retrospectively investigated and compared according to cN2 subclassification; single- vs. multiple-stations, non-bulky vs. bulky (short-axis diameter≧2cm) and discrete vs. infiltrative. **Results:** A total of 146 cN2M0 NSCLC patients received chemoradiotherapy from May 2018 to December 2023, and 98 (67%) patients received durvalumab after chemoradiotherapy. As of January 2025, the median follow-up was 20.9 months. The characteristics of the patients were showed that the median age was 71 (range 40-88) year-old, 77% were male, 89% had smoking history, 99% were ECOG PS 0-1, 44% had histology of adenocarcinoma and 23% were PD-L1 (22C3) ≥50%. Among them, 69 patients (47%) had single-station N2, 90 patients (62%) had non-bulky N2, and 81 patients (55%) had discrete N2. There was no significant difference of the progression-free survival (PFS) in the patients who received chemoradiotherapy between single- vs. multiple-stations (median: 17.5 vs. 12.5 months, HR [95%CI]: 0.90 [0.60–1.37], P = 0.63), non-bulky vs. bulky (median: 15.6 vs. 12.3 months, HR [95%CI]: 0.98 [0.64–1.50], P = 0.92), and discrete vs. infiltrative (median: 18.2 vs. 12.0 months, HR [95%CI]: 0.72 [0.47–1.08], P = 0.11). Similarly, there was no significant difference in the overall survival (OS) in the patients who received chemoradiotherapy between single- vs. multiple-stations (median: NR vs. NR months, HR [95%CI]: 1.01 [0.59–1.72], P = 0.97), non-bulky vs. bulky (median: 51.4 vs. NR months, HR [95% CI]: 1.06 [0.61–1.84], P = 0.84), and discrete vs. infiltrative (median: 51.4 vs. NR months, HR [95%CI]: 0.89 [0.52–1.52], P = 0.67). In the patients who received durvalumab after chemoradiotherapy, there was no significant difference in the PFS and OS according to cN2 subclassification. The time to recurrence in the radiated field showed no significant difference between single- vs. multiple-stations, non-bulky vs. bulky and discrete vs. infiltrative. **Conclusions:** Lymph node characteristics have no impact on clinical outcomes in cN2M0 NSCLC patients treated with chemoradiotherapy. Research Sponsor: None.

Outcomes with neoadjuvant chemotherapy and/or osimertinib in patients with *EGFR*-mutant resectable non-small cell lung cancers.

Prashasti Agrawal, Julia K. Rotow, Gaetano Rocco, William Travis, Eduardo Ortiz, Rebecca Scalabrino, Jaclyn LoPiccolo, Francesco Facchinetti, Helena Alexandra Yu, David R Jones, Jamie E. Chaft; Memorial Sloan Kettering Cancer Center, New York, NY; Lowe Center for Thoracic Oncology, Dana-Farber Cancer Institute, Boston, MA; Lowe Center for Thoracic Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA; Dana-Farber Cancer Institute, Boston, MA; Thoracic Oncology Service, Memorial Sloan Kettering Cancer Center, New York, NY; Department of Medicine, Weill Cornell Medical College, New York, NY

Background: There are currently no *EGFR*-tyrosine kinase inhibitors approved for neoadjuvant treatment of resectable *EGFR*-mutant non-small cell lung cancers (NSCLC). The phase III multi-center trial NeoADAURA aims to evaluate neoadjuvant osimertinib with or without chemotherapy versus chemotherapy alone in patients with resectable *EGFR*-mutant NSCLC. The primary endpoint of NeoADAURA is major pathologic response (MPR) rate. The statistical assumptions for the chemotherapy control arm were derived from the literature in NSCLC but not specific to an *EGFR*-mutant population. The true rates of pathologic response to neoadjuvant chemotherapy in patients with *EGFR*-mutant NSCLC are unknown. We report a multi-institutional analysis of surgical and pathologic outcomes in patients with resectable *EGFR*-mutant NSCLC treated with neoadjuvant therapies. **Methods:** This retrospective study evaluated patients at Memorial Sloan Kettering Cancer Center and Dana Farber Cancer Institute with stage II-IIIB N2 (AJCC v8) NSCLC with *EGFR* exon 19 deletions, exon 21 L858R mutations, or exon 18 G719X mutations who received neoadjuvant platinum-based doublet chemotherapy and/or neoadjuvant off-label osimertinib and underwent surgical resection with curative intent. Clinical characteristics, tumor next-generation sequencing results, R0 resection rate, pathologic complete response (pCR) rate, MPR rate, and downstaging rate were evaluated. **Results:** 51 patients with *EGFR*-mutant NSCLC met eligibility criteria and were treated with neoadjuvant osimertinib alone (N=23, 45.1%), platinum-based doublet chemotherapy alone (N=18, 35.3%), or osimertinib and platinum-based doublet chemotherapy (N=10, 19.6%). R0 resection rates were 91.3% with osimertinib, 72.2% with chemotherapy, and 90% with osimertinib and chemotherapy. Rates of pCR were 17.4% with osimertinib, 0% with chemotherapy, and 0% with osimertinib and chemotherapy. Rates of MPR were 43.5% with osimertinib, 0% with chemotherapy, and 10% with osimertinib and chemotherapy. Pathologic tumor downstaging occurred in 47.8% with osimertinib, 44.4% with chemotherapy, and 40% with osimertinib and chemotherapy; pathologic lymph node downstaging occurred in 34.8% with osimertinib, 27.8% with chemotherapy, and 40% with osimertinib and chemotherapy. Among the 4 patients with pCR, 3 had stage IIIA and 1 had stage IIIB adenocarcinomas at diagnosis; three had ex.19 deletions and 1 had an ex.21 L858R mutation. The most common co-occurring tumor genomic alterations were in *TP53* (49%), *CDKN2A/B* (14%), and *RB1* (10%). **Conclusions:** In this real-world multi-institution series, we did not observe pCR or MPR in patients with *EGFR*-mutant NSCLC treated with neoadjuvant chemotherapy. EGFR inhibitors may play an important role in the preoperative management of *EGFR*-mutant lung cancer. Research Sponsor: National Cancer Institute; P30 CA008748.

8053 Poster Session

Leveraging electronic medical records for early lung cancer diagnosis: An evaluation of the C the Signs AI cancer prediction platform using the Mayo data platform.

Seema Dadhania, Bea Bakshi, Brian Herrick, Sana Raoof, Tufia C. Haddad, Tushar Patel, Irbaz Bin Riaz, Miles Payling; Imperial College, London, London, United Kingdom; C the Signs, Cambridge, MA; Harvard Medical School, Boston, MA; Memorial Sloan Kettering Cancer Center, New York, NY; Mayo Clinic, Rochester, MN; Mayo Clinic Comprehensive Care Center, Jacksonville, FL; Mayo Clinic, Phoenix, AZ

Background: In the US, only 27.4% of lung cancer cases are diagnosed early, with 5-year survival rates of 63% for localized and 27% for late-stage cancers. Despite recommendations since 2012 for screening high-risk individuals with low-dose CT, uptake has been limited, and most lung cancer diagnoses occur after symptoms appear. Similarly, chest x-rays, while commonly used as an initial test to investigate patients with symptomatic suspected lung cancer, have demonstrated limited sensitivities between 50-70% and specificities over 80%. Symptoms often overlap with common conditions, making detection challenging, and studies have identified median delays of 187 days from symptom onset to diagnosis. This prolonged interval presents an opportunity for improvement. This study examines the use of the AI cancer prediction platform, C the Signs, to passively screen for lung cancer by leveraging electronic medical records (EMRs) for early lung cancer detection. **Methods:** Utilizing the Mayo data platform, we conducted a retrospective analysis of EMR data from 894,409 patients, including 7,395 individuals diagnosed with lung cancer. We assessed the sensitivity and specificity of the AI cancer prediction platform, in identifying patients at risk of lung cancer. Additionally, we compared the timing of lung cancer risk identification by the AI cancer prediction platform with the timing of diagnoses made by physicians to determine whether the platform enabled earlier detection. **Results:** The AI cancer prediction platform detected 6,749 cases of lung cancer among the 7,395 individuals diagnosed, resulting in an early detection sensitivity of 91.5%. The platform identified 423,249 false positives among the 887,014 patients who did not have lung cancer, leading to a specificity of 52.3%. Additionally, it identified the risk of a lung cancer diagnosis in 26.6% of patients up to five years earlier than the diagnoses made by physicians. **Conclusions:** This study highlights the potential of leveraging EMR data and AI platforms like C the Signs to enhance early lung cancer detection. Chest X-rays, with their reduced sensitivity for early-stage lesions and reliance on symptom-driven use, remain limited as a screening tool. In contrast, the AI platform achieved a sensitivity of 91.5% and identified 26.6% of cases up to five years earlier than traditional diagnoses. These findings underscore the promise of AI-based platforms as supplementary tools for improving early detection and facilitating timely intervention to enhance patient outcomes. Research Sponsor: None.

Survival impact of lymphocytopenia during chemoradiation in locally advanced NSCLC patients treated with adjuvant durvalumab.

Monika Satoskar, Songzhu Zhao, Kenneth Chian, Natalie Johns, Alexander Rudich, Adam Khorasanchi, Lai Wei, Jinesh S. Gheeya, Logan Roof, Asrar Alahmadi, Regan Michelle Memmott, Jacob Kaufman, Carolyn J. Presley, Kai He, Peter G. Shields, David Paul Carbone, Mingjia Li, Dwight Hall Owen; The Ohio State University, Columbus, OH; The Ohio State University College of Medicine, Columbus, OH; Center for Biostatistics, Department of Biomedical Informatics, The Ohio State University, Columbus, OH; The Ohio State University Comprehensive Cancer Center – James Cancer Hospital and Solove Research Institute, Columbus, OH; The Ohio State University Wexner Medical Center, Columbus, OH; The James Cancer Hospital and Solove Research Institute, Columbus, OH; Ohio State University, Columbus, OH; James Cancer Hospital and Solove Research Institute, Columbus, OH; The Ohio State University Comprehensive Cancer Center and the Pelotonia Institute for Immuno-Oncology, Columbus, OH; Division of Medical Oncology, The Ohio State University Comprehensive Cancer Center, Columbus, OH; Division of Medical Oncology, Department of Internal Medicine, Ohio State University, Columbus, OH

Background: Adjuvant durvalumab has transformed the treatment landscape for patients with locally advanced non-small cell lung cancer (NSCLC) following concurrent chemoradiotherapy (CRT). However, in the landmark PACIFIC trial, only one-third of patients achieved long-term disease-free survival, underscoring the need for additional biomarkers to guide patient selection. Lymphocytopenia, a common side effect of CRT, has been associated with poor responses to immunotherapy. In this study, we investigate the incidence, degree, and timing of CRT-induced lymphocytopenia and association with survival among patients receiving durvalumab adjuvant therapy. **Methods:** This retrospective study included patients with unresectable Stage III NSCLC who underwent CRT followed by at least one dose of durvalumab at The Ohio State University. Clinical data was extracted through review of electronic medical records. Absolute lymphocyte count (ALC) was collected at baseline prior to CRT initiation, the lowest ALC during CRT, and 30 days post-CRT. Lymphocytopenia was classified using the Common Terminology Criteria for Adverse Events V5. Overall survival (OS) was calculated from CRT initiation to date of death or loss to follow-up. Cox proportional hazards model was used to evaluate the associations of baseline, lowest, post-CRT ALC, as well as the percentage change in ALC from baseline to lowest (relative ALC change) with OS. **Results:** This study included 118 patients with a mean age of 63.9 years (SD: 9.7), who received durvalumab within 12 weeks of completing CRT. Baseline characteristics were obtained (Table 1). Median baseline ALC was 1645 cells/μL (IQR: 1340–2190), dropping to 300 cells/μL (IQR: 200–450) during CRT and 755 cells/μL (IQR: 510–1040) post-CRT. Grade $\geq$3 lymphocytopenia occurred in 97 patients (82.2%) during CRT. Baseline, lowest, and post-CRT ALC were not associated with OS, but the relative decline in ALC from baseline was strongly associated. A 10% decrease in ALC from baseline was associated with a 48% increased risk of death (HR = 1.48; 95% CI: 1.14–1.91; $p < 0.01$) after adjusting for age, ECOG performance status (PS), histology, PD-L1 expression, chemotherapy regimen, and RT duration. **Conclusions:** Dynamic change in ALC from pre-treatment baseline to nadir during CRT is a strong prognostic indicator for OS in patients with advanced NSCLC receiving adjuvant durvalumab. Studies are warranted to elucidate the underlying mechanisms. Additionally, this highlights lymphocytopenia as a potentially modifiable side effect, which could be addressed with myeloprotective treatment. Research Sponsor: None.

Baseline characteristics.

Characteristic	No. of Patients (%)
ECOG PS = 0	18 (15.4)
ECOG PS = 1	80 (68.4)
Positive PD-L1 expression	80 (76.9)
Squamous cell vs. other	51 (43.2); 67 (56.8)
Weekly carboplatin/paclitaxel vs. other	88 (74.6); 30 (25.4)

8055 Poster Session

Lung cancer screening in high-risk never-smokers with artificial intelligence (LC-SHIELD study).

Molly SC Li, Joyce Chan, Aliss Chang, Jenny Ngai, Alvin H.K. Cheung, Matthew Lun Wong, Kevin Mok, Chapman Lee, Candy Tang, Karina Lau, Kelvin Lam, Tsz Tung Kwong, Chi Hang Wong, Yuxuan Zhang, Yuting Zhang, Tony S.K. Mok, Calvin Ng, Wing Hung Lau; The Chinese University of Hong Kong, Hong Kong, China; Prince of Wales Hospital, Hong Kong, China; Department of Anatomical and Cellular Pathology, The Chinese University of Hong Kong, Hong Kong, Hong Kong; Department of Imaging and Interventional Radiology, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong, China; Imsight Technology Co Limited, Hong Kong, China; Chinese University of Hong Kong, Hong Kong, China; The Chinese University of Hong Kong, Hong Kong, Hong Kong

Background: Approximately 50% of Asian lung cancer patients are never smokers. Screening with low-dose computed tomography (LDCT) of thorax in high-risk never-smokers with family history may reduce mortality. However, implementation of LDCT screening in Asia faces barriers including high cost and shortage of radiologists. Artificial intelligence (AI) programmes designed for automated detection of lung nodules may serve as first-readers, facilitating cost reduction and improving efficiency. LC-SHIELD is a prospective study designed to evaluate the feasibility and clinical utilization of AI-based lung cancer screening in a high-risk never smoker population. **Methods:** This study enrolled never smokers, defined as individuals with a lifetime exposure to fewer than 100 cigarettes, aged between 50 and 75 years, with at least one first-degree relative diagnosed with lung cancer. Participants underwent LDCT of thorax, and the scans were analyzed using LungSIGHT, an AI-assisted software fine-tuned with local data for lung nodule detection. Nodules with a maximum diameter of ≥5mm are classified as AI-positive and referred to radiologists for formal reporting and workup. As a gold standard all scans are retrospectively reviewed by radiologists who are blinded to the LungSIGHT results. Primary endpoint is baseline detection rate of early stage lung cancer and secondary endpoints include sensitivity and specificity of LungSIGHT in nodule detection compared to radiologist assessment. The target sample size is 1000 and here we report the interim analysis. **Results:** Between July and December 2024, total of 405 subjects were enrolled. Median age was 61 (range 50-75) and 266 (66%) were female. Three patients were diagnosed with invasive adenocarcinoma (lung cancer detection rate 0.7%, all EGFR mutation positive) and 12 individuals (3.0%) had suspicious lung nodules requiring further diagnostic workup. Testing of AI algorithm was based on the first 181 subjects. At the testing phase, 78 (43%) were AI-positive with sensitivity and specificity at 81% and 85%, respectively. In the validation cohort (n=224), 86 (39%) were AI-positive with sensitivity and specificity at 73% and 77%, respectively. **Conclusions:** AI assisted first-reader of screening LDCT in high-risk never smokers is feasible. LungSIGHT showed high sensitivity and specificity in lung nodule detection using standard radiologist assessment as gold standard comparator. Recruitment for the study is ongoing. Clinical trial information: NCT06295497. Research Sponsor: AstraZeneca.

8057 Poster Session

Enhancing early detection of lung cancer: Methylation anchor probe for low-signal enrichment (MAPLE).

Wenzhao Zhong, Jun Zhao, Chao-Yang Liang, Xiaosheng He, Nan Lin, Yangjunyi Li, Nina Guanyi Xie, Liyuan Zhao, Zhihui Xu, Lei Song, Yujie Chen, Chen Zhu, Zhijun Zhao, Chenquan Xue, Feng Xu, Yanzhan Yang, Yonghui Li, Xueguang Sun, Xiaohui Wu, Shaohua Ma; Guangdong Lung Cancer Institute, Guangdong Provincial People's Hospital (Guangdong Academy of Medical Sciences), Southern Medical University, Guangzhou, China; Peking University Cancer Hospital and Institute, Beijing, China; China-Japan Friendship Hospital, Beijing, China; The Sixth Affiliated Hospital, Sun Yat-sen University, Guangzhou, China; The Third Affiliated Hospital, Sun Yat-sen University, Guangzhou, China; Shanghai Xiaohe Medical Laboratory Co., Ltd., Shanghai, China

Background: Non-Small Cell Lung Cancer (NSCLC) is among the most lethal cancers worldwide. Lung adenocarcinoma (LUAD) and lung squamous cell carcinoma (LUSC) represent approximately 80% of NSCLC cases in China. While low-dose computed tomography (LDCT) is widely used for annual screening, its high false-positive rate highlights the need for more accurate early detection methods. Circulating tumor DNA (ctDNA) analysis provides a promising non-invasive alternative for early cancer detection. However, conventional hybrid capture methods lack the sensitivity to detect low-abundance ctDNA in early-stage cancers. Previously, we developed ultra-sensitive Methylation Anchor Probes for Low signal Enrichment (MAPLE) that significantly improved the detection of colorectal cancer (Xie et al., 2024). Here, we have advanced this technology to develop a novel assay to enhance early detection of NSCLC and distinguish LUAD from LUSC, paving the way for more personalized treatment strategies. **Methods:** NSCLC-related methylation haplotypes were identified using in-house whole-genome bisulfite sequencing data from lung cancer tumor tissues and paired normal adjacent tissues (NATs). Haplotype selection was performed by filtering for those with a frequency difference greater than 0.1 between tumor and NATs and a frequency below 0.001 in healthy cfDNA, resulting in a panel targeting 12,904 methylation haplotypes. The panel was evaluated on 234 clinical samples, including 44 LUSC patients, 43 LUAD patients, 19 individuals with chronic obstructive pulmonary disease (COPD), and 128 healthy controls. All cfDNA samples underwent bisulfite conversion, library preparation, hybrid capture using the custom panel, and next-generation sequencing (NGS). The dataset was split into a 75% training set and a 25% validation set. A primary classifier was developed to identify cancer samples, and true positives were further analyzed with a subtype classifier to differentiate between LUAD and LUSC. Model performance was assessed for robustness using 40 resampling processes. **Results:** The methylation panel combined with a machine-learning classifier achieved an AUC of 0.93 (0.93–0.93) in the training set and 0.91 (0.91–0.92) in the validation set in the detection of NSCLC. Furthermore, the assay effectively distinguished COPD patients from cancer cases, with a specificity of 92.5% (90.0%–95.9%). Additionally, the subtype classifier accurately differentiated LUAD from LUSC with 100% accuracy. **Conclusions:** We developed a technique to specifically enrich NSCLC-related methylation haplotypes, improving sensitivity for early-stage NSCLC detection. The assay demonstrated strong performance in accurately distinguishing LUAD from LUSC, highlighting its potential to guide treatment decisions. The MAPLE platform is versatile and shows promise for broader applications in cancer early detection. Research Sponsor: Shanghai Xiaohe Medical Laboratory Co., Ltd.

Hypofraction radiotherapy followed by immune checkpoint inhibitors for locally advanced non-small cell lung cancer: A phase I/II trial.

Xiao-yang Li, Yan Li, Bing Yan, Dong Qian; Anhui Provincial Hospital, Hefei, China; Department of Radiation Oncology, The First Affiliated Hospital of USTC, Division of Life Sciences and Medicine, University of Science and Technology of China, Hefei, China

Background: To explore the safety and primary efficacy of hypofraction radiotherapy followed by immune checkpoint inhibitors (ICI) for stage III locally advanced non-small cell lung cancer patients. **Methods:** Patients with stage III non-small cell lung cancer were enrolled to receive hypofraction radiotherapy (48-64Gy/12-16f) followed by ICI maintenance treatment. After the completion of radiotherapy, one-year maintenance ICI treatment was encouraged. The primary objective was to explore the toxicity of hypofractionated radiotherapy with immunotherapy. The secondary objective was survival outcome. We also performed multicolor immunohistochemistry (mIHC) of tumor tissues, peripheral blood single-cell RNA sequencing (scRNA-seq) and flow cytometry to characterize the immune microenvironment of enrolled patients. **Results:** According to the inclusion criteria, totally 51 patients were enrolled from June 2021 to January 2024. The median follow-up time was 28 months (8-22 months). After the completion of hypofractionated radiotherapy, 13 patients received no or less than 5 cycles of immunotherapy. All kinds of radiation-induced toxicity (≥ grade 3) occurred in 17 patients (33.3%). The rate of over grade 3 PBT injury and over grade 3 radiation-induced pneumonitis was 3.9% and 17.6% respectively, resulting in 11.8% of over grade 3 cough and 9.8% of over grade 3 dyspnea. No over grade 3 radiation-induced esophagitis occurred. The median progression-free survival (PFS) was 28 months with 1-year PFS rate of 72.1% and 2-year PFS rate of 54.7%. The median overall survival (OS) was not reached with 1-year OS rate of 84.0% and 2-year OS rate of 61.6%. In subgroup analysis, high-dose (60-64Gy/15-16f) group did not demonstrate survival benefit to low-dose group (48-52Gy/12-13f), but more grade III and higher toxicity (41.2% vs. 17.6%, p=0.002). In addition, mIHC, scRNA-seq and flow cytometry showed an increase in the number of anti-tumor immune cells in the treated tumor tissues, as well as an expansion of T-cell clones with cytotoxic T-cell phenotype and enhanced anti-tumor activity of neutrophils in the peripheral blood. **Conclusions:** Hypofraction radiotherapy (48-64 Gy/12-16f) with ICI treatment was safe and efficient. But the use of high dose (over 60Gy/15f) should be alerted due to its toxicity. Further, hypofraction radiotherapy can provide patients with an immune-activated tumor microenvironment that makes them respond better to immunotherapy. Clinical trial information: NCT05269485. Research Sponsor: NSFC 82102821.

Clinical characteristic of total patients.

	Total patients n=51	High-dose Subgroup (≥60 Gy) n=34	Low-dose Subgroup (<60 Gy) n=17	Statistical Method and p value
Gender				
Male	48 (94.1%)	33 (97.1%)	15 (88.2%)	χ^2 test
Female	3 (5.9%)	1 (2.9%)	2 (11.8%)	p=0.255
Age				
Median (Range)	69 (41-84)	65 (51-83)	70 (41-84)	Independent sample t-test p=0.916
Clinical Stage				
II	4 (7.8%)	2 (5.9%)	2 (11.8%)	Mann-Whitney
IIIA	11 (21.6%)	8 (23.5%)	3 (17.6%)	p=0.304
IIIB	23 (45.1%)	13 (38.2)	10 (58.8%)	
IIIC	13(25.5%)	11 (32.4)	2 (11.8%)	
Pathology				
Squamous Cell Carcinoma	41 (80.4%)	29 (85.3%)	12 (70.6%)	χ^2 test
Adenocarcinoma	10 (19.6%)	5 (14.7%)	5 (29.4%)	p=0.190
Tumor Location				
Centrally Located	38 (74.5%)	30 (88.2%)	8 (47.1%)	χ^2 test
Peripherally Located	13 (25.5%)	4 (11.8%)	7 (52.9%)	p=0.003
Treatment Modality				
No Inductive ICI Therapy	24 (47.1%)	19 (55.9%)	5 (29.4%)	χ^2 test
Inductive ICI Therapy	14 (27.5%)	6 (17.6%)	8 (47.1))	p=0.071
CRT only	13 (25.5%)	9 (26.5%)	4 (23.5%)	
Cycles of ICI Treatment				
Median (Range)	3 (0-24)	2 (0-24)	4 (0-24)	Independent sample t-test p=0.776
Type of ICI				
PD-1 Inhibitors	21 (41.2%)	11 (32.4%)	10 (58.8%)	χ^2 test
PD-L1 Inhibitors	16 (31.4%)	13 (38.2%)	3 (17.6%)	p=0.220
PD-L1 level				
<1%				
1-50%				
>50%				
ITV Volume				
Median (Range)	69.44 (17.05-297.10)	73.24 (21.96-297.10)	69.44 (17.05-144.92)	Independent sample t-test p=0.198
PTV Volume				
Median (Range)	169.19 (64.75-548.64)	174.78 (78.11-548.64)	155.27 (64.75-323.03)	Independent sample t-test p=0.370

8059 Poster Session

Clinical outcomes with definitive surgery or radiotherapy after neoadjuvant immunochemotherapy in stage II-III NSCLC: Full cohort pragmatic analysis.

Jie He, Zhenlin Yang, Shuaibo Wang, Xiangyang Yu, Xiaotong Guo, JianJiao Ni, Linhai Zhu, Jian Hu, Guoqing Zhang, Chun Chen, Chun Chen, Guangjian Zhang, Bin Hu, Cui Gao, Lipin Liu, Pan Chen, Huajie Xing, Chuanbao Xia, The NeoR-World Research Group; National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China; Department of Thoracic Surgery, Beijing Institute of Respiratory Medicine and Beijing Chao-Yang Hospital, Capital Medical University, Beijing, China; National Cancer Center/National Clinical Research Center for Cancer, Cancer Hospital & Shenzhen Hospital, Shenzhen, Guangdong, China; Department of Radiation Oncology, Fudan University Shanghai Cancer Center, Shanghai, China; The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China; The First Affiliated Hospital of Medical School of Zhejiang University, Hangzhou, Zhejiang, China; The First Affiliated Hospital of Zhengzhou University, Zhengzhou, China; Fujian Medical University Union Hospital, Fuzhou, Fujian, China; Department of Thoracic Surgery, Fujian Medical University Union Hospital, Fuzhou, China; The First Affiliated Hospital of Xian Jiaotong University, Xian, shaanxi, China; Department of Radiotherapy, Beijing Hospital, National Center of Gerontology, Institute of Geriatric Medicine, Chinese Academy of Medical Sciences, Beijing, China; Zunyi Medical University Affiliated Hospital, Zunyi, China; Department of Thoracic Surgery, Chongqing University Cancer Hospital, Chongqing, China; The Affiliated People's Hospital of Fujian University of Traditional Chinese Medicine, Fujian, China

Background: Recently, several landmark randomized controlled trials on neoadjuvant immunochemotherapy (NIC) have significantly changed the treatment paradigm for locally advanced NSCLC. However, 8.8-19.0% of patients (pts) receiving NIC did not undergo surgery due to various reasons. The treatment strategies and clinical outcomes following NIC for stage II-III NSCLC, encompassing both surgical and non-surgical approaches, remain unclear. **Methods:** We conducted a multicenter, retrospective cohort study involving stage II-III (T1-4N0-2) pts who underwent radical surgery or radiotherapy after NIC in routine clinical practice across 12 medical centers in China between January 2018 and December 2023. For pts receiving radical radiotherapy, we documented the reasons for non-surgical management, and planned surgical procedures. Propensity score matching (PSM) was performed based on age, gender, smoking history, clinical stage, and histology to balance the clinicopathologic characteristics. The primary outcomes were progression free survival (PFS) and overall survival (OS). **Results:** 967 pts were included: 683 (70.6%) underwent surgery and 284 (29.4%) received radiotherapy. Reasons for radiotherapy after NIC included potentially resectable but declined surgery after shared decision-making (65.5%, 186/284), functionally unresectable (14.4%, 41/284), and technically unresectable (20.1%, 57/284), respectively. At the database lock (November 24, 2024; median follow-up: 23.3 months), PFS (HR: 0.32, 95% CI: 0.23-0.44, p<0.001) and OS (HR: 0.41, 95% CI: 0.26-0.66, p<0.001) were significantly improved in pts undergoing surgery after PSM. PFS across most key subgroups favored surgery: stage IIIA (HR: 0.34, 95% CI: 0.21-0.55, p <0.001), stage IIIB (HR: 0.39, 95% CI: 0.24-0.63, p <0.001), (planned) pneumonectomy (HR: 0.47, 95% CI: 0.26-0.85, p=0.013) and (planned) lobectomy (HR: 0.24, 95% CI: 0.13-0.45, p<0.001). However, the pts planned for pneumonectomy in radiotherapy group exhibited similar OS compared to those undergoing pneumonectomy. **Conclusions:** Among pts with locally advanced NSCLC treated with NIC, radical surgery demonstrated long-term clinical benefit. Research Sponsor: None.

	Subgroups	N (S)	N (R)	HR (95% CI)	p-value
PFS	All patients	365	183	0.32 (0.23, 0.44)	<0.001
	Disease stage				
	II	34	17	0.05 (0.01, 0.24)	<0.001
	IIIA	175	89	0.34 (0.21, 0.55)	<0.001
	IIIB	142	76	0.39 (0.24, 0.63)	<0.001
	(Planned) Surgery				
	Pneumonectomy	66	66	0.47 (0.26, 0.85)	0.013
	Left pneumonectomy	46	46	0.52 (0.26, 1.04)	0.066
	Lobectomy	106	54	0.24 (0.13, 0.45)	<0.001
OS	All patients	365	183	0.41 (0.26, 0.66)	<0.001
	Disease stage				
	II	34	17	0.08 (0.01, 0.44)	0.004
	IIIA	175	89	0.60 (0.28, 1.25)	0.17
	IIIB	142	76	0.45 (0.23, 0.87)	0.018
	(Planned) Sugery				
	Pneumonectomy	66	66	0.87 (0.37, 2.06)	0.76
	Left pneumonectomy	46	46	0.59 (0.23, 1.49)	0.26
	Lobectomy	106	54	0.33 (0.14, 0.76)	0.009

ImmunoDriver-1: Driver alterations (dAlts) and their immunological implications in early and metastatic non-small cell lung cancer (NSCLC).

Jay M. Lee, Brooke Rhead, Edward B. Garon, Jonathan W. Goldman, Maria Antonia Velez Velez, Arjan Gower, Aaron Lisberg, Paul Christopher Boutros, Steven M. Dubinett, Edward Williams, Catherine Traverso, Stamatina Fragkogianni, Michael A. Thompson, Jacob Mercer, Amy Lauren Cummings; Division of Thoracic Surgery, University of California, Los Angeles (UCLA), Los Angeles, CA; Tempus AI, Inc., Chicago, IL; Division of Hematology/Oncology, University of California, Los Angeles, Los Angeles, CA; Department of Medicine, Division of Hematology/Oncology, University of California, Los Angeles (UCLA), Los Angeles, CA; Department of Medicine, Division of Hematology/Oncology, University of California, Los Angeles, Los Angeles, CA; Jonsson Comprehensive Cancer Center, UCLA, Los Angeles, CA; University of California Los Angeles Translational Oncology Research, Los Angeles, CA

Background: NSCLC treatments and clinical trials include targeted agents and immunotherapy (IO) across stages, yet dAlts and how they relate to the tumor immune microenvironment (TIME) are incompletely characterized in early NSCLC (eNSCLC; stage I-III) and metastatic NSCLC (mNSCLC; stage IV). Here, we evaluated the NSCLC TIME by dAlt status to inform IO biomarker strategies. **Methods:** From the Tempus Database, we selected de-identified lung adenocarcinoma samples sequenced by xT DNA assay (eNSCLC n=5,535; mNSCLC n=10,299), a subset with whole transcriptome analysis. Targetable dAlts were defined as classic (c) (L858R and exon 19 del) or non-classic (nc) *EGFR*, *KRAS* G12C, other non-G12C variants, other guideline defined dAlts (ALK, ROS1, RET, NTRK1-3 fusions, ERBB2 alt, METex14), or no dAlt. Immune cell proportions were estimated by quanTIseq. Additional markers, PD-L1 TPS (IHC) and TMB (mt/mB; DNAseq) were analyzed. Significance ($p<0.05$) was assessed using χ^2 or Wilcoxon/Kruskal-Wallis rank sum tests. **Results:** The dAlt prevalence was similar ($|\Delta| < 2\%$) across early and late stage (Overall %: cEGFR=13, ncEGFR=2.9, KRAS G12C=15 and KRASother=22). The prevalence of other dAlt were less than 4% across stages. The CD8 proportion was higher in eNSCLC than mNSCLC ($p<0.001$). Across stages, CD4 Treg and CD8 proportions in the *KRAS* G12C cohort were nearly identical to the non-dAlt cohort, while c/nc*EGFR* tumors exhibited the lowest percentage of CD8 cells and higher Tregs cells compared to non-dAlt tumors (Table). PD-L1 and TMB were similar between *KRAS* G12C and non-dAlt tumors and lowest among c/nc*EGFR* (Table). **Conclusions:** This real-world analysis demonstrated similar dAlt prevalence across eNSCLC and mNSCLC, while the TIME was distinct across stage and dAlts. The TIME of *KRAS* G12C tumors was similar to non-dAlt tumors, and was least immunogenic in the c/nc*EGFR* cohort. These findings highlight immunological differences across stages and dAlts that should be considered when developing IO strategies. Research Sponsor: Tempus AI, Inc.

Group	IO marker	Overall	No dAlt	cEGFR	ncEGFR	KRAS G12C	KRAS other	Other dAlt
eNSCLC								
	% CD8 cells[1]*	1.3 (0.5, 2.4)	1.4 (0.6, 2.8)	0.9 (0.4, 1.7)	1.0 (0.5, 1.9)	1.4 (0.6, 2.6)	1.3 (0.5, 2.4)	1.1 (0.5, 2.1)
	% Tregs[1]*	6.9 (4.8, 9.2)	6.3 (4.2, 8.8)	7.4 (5.6, 9.4)	8.2 (5.8, 10.3)	7.0 (5.1, 9.3)	7.1 (5.2, 9.3)	6.7 (4.6, 8.6)
	% PDL1[2]*	22	20	9.3	7.9	31	25	24
	TMB*	5.8 (3.2, 9.5)	7.9 (3.7, 13.2)	3.2 (2.1, 4.7	4.2 (2.3, 6.3)	6.8 (4.2, 10.0)	5.8 (3.7, 8.9)	3.2 (1.6, 5.3)
mNSCLC								
	% CD8 cells[1]*	0.6 (0.04, 1.6)	0.8 (0.1, 1.9)	0.4 (0.0, 1.3)	0.5 (0.0, 1.5)	0.7 (0.1, 1.7)	0.5 (0.01, 1.5)	0.5 (0.0, 1.4)
	%Tregs[1]*	4.0 (2.6, 5.9)	3.8 (2.4, 5.6)	4.2 (2.9, 6.1)	4.7 (3.0, 6.8)	4.2 (2.7, 6.0)	4.0 (2.6, 6.0)	3.9 (2.6, 5.6)
	% PDL1[2]*	28	24	15	17	37	34	34
	TMB*	5.8 (3.2, 10.0)	7.9 (4.2, 13.1)	3.7 (2.1, 5.8)	4.2 (2.6, 6.8)	7.4 (5.2, 11.1)	6.3 (4.2, 10.0)	3.2 (1.6, 5.8)

[1]Median (IQR); [2]PDL1 >50; *$p<0.001$, excluding "Overall."

8061 Poster Session

Unique mutational landscape and therapeutic implications in non-small cell lung cancer with comorbid fibrotic interstitial lung disease.

Jacob Michalski, Joel W. Neal; Stanford Health Care, Stanford, CA; Stanford Cancer Institute, Stanford University, Stanford, CA

Background: Patients with established interstitial lung disease (ILD) have both increased risk of developing non-small cell lung cancer (NSCLC) and higher mortality than patients without a history of ILD. We hypothesized the mutational landscape of NSCLC arising in the setting of ILD would be different than sporadic or smoking-associated cancers, potentially leading to different treatment options given the question of safety of immune checkpoint inhibitors (ICIs) in this population. **Methods:** We retrospectively identified 330 patients with NSCLC, of which 77 patients had pre-existing diagnoses of ILD with probable or definite usual-interstitial pattern made by radiographic or biopsy findings for comparison to randomly selected patients with NSCLC without clinically apparent ILD. Clinical characteristics, histologic information, mutational data, and treatment regimens were collected using the Stanford Research Repository and compared between patients with NSCLC and established ILD (LC-ILD) and NSCLC without ILD (LC). Statistical comparisons between groups were done with Mann-Whitney testing with significance set at $p<0.05$. **Results:** Baseline characteristics including age, sex, race, ethnicity, smoking status, NSCLC type, and NSCLC stage at diagnosis did not differ between the LC-IPF and LC groups. There was significantly lower prevalence of *EGFR* mutations in the LC-IPF group (33.0% vs 3.0%, $p<0.0001$) and significantly higher prevalence of *KRAS G12D* mutations (19.0% vs 41.7%, $p=0.05$). Baseline tumor proportion score (TPS) between LC and LC-ILD groups was not significantly different (28.2% vs 16.3%, $p=0.063$) however there were significantly fewer patients with high PD-L1 expression (TPS $\geq$ 50%) in the LC-ILD group (32.0% vs 16.7%, $p=0.036$). Occurrence of clinically significant treatment-related pneumonitis occurred in 15 patients in the LC-ILD group with etiologies identified as radiation (n=8, N=20, 40.0%), surgery (n=1, N=40, 2.5%), osimertinib (n=1, N=1, 100%), pembrolizumab (n=2, N=5, 40.0%), docetaxel (n=2, N=4, 50.0%, and pemetrexed (n=1, N=19, 5.7%). **Conclusions:** These retrospective data highlight the differences in driver mutations in NSCLC in patients with preceding fibrotic lung disease, suggesting potentially divergent biologic underpinnings for tumorigenesis. These results, particularly the under-representation of *EGFR*-mutations, over-representation of KRAS G12D mutations, and scarcity of therapeutically actionable mutations in the LC-ILD population, lead to limited therapeutic options. Surgically-associated pneumonitis was rare, but radiation, docetaxel, and pembrolizumab appeared high risk for pneumonitis in treated patients, suggesting need careful consideration of risks when treating this unique population. Research Sponsor: None.

8062 Poster Session

Differential prognostic significance of distant and locoregional recurrence on survival in surgically resected non-small cell lung cancer post-chemotherapy: Multicenter dynamic prediction with landmark model.

Zeliang Ma, Zhouguang Hui; National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

Background: Recurrence remains a significant challenge in patients with surgically resected non-small cell lung cancer (NSCLC) following adjuvant chemotherapy. Recurrence status evolves over the course of follow-up, dynamically influencing survival outcomes. This study aimed to investigate the differential impact of distant metastasis (DM) and locoregional recurrence (LR) on survival, and to develop prognostic models to guide treatment strategies and individualize follow-up protocols. **Methods:** From four institutions, patients with pN2 NSCLC who underwent complete resection followed by four cycles of platinum-based doublet chemotherapy were included. A dynamic prediction landmark model was constructed to assess the impact of LR and DM on survival. The primary endpoint was overall survival (OS). Baseline factors included age, sex, smoking history, histology, tumor laterality, pT stage, and the number of positive lymph nodes, while DM and LR status were treated as time-dependent covariates. **Results:** A total of 2,120 patients were included in the study, with a median follow-up time of 55.80 months (IQR: 39.47–85.12). The landmark model identified older age, smoking history, advanced T stage, DM, and LR as significant factors associated with worse OS. DM had the most substantial impact on OS (odds ratio [OR], 3.85; 95% CI, 3.32–4.48; $P < 0.01$), while LR also significantly decreased OS (OR, 2.07; 95% CI, 1.73–2.47; $P < 0.01$). Multivariate Cox analysis revealed that the pT stage, number of positive lymph nodes, and histology were independently associated with DM. A nomogram was developed to predict the risk of DM for individual patients, categorizing them into three distinct risk subgroups. Postoperative radiotherapy did not significantly improve OS in the low- or high-risk subgroups but demonstrated a survival benefit in the medium-risk subgroup (hazard ratio [HR], 0.73; 95% CI, 0.63–0.87; $P < 0.01$). Intensified systemic therapy and closer monitoring would be required for patients in the high-risk subgroup. **Conclusions:** The dynamic prediction model estimated future survival probabilities based on individual recurrence status throughout follow-up in patients with surgically resected NSCLC post-chemotherapy. Both DM and LR significantly affected OS, with DM being more detrimental. The DM risk nomogram aids in assessing the benefits of additional treatments and guiding personalized follow-up strategies. Research Sponsor: None.

8063 Poster Session

Neoadjuvant hypofractionated radiotherapy plus tislelizumab with anlotinib followed by adjuvant tislelizumab with anlotinib in patients with resectable non-small cell lung cancer (NSCLC): Preliminary analysis of a phase II trial (NEO-PIONEER).

Min Fang, Taobo Luo, Yongling Ji, Jian Zeng; Zhejiang Cancer Hospital (Zhejiang Cancer Center), Hangzhou, China; Zhejiang Cancer Hospital, Hangzhou, China; Department of Thoracic Surgery, Zhejiang Cancer Hospital, Hangzhou, China

Background: Although neoadjuvant immune checkpoint inhibitors (ICIs) combined with chemotherapy is the current standard of care for resectable NSCLC, the optimal combination strategy to improve efficacy with low toxicity remains to be explored. Preclinical and clinical studies have shown that anti-angiogenic therapy can enhance the efficacy of immunotherapy and sensitize radiotherapy through a variety of mechanisms. We designed a trial to test the activity of triple therapy of radiotherapy, angiogenesis inhibitors and ICIs for resectable NSCLC. **Methods:** This is a prospective, single-arm, phase II (NCT06379087) to explore the efficacy and safety of hypofractionated radiotherapy followed by sequential tislelizumab and anlotinib in the perioperative treatment of resectable NSCLC. A total of 20 eligible patients aged 18 years or older, with histologically confirmed stage II/IIIA resectable NSCLC, and without prior systemic anticancer treatment or known EGFR mutations, ALK rearrangements or ROS1 fusions are enrolled. The treatment regimen involved hypofractionated radiotherapy on d1-3 (24 Gy/3 fractions), followed by tislelizumab plus anlotinib within 1 week for 2 cycles after radiotherapy. Patients without disease progression after two cycles were followed by surgical resection within 4-6 weeks after the last dose of neoadjuvant treatment, and receive adjuvant treatment with tislelizumab plus anlotinib after surgery up to 1 year. The primary endpoint was pCR rate. And the secondary endpoint was MPR rate, 1-year EFS rate and the incidence of treatment-related AE. **Results:** Between May 1, 2024, and December 31, 2024, a total of 10 patients were enrolled. 6 (60%) of them had pathological stage IIIA. All patients enrolled have completed radiotherapy and 2 cycles of neoadjuvant treatment with tislelizumab plus anlotinib. 1 patient experienced disease progression following neoadjuvant and did not receive surgery. 7 patients have underwent surgery. While 2 patients were waiting surgery. Among the 7 patients who underwent surgery, 5 (71.4%) of 7 patients achieved pCR, all 7 patients demonstrated a MPR. In terms of safety, 1 patient experienced grade 3-4 treatment related adverse events, which was alanine aminotransferase and aspartate aminotransferase. There were no treatment-related deaths reported during the study period. **Conclusions:** Preoperative hypofractionated radiotherapy followed by immunotherapy and anti-angiogenesis therapy is tolerable, leads to a clinically significant pCR. Clinical trial information: NCT06379087. Research Sponsor: None.

Five-year survival outcomes from CRES^{3}T: S-1 plus cisplatin with concurrent radical-dose radiotherapy followed by surgery for superior sulcus tumor.

Kazuya Takamochi, Kenji Suzuki, Morihito Okada, Seiji Niho, Satoshi Ishikura, Shunsuke Oyamada, Takuhiro Yamaguchi, Hirotoshi Horio, Norihiko Ikeda, Fumihiro Tanaka, Satoshi Shiono, Tomohiro Haruki, Hidemi Suzuki, Hiroyuki Ito, Hidetaka Uramoto, Norihito Okumura, Masahiro Tsuboi, Advanced Clinical Trial Chest Surgery Group (ACTG); Department of General Thoracic Surgery, Juntendo University School of Medicine, Tokyo, Japan; Department of Surgical Oncology, Hiroshima University, Hiroshima, Japan; Department of Thoracic Oncology, National Cancer Center Hospital East, Mibu, Japan; Department of Radiation Oncology, St. Luke's International Hospital, St. Luke's International University, Tokyo, Japan; Department of Biostatistics, Japanese Organisation for Research and Treatment of Cancer (JORTC) Data Center, Tokyo, Japan; Division of Biostatistics, Tohoku University Graduate School of Medicine, Sendai, Japan; Department of Thoracic Surgery, Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, Tokyo, Japan; Department of Surgery, Tokyo Medical University, Tokyo, Japan; University of Occupational and Environmental Health, Kitakyushu, Japan; Department of Thoracic Surgery, Yamagata Prefectural Central Hospital, Yamagata, Japan; Division of General Thoracic Surgery, Department of Surgery, Faculty of Medicine, Tottori University, Tottori, Japan; Department of General Thoracic Surgery, Chiba University Graduate School of Medicine, Chiba, Japan; Kanagawa Cancer Center, Yokohama, Japan; Division of Thoracic Surgery, Saitama Cancer Center, Saitama, Japan; Department of Thoracic Surgery, Kurashiki Central Hospital, Kurashiki, Japan; Department of Thoracic Surgery and Oncology, National Cancer Center Hospital East, Kashiwa, Japan

Background: CRES^{3}T is a multicenter, single-arm, confirmatory trial of S-1 plus cisplatin and concurrent radical-dose thoracic radiotherapy (TRT) followed by surgery in patients with superior sulcus tumor (SST). The 3-year overall survival (OS) and progression-free survival (PFS) rates were 73% (95% confidence interval [CI]; 60–83%) and 53% (95% CI; 40–65%), respectively. The primary endpoint, 3-year OS rate, was met. We report the exploratory analyses of survival outcomes approximately 5 years after the last patient was enrolled. **Methods:** Patients with SST (pathologically proven non-small cell lung cancer that directly invades the chest wall, including the first rib or further cephalad, subclavian artery, or subclavian vein according to computed tomography or magnetic resonance imaging) received induction therapy comprising three cycles of S-1 plus cisplatin with concurrent TRT (66 Gy in 33 fractions) followed by surgery. S-1 was administered orally at 40 mg/m^2 twice daily for 14 days along with an intravenous infusion of cisplatin (60 mg/m^2) on day 1. The treatment cycles were repeated every four weeks. The 5-year OS, 5-year PFS, and patterns of postoperative recurrence were analyzed. Prognostic factors of OS were analyzed in patients who underwent surgical resection using Cox proportional hazard model. **Results:** The median follow-up duration for 60 eligible patients was 67.1 months. The 5-year OS and PFS rates were 66.3% (95% CI; 52.8–76.8) and 48.1% (95% CI: 35.0–60.0), respectively. The median follow-up duration for 49 patients with surgical resection was 71.0 months. The 5-year OS and PFS rates were 71.0% (95% CI; 56.0–81.7) and 52.8% (95% CI: 37.9–65.6), respectively. Age was the only significant prognostic factor for OS (P = 0.01, HR 1.1, 95% CI; 1.02–1.20). Sex, smoking status, clinical T stage, clinical N stage (cN0 versus cN1/ipsilateral supraclavicular cN3), symptoms associated with brachial plexus involvement, histology, preoperative serum CEA and CYFRA levels, pathological complete response, and major pathological response had no significant prognostic impacts on OS. Twenty (41%) patients developed postoperative relapse. The patterns of postoperative relapse were locoregional only in one (2%), distant metastasis only in 16 (33%), and both in three (6%) patients. **Conclusions:** Better 5-year survival outcomes of CRES^{3}T compared to those in the pivotal studies (5-year OS: 56% in JCOG9806 and 44% in SWOG9416/INT0160) indicated that induction therapy using S-1 plus cisplatin and concurrent radical-dose TRT followed by surgery could be a new standard treatment for patients with SST. Clinical trial information: s031180401. Research Sponsor: None.

8065 Poster Session

Initial results of a screening trial for evaluating oncogenic drivers in Japanese patients with surgically resected early-stage non-small cell lung cancer: LC-SCRUM-Advantage.

Yuki Matsumura, Kiyotaka Yoh, Yoshitaka Zenke, Shingo Kitagawa, Joji Samejima, Toshio Kasugai, Hiroshi Saijo, Takafumi Hashimoto, Ryu Kanzaki, Ikue Kamei, Gaku Yamamoto, Yu Tanaka, Hiroki Izumi, Tetsuya Sakai, Eri Sugiyama, Shigeki Umemura, Shingo Matsumoto, Masahiro Tsuboi, Koichi Goto; National Cancer Center Hospital East, Kashiwa, Japan; Nippon Medical School Hospital, Tokyo, Japan; Matsunami General Hospital, Gifu, Japan; Sapporo Minami-Sanjo Hospital, Sapporo, Japan; Oita Prefectural Hospital, Oita, Japan; Osaka International Cancer Institute, Osaka, Japan; Itami City Hospital, Hyogo, Japan

Background: The LC-SCRUM-Advantage is a screening trial to evaluate oncogenic drivers in patients with surgically resected early-stage non-small cell lung cancer (NSCLC). Recent clinical trials, such as the ADAURA and ALINA trials, have demonstrated the efficacy of molecular targeted therapy as adjuvant therapy following surgery for patients with early-stage NSCLC harboring oncogenic drivers. Our study aims to determine the proportion of early-stage NSCLC with any actionable oncogenic drivers that are candidates for adjuvant targeted therapy. This abstract presents the initial data collected until Dec 2024. **Methods:** Patients with operable clinical stage I to III NSCLC were eligible for this study. Surgical tumor samples were collected post-surgery, and genomic analysis of oncogenic drivers was centrally evaluated using a next-generation sequencing system, the Oncomine Precision Assay, which targets 50 gene alterations. PD-L1 immunohistochemistry using the 22C3 antibody was also performed on the submitted tumor samples. If possible, preoperative biopsy tumor samples were also collected and evaluated using the AmoyDx Pan Lung Cancer PCR Panel. An actionable oncogene was defined as EGFR, ALK, ROS1, KRAS, BRAF, HER2, RET, MET, NRG1, or NTRK genes. **Results:** Between August 2022 and December 2024, 646 patients were enrolled in the LC-SCRUM-Advantage. Among them, 57% had stage I, 27% had stage II, 16% had stage III, and 71% had adenocarcinoma histology. Of the 591 evaluable patients in this analysis, an actionable oncogenic driver was found in 46% of cases (274/591). Identified oncogenic drivers included 190 (24%) EGFR mutations (89 L858R, 77 ex19del, 10 ex20ins, 14 uncommon), 26 (4%) MET ex14 skipping, 20 (3%) KRAS G12C, 18 (3%) HER2 mutations (including ex20ins), 7 (1%) ALK fusion, 5 (1%) NRG1 fusion, 4 (1%) BRAFV600E, 2 (<1%) RET fusions, 1 (<1%) ROS1 fusion, and 1 (<1%) NTRK fusion. PD-L1 expression was observed in 19% for >50%, 40% for 1-49%, and 41% for <1%. Among patients with paired tumor samples from surgery and preoperative biopsy, the concordance rate of detected actionable oncogenic drivers was 95%. **Conclusions:** Our study found actionable oncogenic drivers in 46% of Japanese patients with surgically resected early-stage NSCLC. Based on historical control, the proportion of any oncogenic drivers in early-stage NSCLC is similar to that in advanced NSCLC. Comprehensive genomic screening of patients with early-stage NSCLC will accelerate the development of clinical trials for adjuvant-targeted therapy. Research Sponsor: CHUGAI PHARMACEUTICAL CO., LTD., Eli Lilly Japan K.K.

Are we casting the net wide enough? Applying the proposed lung cancer screening criteria in single centre lung cancer resections.

Clement Lim, Donna Cribb, Andrew Byrne, Leeona Gallagher, Tara Hannon, Timothy Dudley Clay, Pragnesh Joshi, James Edelman, Eli Gabbay, Kuan Pin Lim; St John of God Subiaco Hospital, Perth, Australia; St. John of God Subiaco Hospital, Perth, Australia; St. John of God Hospital, Perth, Australia; St. John of God Subiaco Hospital, Perth, Western Australia, Australia

Background: The Australian National Lung Cancer Screening Program (NLCSP) commences in July 2025. Thoracic surgery is a key treatment option in screen-detected early-stage lung cancers. St. John of God Subiaco Hospital is a private hospital in Western Australia (WA) and is part of the Australian and New Zealand Thoracic Clinical Quality Registry (ANZTHOR) collaborative database as one of the inaugural sites. We examined the resected primary lung cancers at our centre to assess if our cohort aligned with the characteristics of the targeted at-risk patient population as defined by the NLCSP proposed screening criteria. **Methods:** Demographic patient data was retrieved from ANZTHOR at our centre who underwent surgical resection for primary lung cancer between March 2023 to November 2024. Retrospective data analysis was then conducted on the mode and symptoms at time of diagnosis, age and smoking history. The NLCSP criteria for screening (aged 50-70 years, history of ≥30 pack-years smoking in current smokers or ex-smokers who quit within the last 10 years) was then applied to this cohort of privately insured primary lung cancer patients to evaluate the proportion of patients that would have been eligible/ineligible for screening. **Results:** Of the 107 patients, median age was 71 (range 42-87) and 67 (63%) were females. 96 (90%) patients were asymptomatic and 98 (92%) were early-stage cancers (Stage 2 and below). 58 (54%) patients were >70 years old and 34 (32%) were never-smokers. **Conclusions:** A substantial proportion (86%) of this cohort of asymptomatic resected lung cancer patients would not have been identified via lung cancer screening by NLCSP screening criteria. This is likely in part related to the different demographics of patients attending private hospitals but nonetheless raises the possibility that the current screening criteria is overly stringent and will miss many primary lung cancer presentations. Supplementary methods (i.e. blood biomarker testing) may improve screen detection rates of lung cancer and enable better identification of at-risk groups. Research Sponsor: Bendat Family Research and Development Fund.

	Total patients (n=107)	Asymptomatic patients (n=96)
Ineligibility based on age	61 (57%)	56 (58%)
Ineligibility based on smoking history	73 (68%)	67 (70%)
Ineligibility based on full NLCSP criteria	91 (85%)	83 (86%)

Commission on Cancer lung cancer surgery quality metric and overall survival in a population-based cohort.

Sora Ely, Olawale Akinbobola, Matthew Paul Smeltzer, Carrie Fehnel, Andrea Saulsberry, Kourtney Dortch, Meredith Ray, Osarenren Ogbeide, Raymond U. Osarogiagbon; George Washington University, Washington, DC; Baptist Cancer Center, Multidisciplinary Thoracic Oncology Program, Memphis, TN; University of Memphis, School of Public Health, Memphis, TN

Background: The American College of Surgeons Commission on Cancer (CoC) quality metric for curative-intent lung cancer surgery, Operative Standard 5.8 (OS 5.8), requires lymph node sampling from ≥3 mediastinal and ≥1 hilar ("3+1") stations. We assessed association between adherence to this standard and overall survival in a population-based lung cancer resection cohort. **Methods:** We evaluated the Mid-South Quality of Surgical Resection cohort, which includes data from all 14 hospitals performing ≥5 annual lung cancer resections across five Hospital Referral Regions in MS, AR, and TN. We compared clinical stage I-III curative-intent resections from 2009 to 2020, examining demographics, tumor characteristics, and outcomes between CoC OS 5.8-concordant and non-concordant groups using chi-squared tests. We calculated adjusted odds ratios (aORs) to quantify concordance association with binary outcomes using logistic regression and adjusted hazard ratios (aHRs) for overall survival with proportional hazards models, adjusting all models for age, race, sex, Charlson comorbidity index, insurance, rurality, institutional volume, smoking status, clinical stage, histology, surgical technique, extent of resection, margin status, and neoadjuvant therapy. **Results:** Of 5,536 patients, 1,859 (41%) were concordant and 2,677 (59%) were non-concordant. Concordant cases included more White patients (80% v 76%, p<0.0001), metropolitan residents (61% v 47%, p<0.0001), clinical stage II/III cases (25% v 22%, p=0.0055), and anatomic resections (99% v 87%, p<0.0001). Surgical complications were more common in concordant cases (48% v 42%, p=0.0001). After adjustment for key variables, concordance with OS 5.8 was associated with more frequent nodal upstaging (aOR 1.34, 95% CI: 1.11–1.60), adjuvant chemotherapy use (aOR 1.58, 95% CI: 1.33–1.88), and more complications (aOR 1.21, 95% CI: 1.06–1.38). Patients with OS 5.8 concordant resections had significantly lower hazard of death (aHR 0.85, 95% CI: 0.77–0.93, Table). **Conclusions:** Adherence to CoC OS 5.8 lymph node sampling standards for lung cancer resections was associated with greater nodal upstaging, adjuvant therapy use, and likelihood of postoperative morbidity. Overall survival was significantly better among OS 5.8-concordant cases, supporting the use of this quality metric for curative-intent lung cancer surgery. Research Sponsor: U.S. National Institutes of Health; R01CA172253.

Oncologic characteristics and outcomes in CoC OS 5.8-concordant v non-concordant resections.

	Concordant n=1859	Non-concordant n=2677	P-value
Clinical stage I	74%	78%	0.0055
Clinical stage II	17%	14%	
Clinical stage III	8%	8%	
Nodal upstaging	16%	14%	0.0209
Adjuvant therapy	22%	14%	<0.0001
Median overall survival, years (95% CI)	7.8 (7.1-8.6)	6.2 (5.7-6.7)	0.0001
5-year overall survival (95% CI)	60% (58-62)	55% (53-57)	0.0001
aHR (95% CI)	0.85 (0.77-0.93)	Ref	0.0004

Racial and ethnic disparities in receipt of guideline concordant treatment for early-stage non-small cell lung cancer in Los Angeles County.

Miriam L. Gorbatov, Angel Arizpe, Elizabeth A. David, Lihua Liu, Albert Farias; Department of Population and Public Health Sciences, Keck School of Medicine of USC, Los Angeles, CA; University of Southern California, Los Angeles, CA; University of Southern Califorinia, Sacramento, CA; Keck School of Medicine of the University of Southern California, Los Angeles, CA

Background: Non-small cell lung cancer (NSCLC) is the leading cause of cancer mortality in California. Black patients experience the highest mortality rates (39 per 100,000) compared to Non-Hispanic White (NHW) (34 per 100,000), Asian/Pacific Islanders (A/PI) (23 per 100,000), and Hispanic patients (17 per 100,000). The most modifiable factor contributing to these differences is the receipt of guideline-concordant treatment (GCT), with surgical resection or radiation therapy recommended for all medically operable patients with stage I-II NSCLC. Despite rigorous clinical evidence supporting these guidelines, a higher proportion of Non-Hispanic Black (NHB) and Hispanic patients do not receive GCT compared to NHW patients. This study analyzed differences in receipt of GCT across racial and ethnic groups, leveraging data from a robust, population-based cohort of all early-stage NSCLC cases diagnosed in Los Angeles County. **Methods:** Patients diagnosed with early-stage NSCLC (tumors <4cm, no lymph node involvement, and no metastases) between 2012-2022 were identified from the Los Angeles County Cancer Surveillance Program. Using a logistic regression model, we evaluated the association between race and ethnicity and receipt of guideline concordant treatment, adjusting for confounders including age, sex, socioeconomic status, insurance type, marital status, and tumor size. Outcomes were defined as receipt of GCT (surgery or radiation only), while non-GCT included no treatment or any combination of multiple treatments. **Results:** A total of 2,033 patients with early-stage NSCLC were identified of which 57.2% were NHW, 8.9% were NHB, 14.8% were Hispanic, and 18.2% were A/PI. Patients with early-stage NSCLC were on average 70.3 years of age, majority female (63.7%), and had an average tumor size of 1.9 cm. While most patients (85.6%) received GCT, NHB patients had the highest proportion of non-GCT treatment (21.1%) followed by Hispanic patients (16.9%). NHB patients had significantly higher oddsof not receiving GCT compared to NHW patients (OR: 1.62, 95% CI: 1.05-2.46; $p<0.05$). No statistically significant differences in GCT receipt were observed for A/PI or Hispanic patients compared to NHW patients. **Conclusions:** Addressing disparities in GCT for patients diagnosed with early-stage NSCLC is critical to improving survival outcomes. Future studies identifying factors influencing a patient's decision to receive GCT and a physician's decision to recommend and adhere to GCT guidelines is needed to understand the complexity of treatment decision-making. Research Sponsor: American Cancer Society.

8069 Poster Session

Impact of time to neoadjuvant treatment initiation (TTI) for resectable non-small cell lung cancer (NSCLC) on clinical outcomes.

Srinidhi Radhakrishnan, Olga G. Goloubeva, William Wooten, Katherine Ann Scilla, Ranee Mehra, Samuel Rosner; University of Maryland, Baltimore, MD; University of Maryland Marlene and Stewart Greenebaum Cancer Center, Baltimore, MD; University of Maryland Department of Biostatistics/Informatics, Baltimore, MD; University of Maryland Greenebaum Comprehensive Cancer Center, Baltimore, MD; University of Maryland Medical Center, Baltimore, MD

Background: There has been significant progress in the management of resectable NSCLC, now utilizing biomarker selected criteria. However, in the era of these new perioperative treatments, the impact of treatment initiation and surgical timing on clinical outcomes have yet to be explored. **Methods:** Using the NCDB, we compiled an analytic data set of patients with stage IB-IIIB (per AJCC 8th staging edition) who underwent definitive resection after receiving neoadjuvant systemic therapy between 2010-2021. These patients received neoadjuvant chemotherapy (CT), chemoradiotherapy (CRT) or chemoimmunotherapy (CIO). The following clinically relevant time intervals were estimated: time from diagnosis to systemic therapy initiation, from diagnosis to definitive surgery and from systemic therapy initiation to surgery. The association between these time intervals and overall survival (OS) were assessed using multivariable Cox proportional hazards model, stratified by clinical T-stage. Cox model was adjusted for year of diagnosis and age, treatment modalities, sex, race, Charlson score, income, and hospital affiliation. Data were analyzed using R studio and statistical significance was set at $\alpha = 0.05$. **Results:** The analytic data set included 13,372 eligible patients. 40.5% of patients had stage I/II disease and 59.5% were diagnosed with stage III disease. Treatment included 45.2% CT, 48.3% CRT, 6.4% CIO, with median TTI being 108, 97 and 107 days, respectively. Compared to neoadjuvant CT, CIO combination conferred a positive impact on OS (HR=0.62, 95%CI: 0.52-0.74). Both time from diagnosis to treatment initiation and time from systemic therapy start to surgery increased by 7 days between 2010-2018 and 2019-2021. Time to neoadjuvant treatment initiation did not impact OS. However, surgical resection done later than 150 days from diagnosis was associated with lower OS (HR=1.12, 95%CI:1.04-1.19). Based on the multivariable Cox regression model, patients' survival was longer if they were diagnosed between 2019-2021, treated at an academic hospital, age $<$ 63 years at diagnosis, female, non-white, had lower Charlson score, income $>$ 40K, private-payer insurance, and if surgical resection was performed $\leq$ 150 days from diagnosis. **Conclusions:** Exploring the NCDB, neoadjuvant CIO showed significantly favorable impact on OS compared to CT. Despite increased TTI between the years of 2019-2021, there was no appreciable impact on timing of systemic therapy initiation on OS across our cohort. Time to surgical resection within 150 days, adjusted for other clinical and demographic parameters, was associated with improved OS. Pertinent demographic variables, including race, insurance status, and income level, significantly impacted OS and warrant further investigation in this clinical setting. Research Sponsor: None.

Driving precision oncology in lung cancer: Patient stratification through comprehensive genomic profiling.

Vidya H. Veldore, V.P. Gangadharan, Amit Jain, Navneet Singh, Paridhy Subramanyam, Jinumary John, Vyomesh J., Sreekanth S.P., Sudip Shreshtha, Sameer Shrirangwar, Minit Jalan Shah, Rushabh Kiran Kothari, Raja Thirumalairaj, Ramakant Deshpande, Saurabh Mishra, Harsh Vardhan Atreya, Bhuvan Chugh, Giridharan Periyasamy, Hitesh Goswami, Kumar Prabash; 4baseCare Precision Health Pvt Ltd., Bangalore, India; Lakeshore Hospital, Cochin, India; Valentis Cancer Hospital, Meerut, India; PGIMER, Chandigarh, India; 4baseCare Precision Health Pvt Ltd., Bamgalore, India; 4baseCare Precision Health Pvt Ltd., Bengaluru, India; Nepal Cancer Hospital and Research Centre, Lalitpur, Nepal; National Cancer Institute, Nagpur, India; Tata Memorial Centre, Mumbai, India; Tata Memorial Centre, Dharni, India; Apollo Speciality Hospital, Chennai, India; ACI Cumballa Hill Hospital, Mumbai, India; Tenderpalm Hospital, Lucknow, India; Medanta Hospital, Lucknow, India; Max Super Speciality Hospital, New Delhi, India

Background: Next Generation Sequencing (NGS)-guided targeted therapy is a standard practice in lung cancer, as recommended by professional guidelines. Various gene panels, exome, and genome sequencing strategies are employed to detect therapeutic targets. Selecting the right test is critical for achieving favorable patient outcomes. This study compares the efficacy and clinical utility of gene panels and exome sequencing in stratifying patients for different therapeutic options. **Methods:** We retrospectively analyzed genomic profiles of 1,224 advanced lung cancer patients (Stage III and Stage IV) sequenced using small gene panel (SP; 72 genes, NCCN biomarker driven TarGT First) and broad gene panel (BP; 1,212 genes, NCCN and pathways driven TarGT IndieGene. Tumor FFPE samples were screened for SNVs/InDels, CNVs, gene fusions, and immunotherapy biomarkers, including TMB, MSI, and PD-L1 expression. **Results:** Among the 1,224 patients, 791 were screened with small panels, 552 with broad panels, and 42 with exome sequencing. Sequencing with BP identified at least one driver/pathogenic mutation in 89.7% patients, which was higher than that detected in SP (73.6%). BP detected a higher proportion of patients with therapeutically targetable variants than SP (80.6% vs. 73.3%). Both SP and BP detected equivalent proportion of patients as eligible for level 1 (FDA-approved) therapy (SP 38.7% vs. BP 37.5%) and level 2 therapy (3.2% vs. 4%) and while a significantly higher number of patients eligible for level 3 (clinical trials) therapies were detected in BP (SP 31.5% vs. BP 39.1%). In a subset of 172 patients screened with both SP and BP. BP identified driver/pathogenic mutations in all patients (100% diagnostic yield) while SP identified mutations in 62.8% of the patients. BP also detected targetable variants in 84.9% of cases, compared to 62.8% detected in SP. Patients eligible for FDA-approved therapy (48.3% vs. 41.9%), off-label therapy (5.2% vs. 3.5%), and clinical trial therapies (38.4% vs. 17.4%) were more frequently detected with BP than in SP. **Conclusions:** BP outperform SP in detecting clinically significant drivers and therapeutic biomarkers, demonstrating their utility in precision oncology. This study highlights the advantages of comprehensive genomic profiling (CGP) over small panels for guiding prognosis and therapy decisions in advanced lung cancer during disease progression. Research Sponsor: 4baseCare internal funding.

	Patients with targetable variants (No. of patients; %)	Level 1 therapy (No. of patients; %)	Level 2 therapy (No. of patients; %)	Level 3 therapy (No. of patients; %)	No therapy (No. of patients; %)
Small panel sequencing (SP) (n=791 patients)	580; 73.3%	306; 38.7%	25; 3.2%	249; 31.5%	211; 26.7%
Broad panel sequencing (BP) (n=552 patients)	445; 80.6%	207; 37.5%	22; 4%	216; 39.1%	107; 19.4%

Real-world (rw) study to identify disparities in outcomes for patients (pts) with early-stage resected NSCLC who received biomarker-targeted adjuvant treatment (BTRx).

Raymond U. Osarogiagbon, Robert Hsu, Melinda Laine Hsu, Sandip Pravin Patel, Matthew Paul Smeltzer, Greg Ursino, Martina Lupicka, Yanique Rattigan-Brown, Ilker Arslan, Emre Baser, Michael Stokes, Rajrupa Gosh, Charlotte Pettersson, Yi Liang, Martin Sandelin, Rachel Salomonsen; Baptist Cancer Center, Multidisciplinary Thoracic Oncology Program, Memphis, TN; University of Southern California Norris Comprehensive Cancer Center, Keck School of Medicine of USC, San Diego, CA; University Hospitals Seidman Cancer Center, Case Western Reserve University, Cleveland, OH; San Diego Center for Precision Immunotherapy, Clinical Trials Office, Moores Cancer Center, San Diego, CA; University of Memphis School of Public Health, Memphis, TN; AstraZeneca, Gaithersburg, MD; Evidera PPD, Waltham, MA; AstraZeneca, Uppsala, Sweden

Background: BTRx improves survival of pts with resected early-stage NSCLC, making thorough biomarker testing critical in this setting. Disparities in testing and receipt of guideline-supported BTRx may adversely impact outcomes. We evaluated rw biomarker testing patterns, outcomes, and receipt of BTRx in pts with resected NSCLC. **Methods:** This was a retrospective US cohort study of Flatiron Health data from pts with stage IB–IIIB (T3N2) NSCLC diagnosed during 2021–2023, who had surgical resection. Biomarker testing, BTRx rates, and clinical outcomes (rw recurrence-free survival [rwRFS]; overall survival [OS]) were evaluated and compared across clinical and sociodemographic groups. BTRx was defined as 1) osimertinib for EGFR+ (Ex19del/L858R) NSCLC; 2) atezolizumab or pembrolizumab (per PD-L1 status) for EGFR- and ALK-negative (-) NSCLC. **Results:** In this cohort (N=885), biomarker testing rates were lower among stage I (75%) vs III (93%), older (83%) vs younger (87%), non-Hispanic Black (74%) vs White (84%), and pts with smoking (83%) vs no smoking history (89%) (Table). 539 (61%) pts received adjuvant therapy; 231 (43%) had actionable biomarkers, of whom 137 (59%) received BTRx, with rates highest for pts with EGFR+ disease (85%) and lowest for pts with EGFR-/ALK- disease (49%). BTRx was received more often by pts who never smoked (76% vs 55% of pts who smoked) and pts of Asian ethnicity (100% vs 56% White) (all $p<0.05$). At 24 months, 90% of pts who had BTRx were alive vs 77% who did not ($p<0.05$). Median rwRFS was 35 months for BTRx vs 28 months for non-BTRx cohort ($p<0.05$). In multivariable analysis among pts who had BTRx, younger age was significantly associated with OS. **Conclusions:** In this large rw analysis, BTRx was significantly associated with OS in early-stage NSCLC, irrespective of age, stage and sex. Ensuring biomarker testing and BTRx for all pts may reduce outcomes disparities in NSCLC. Research Sponsor: AstraZeneca.

Table	Overall	Stage IB	Stage IIIB	<65 yrs	≥65 yrs	Male	Female	Non-Hispanic White	Non-Hispanic Black	Smoked	Never smoked	SES Quintile 1	SES Quintile 5
≥1 Biomarker test after diagnosis, %	84	75	93*	87	83	85	83	84	74	83	89	80	86
Received adjuvant Rx (n=539), %	61	31	90*	74	56*	59	63	62	60	60	64	63	65
BTRx rate in pts with actionable bioms (n=231), %	59	64	73	57	60	63	57	56	61	55	76*	51	68
24-mo OS, % (95% CI) (all pts)	84 (81–87)	87 (80–92)	72 (46–87) **†	92 (86–96)	81 (77–85) **†	81 (75–85)	87 (82–90) **†	86 (82–89)	88 (70–96)	83 (80–87)	89 (79–94)	85 (74–92)	88 (80–93)
24-mo OS, % (95% CI) (pts with BTRx)	90 (80–95)	91 (51–99)	NR	100 (100–100)	86 (71–93) **	83 (58–94)	94 (82–98)	88 (73–95)	100 (100–100)	89 (76–95)	95 (68–99)	80 (41–95)	86* (53–96)

*$\chi 2$-test $p<0.05$.
**Log-rank $p<0.05$, for comparisons within stage and sociodemographic groups.
†Results significant in multivariable Cox regressions adjusted for age, sex, stage and practice type. NR, not reached.

Definitive radiation as a nonsurgical option after chemoimmunotherapy for stage III lung cancer.

Giorgio Caturegli, Maureen Canavan, Oluwaseun Ayoade, Gavitt Alida Woodard, Daniel J. Boffa, Benjamin Resio; Yale School of Medicine, New Haven, CT

Background: The immunotherapy era has led to a resurgence of interest in surgical management of clinical Stage III non-small cell lung cancer (NSCLC). However, patient eligibility or interest in surgery may decline after neoadjuvant treatment, leaving many in need of a non-operative form of local therapy. Here we evaluate outcomes of definitive radiation after chemoimmunotherapy as a potential nonsurgical option for stage III NSCLC patients. **Methods:** Clinical Stage III lung adenocarcinoma and squamous cell carcinoma patients diagnosed in the National Cancer Database between 2017 and 2021 who received chemoimmunotherapy followed by thoracic radiation within 20 weeks were included. Patients receiving any palliative therapies were excluded. Three-year overall survival was assessed by Cox proportional hazards models and by the Kaplan-Meier method, after landmarking at 10 weeks (median time from immunotherapy to radiation). Propensity-matching was performed 2:1 on year, age, sex, race/ethnicity, Charlson-Deyo score, insurance, region, facility type, histology, and clinical T and N stage. **Results:** 873 patients were treated with radiation after chemoimmunotherapy. Over 90% received a total radiation dose of at least 50 Gy, and 90-day mortality after initiation of radiation was 4.9%. To evaluate radiation as a local therapy after chemoimmunotherapy, these patients were compared to those who received chemoimmunotherapy only (Table). Patients receiving radiation were less likely to have T4 tumors (37.7% vs. 44.2%, $p<0.0001$) but had a similar proportion of N3 tumors (28.2% vs. 29.9%, $p=0.73$) compared to chemoimmunotherapy alone. Three-year overall survival of propensity-matched patients was superior in the radiation group (50.8%) versus chemoimmunotherapy alone (35.9%, $p<0.001$). In a Cox model, the addition of radiation was associated with lower mortality risk (HR 0.66, 95% 0.58-0.84, $p<0.0001$) compared to chemoimmunotherapy alone. **Conclusions:** Radiation after chemoimmunotherapy appears to be a safe and effective regimen for Stage III NSCLC. Further study is indicated to evaluate radiation as a nonsurgical option for clinical stage III patients who begin with chemoimmunotherapy but do not progress to surgery.
Research Sponsor: None.

Characteristics and survival of patients receiving chemoimmunotherapy with or without subsequent radiation.

	Chemoimmunotherapy followed by radiation (n=873)	Chemoimmunotherapy only (n=1408)	P (Chi-squared or Wilcoxon rank sum)
Age (median, IQR)	67 (60-73)	69 (62-75)	**<0.0001**
Female	369 (42.3%)	667 (47.4%)	**0.02**
Charlson-Deyo ≥ 2	131 (15.0%)	242 (17.2%)	0.34
Adenocarcinoma	463 (54.0%)	886 (62.9%)	**<0.0001**
Stage 3A	350 (40.1%)	579 (41.1%)	0.78
Stage T4	329 (37.7%)	622 (44.2%)	**0.0022**
Stage N3	255 (29.2%)	421 (29.9%)	0.73
3-Year Survival*	489 (56.0%)	630 (44.7%)	**<0.0001**

For reference: 3-year survival of immunotherapy after chemoradiation for Stage III NSCLC in the PACIFIC trial was 57%.

8073 Poster Session

Sequential versus concurrent strategy of immunotherapy and radiotherapy in advanced non-small-cell lung cancer: A territory-wide multicenter study (OCEANUS study).

Han Zhou, Sichao Wang, Chen Hu, Feng-Ming (Spring) Kong; The University of Hong Kong-Shenzhen Hospital, Shenzhen, China; University of Hong Kong, Shenzhen, China; Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins School of Medicine, Baltimore, MD; Hong Kong University, Shenzhen, China

Background: Combination of immunotherapy with radiotherapy (iRT) has been a hot topic of research during last 10+ years with controversial results. In advanced non-small cell lung cancer (NSCLC), the optimal combination of iRT is not clear in the PACIFIC series of study. Using a prospective territory-wide multicenter study, this OCEANUS study aimed to compare the survival between sequential and concurrent iRT in locally advanced NSCLC. **Methods:** This real-world evidence study evaluated NSCLC patients treated in Hong Kong between January 1, 2010, and December 31, 2021. Patients diagnosed with unresectable locally advanced, de novo metastatic, or progressive NSCLC who received at least one cycle of immunotherapy combined with radiotherapy were included. The primary endpoint was real-world overall survival (rwOS). Survival outcomes were compared across various iRT combinations, with a focus on the impact of iRT strategies (concurrent versus sequential), the iRT time interval, and immune checkpoint inhibitor (ICI) maintenance duration. **Results:** A total of 3,522 patients received immunotherapy, of whom 338 underwent iRT (151 with initial iRT and 187 with salvage iRT). Patients who received iRT had significantly better overall survival (OS) compared to those who did not. Sequential iRT demonstrated significantly superior survival compared to concurrent iRT, with a 5-year rwOS of 45.3% (95% CI, 35.6–57.7%) versus 15.7% (95% CI, 7.2–33.8%; HR, 0.587; 95% CI, 0.382–0.901; P = 0.014). For salvage iRT, radiotherapy combined with maintenance ICIs achieved a median rwOS of 11.7 months (95% CI, 7.4–15.5), outperforming RT administered after ICI discontinuation (HR, 0.679; 95% CI, 0.470–0.979; P = 0.014). Shorter iRT intervals (<1 week) and 1 year of ICI maintenance were associated with additional survival benefits. **Conclusions:** The OCEANUS study provides significant real-world evidence supporting sequential iRT as the preferred strategy for unresectable locally advanced and de novo metastatic NSCLC. Salvage RT combined with maintenance ICIs was associated with improved rwOS in patients with progressive NSCLC. These findings offer actionable insights for optimizing iRT strategies in advanced NSCLC. Research Sponsor: the Shenzhen Science and Technology Program; KQTD20180411185028798; National Natural Science Foundation of China; 82403787; Shenzhen Medical Research Fund; A2403002.

Evaluating lung cancer clinical characteristics and tumor subtypes using cell-free DNA fragmentomes.

Milou Schuurbiers, Jamie E. Medina, Zachary L. Skidmore, Paul van der Leest, Garrett Graham, Stephen Cristiano, Alessandro Leal, Bryan Chesnick, Kim Monkhorst, Nicholas C. Dracopoli, Peter Brian Bach, Robert B. Scharpf, Victor E. Velculescu, Daan van den Broek, Michel M. van den Heuvel, Lorenzo Rinaldi; Radboud University Medical Center, Nijmegen, Netherlands; Delfi Diagnostics, Inc., Baltimore, MD; Netherlands Cancer Institute, Amsterdam, Netherlands; Perlmutter Cancer Center, NYU Langone Health, New York, NY; The Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University School of Medicine, Baltimore, MD

Background: Liquid biopsies provide an opportunity for non-invasive lung cancer detection and tumor subtyping when tumor tissue is not available. Here we evaluate a blood-based liquid biopsy approach and its relationship to clinical and tumor subtype characteristics of lung cancer cases using a cohort of 578 individuals from a prospective clinical trial (LEMA, NCT02894853). **Methods:** Pre-treatment plasma samples were processed using the DELFI assay, a cell-free DNA (cfDNA) approach using a genome-wide fragmentomics based machine learning classifier. Clinical data, including overall cancer stage (I=164, II=59, III=133, IV=184), tumor stage, histologic subtypes, lymph node invasion, comorbidities, medications, smoking history, treatment type, and overall-survival (OS) data were collected for all patients. Tissue molecular profiling was performed to identify actionable alterations in driver oncogenes (ALK, BRAF, EGFR, ERBB, KRAS, ROS1, RET, MET) and cancer-specific protein levels (CEA, CA153, CA125, CYFRA, HE4) were measured in the plasma collected from 445 cancer cases. **Results:** DELFI scores were significantly higher with increasing tumor stage. T2 cases had a 1.3-fold increase in mean scores compared to T1 ($p<0.001$, Wilcoxon rank-sum), while T4 cases had a 16.2-fold increase ($p<0.0001$). A similar trend was observed with node staging, with N2 cases having an 11.3-fold higher mean scores compared to N0 ($p<0.0001$, Wilcoxon rank-sum), while N3 stage cases had a 27-fold increase ($p<0.0001$). Lung adenocarcinoma (ADC) displayed lower DELFI scores compared to squamous cell carcinomas (SCC) ($p<0.01$, Wilcoxon rank-sum), while small-cell lung cancer cases had the highest scores among all subtypes ($p<0.0001$, Wilcoxon rank-sum). cfDNA fragmentome changes in patients with ADC and SCC reflected chromosomal alterations observed in TCGA cohorts (ADC n=518; SCC n=501). The combination of DELFI cfDNA fragmentome characteristics with plasma protein measurements were used to train and cross-validate a classifier that could differentiate ADC from SCC (AUC for stage I=0.71, II=0.85, III=0.85, IV=0.82). Patients with low DELFI scores (below the median) had longer overall-survival (OS) compared to patients with high DELFI score (low DELFI score=18.51 months; high DELFI score=6.58 months; $p<0.01$, log-rank). DELFI scores were unaffected by underlying patient comorbidities, tumor-specific mutations, or medication status. **Conclusions:** Overall, this study revealed that DELFI scores are related to tumor burden, predict survival outcomes, and that cfDNA fragmentome analyses can be used to identify lung cancer subtypes. These results suggest future opportunities for subtype-specific treatments in lung cancer based on non-invasive plasma-only analyses. Clinical trial information: NCT02894853. Research Sponsor: None.

8075 Poster Session

EMBER-Lung: Electronic medical record boosting molecular testing in early stage NSCLC.

Willdragon Wang, Dylan Scholes, Megan Roy, Sunil Singhal, John Kucharczuk, Doraid Jarrar, Jarrod Predina, Taine Pechet, Lova Sun, Aditi Puri Singh, Roger B. Cohen, Corey J. Langer, Charu Aggarwal, Melina Elpi Marmarelis; University of Pennsylvania, Philadelphia, PA; Penn Medicine, Philadelphia, PA; University of Pennsylvania Perelman School of Medicine, Philadelphia, PA; Hospital of the University of Pennsylvania, Philadelphia, PA; Division of Hematology/Oncology, University of Pennsylvania, Philadelphia, PA; Perelman School of Medicine at the University of Pennsylvania, Abramson Cancer Center, Philadelphia, PA

Background: Actionable alterations are identified in 30-40% of patients with advanced non-squamous (NSq) non-small cell lung cancer (NSCLC). Although previous efforts focused on testing for actionable alterations in the metastatic setting, the emergence of adjuvant targeted therapies and perioperative chemoimmunotherapy has made it imperative to perform molecular testing in the early stage setting as well. We present a prospective clinical trial evaluating an electronic medical record (EMR)-based nudge intervention to promote timely completion of molecular testing in patients (pts) with early stage NSq NSCLC. **Methods:** The EMBER-Lung trial prospectively enrolled pts undergoing surgical resection in the University of Pennsylvania Health System. The intervention included an EMR-based nudge at the time of the 1st post-operative visit prompting the clinician to accept an order for comprehensive molecular testing based on NCCN guidelines. A reflex alert detailing therapeutic options was sent to the pt's care team provided that the pt had at least one actionable alteration detected and tissue was consistent with NSq NSCLC. The primary endpoint was the proportion of pts who underwent comprehensive molecular testing in the pre and post intervention cohorts. Secondary outcomes included the delivery of appropriate adjuvant targeted therapy if a targetable alteration was detected. Clinical characteristics of the pre- and post-intervention cohorts were compared using the Chi-square test or Z score. **Results:** Between July 2021 and November 2023, 460 pts were included: 243 pts in the post-, and 217 pts in the pre-intervention cohorts. Median age was 68.4 years, 64.3% female; 74.1% were former or current smokers, and mostly stage I (I/II/III; 75.9%, 14.1%, 10.0%, respectively). Pt demographics, smoking, tumor stage, and histology were similar in the pre- and post-intervention cohorts. The proportion of pts with any molecular testing improved after the intervention (101/217, 46.5% vs 208/243, 85.6%, $p<0.00001$). Moreover, the proportion of pts whose molecular testing was comprehensive also increased post-intervention (80/217, 36.9% vs 197/243, 81.1%, $p<0.00001$); and this increase was observed across all stages (I-III). A greater proportion of pts with classical *EGFR* mutations were detected in the post-intervention setting (14/217, 6.5% vs 41/243, 16.9%, $p<0.001$). No *ALK* fusions were detected in the pre-intervention cohort, while 5/243 (2.1%) were detected in the post-intervention cohort. Of note, a higher proportion of *KRAS* G12C mutations were also found post intervention (12/217, 5.5%, vs 33/243, 13.6%, $p<0.01$). **Conclusions:** An EMR-based nudge intervention during the post-operative visit after resection of early stage NSCLC improved the proportion of patients with molecular testing. The intervention was feasible, and future research will incorporate this strategy earlier to inform neoadjuvant therapy. Research Sponsor: None.

A retrospective study of induction immunochemotherapy followed by definitive chemoradiotherapy and consolidation immunotherapy in unresectable locally advanced non-small cell lung cancer.

Yuliang Meng, Linlin Wang; Shandong Cancer hospital and institute, Jinan, China; Shandong Cancer Hospital and Institute, Jinan, Shandong, China

Background: The standard treatment for patients with unresectable stage III non-small cell lung cancer (NSCLC) involves concurrent chemoradiotherapy (cCRT) followed by one year of durvalumab consolidation therapy. Numerous clinical studies have sought to optimize this treatment paradigm to enhance clinical outcomes. In this retrospective real-world study, we evaluated the efficacy and safety of the addition of induction chemoimmunotherapy prior to the PACIFIC regimen compared with the standard PACIFIC regimen. The aim was to determine whether introducing immunotherapy earlier into the treatment strategy for unresectable stage III NSCLC could improve disease control rates. **Methods:** This study included patients with unresectable stage III NSCLC. Patients received either induction chemoimmunotherapy followed by cCRT or sequential chemoradiotherapy (sCRT) with consolidation immunotherapy, or cCRT/sCRT directly followed by consolidation immunotherapy. The primary endpoint was progression-free survival (PFS), defined as the time from the initiation of consolidation immunotherapy to disease progression or death. The incidence of radiation-induced immune pneumonitis was also assessed between the two groups. **Results:** A total of 210 patients with unresectable stage III NSCLC were included in this study, enrolled between July 2019 and April 2023. Among them, 76 patients received induction chemoimmunotherapy, and 134 patients were treated without induction chemoimmunotherapy. Baseline characteristics between the two groups showed no significant differences. The proportion of patients receiving cCRT in the induction chemoimmunotherapy group and the non-induction chemoimmunotherapy group was 29/76 (38.1%) and 110/134 (82.1%), respectively. Within each group, there was no statistically significant difference in progression-free survival (PFS) between patients treated with cCRT or sCRT. The induction chemoimmunotherapy group demonstrated superior median PFS (mPFS) compared to the non-induction chemoimmunotherapy group (not reached vs. 17.2 months, P=0.01). Overall survival (OS) data remain immature for analysis. The incidence of pneumonitis was observed in 52/76 (68.4%) patients in the induction chemoimmunotherapy group, with ≥Grade 2 pneumonitis occurring in 18/76 (23.7%) patients. In the non-induction chemoimmunotherapy group, pneumonitis occurred in 86/134 (64.2%) patients, with ≥Grade 2 pneumonitis in 30/134 (22.4%) patients. No significant differences in pneumonitis incidence or severity were observed between the two groups. **Conclusions:** The addition of induction chemoimmunotherapy prior to the PACIFIC regimen demonstrated improved disease control rates compared to the standard approach, with no increased risk of pneumonitis. Research Sponsor: None.

Association of radiomic features with disease-free survival following neoadjuvant chemoimmunotherapy in resectable NSCLC.

Bryan Berube, MohammadHadi Khorrami, Ryan Brown, Sumaiya Alam, Amr Ali, Kübra Canaslan, Fatemeh Ardeshir Larijani, Michael E. Menefee, Marc A. Shapiro, Khaled Aref Hassan, James Stevenson, Alex A. Adjei, Nathan A. Pennell, Anant Madabhushi, Lukas Delasos; Cleveland Clinic, Cleveland, OH; Winship Cancer Institute, Emory University, Atlanta, GA; Emory University School of Medicine, Atlanta, GA; Emory University, Atlanta, GA; Dokuz Eylul University, Faculty of Medicine, Department of Medical Oncology, Izmir, Turkey; Winship Cancer Institute, Atlanta, GA; Cleveland Clinic Taussig Cancer Institute, Cleveland, OH; Cleveland Clinic Taussig Cancer Center, Cleveland, OH

Background: Neoadjuvant chemoimmunotherapy (chemo-IO) has emerged as a promising approach to improve disease-free survival (DFS) in patients with surgically resectable non-small cell lung cancer (NSCLC). While recent clinical trials have demonstrated the efficacy of combining chemotherapy with immune checkpoint inhibitors in this setting, DFS remains variable among patients. Currently, there is no reliable biomarker to predict the risk of recurrence in this population. Predictors such as PD-L1 expression have shown limited utility, underscoring an unmet clinical need to identify robust biomarkers for DFS. This study investigates whether radiomic texture features derived from pre-treatment CT scans are associated with DFS in patients with NSCLC undergoing neoadjuvant chemo-IO prior to surgery. **Methods:** The study included 101 patients with NSCLC (median age: 66 years, range: 34–85) treated at the Cleveland Clinic. All patients received neoadjuvant platinum-doublet chemotherapy combined with an anti-PD-1 inhibitor prior to surgery. Radiomic features characterizing tumor heterogeneity were extracted from pre-treatment CT images. Patients were divided into a training set (St=50) and a validation set (Sv=51). A least absolute shrinkage and selection operator (LASSO) Cox regression model was used to identify prognostic features for DFS in St. A radiomic risk score (RRS) was computed as a linear combination of the selected features and their corresponding coefficients. High- and low-risk groups were determined based on the median RRS in St. A Cox regression analysis was performed to assess the impact of each factor on DFS. Kaplan–Meier survival analysis, accompanied by log-rank tests, was conducted to evaluate the prognostic performance of the biomarkers. **Results:** In a univariable analysis, the RRS was significantly associated with DFS in both St (HR = 2.77, 95% CI: 1.84 – 4.1, $P < 0.0001$) and Sv (HR= 2.28, 95% CI: 1.48 – 3.5, P = 0.0002). Kaplan-Meier analyses revealed significantly shorter DFS in the high-risk group compared to the low-risk group in both St ($P < 0.0001$) and Sv ($P < 0.011$). In a multivariable analysis that included clinicopathologic factors (age, race, tumor stage, and PD-L1 expression) along with RRS, both RRS and PD-L1 expression were significantly associated with DFS in St (RRS: HR = 2.99, 95% CI: 1.89 – 4.7, $P < 0.0001$; PD-L1: HR = 1.57, 95% CI: 1.14 – 2.15, P = 0.005). However, in Sv, RRS was the only factor significantly associated with DFS (RRS: HR= 2.31, 95% CI: 1.49 – 3.6, P = 0.0001), while PD-L1 expression was not (HR = 1.27, 95% CI: 0.35 – 4.6, P = 0.71). **Conclusions:** Identifying patients with locoregional NSCLC at risk of recurrence after neoadjuvant chemo-IO is crucial for effective treatment planning. Preliminary findings suggest that radiomic features hold promise as a reliable, non-invasive biomarker for risk stratification and guiding treatment decisions. Research Sponsor: None.

Real-world surgical and treatment patterns after neoadjuvant checkpoint inhibition in US patients with stage II/III non-small cell lung cancer.

Jay M. Lee, Daniel Simmons, Tiernan Mulrooney, Jeremy Snider, Lana Kovacevic, Karen Schwed, Aditya Juloori; Division of Thoracic Surgery, University of California, Los Angeles (UCLA), Los Angeles, CA; AstraZeneca, Gaithersburg, MD; Flatiron Health, New York, NY; University of Chicago, Chicago, IL

Background: Since 2021, several immuno-oncology (IO) agents were approved for use in patients with resectable non-small cell lung cancer. In the phase III neoadjuvant and perioperative IO trials, 16-26% of patients did not undergo surgery. The objectives of this study were to evaluate the real-world rate of surgery following neoadjuvant IO, reasons for preoperative attrition to resection, and subsequent treatment patterns for those who did not undergo surgery. **Methods:** This retrospective observational study used the nationwide Flatiron Health electronic health record-derived deidentified database. Included were patients diagnosed with stage II or III NSCLC between Jan 2022 and Oct 2023 who received nivolumab (nivo) and doublet chemotherapy (CT) as the first therapy within 90 days of diagnosis. We excluded patients with no documented neoadjuvant intent from the no surgery group. Per approved protocol, descriptive statistics were utilized for patient characteristics and treatment patterns. **Results:** A total of 484 patients received nivo. Among these, the average age was 67 years, 253/484 (52.3%) were male, 339/484 (70.0%) were white, and 403/484 (83.3%) were treated in a community setting. The rate of surgery was 317/484 (65.5%). Rates by stage and ECOG are found in Table 1. Among those most similar to the population in clinical trials (ECOG 0-1 and Stage IIA-IIIA) the rate was 238/334 (71.3%). The most common reasons for attrition were medical fitness (45/484; 9.2%), tumor resectability (30/484; 6.2%), and progression (28/484; 5.8%). Of those not receiving surgery, 131/167 (78.4%) received subsequent treatment, including 57 who received radiation (+/- chemo) during the follow-up period (median 10.5 months from diagnosis). **Conclusions:** In this real-world analysis, most patients were treated in community centers. The resection rate following neoadjuvant CT-IO in stage II and III NSCLC was high and comparable to the clinical trials. Medical operability, tumor resectability, and progression of disease as reasons for preoperative attrition to surgery occurred in a minority of patients that received neoadjuvant therapy. Many of the patients who did not undergo resection received subsequent therapy including consolidation radiation. Future research is needed to determine ways to improve surgical rates following neoadjuvant CT-IO. Research Sponsor: AstraZeneca.

Surgical rates by ECOG and stage at diagnosis.

	Stage IIA	Stage IIB	Stage II (unspecified)	Stage IIIA	Stage IIIB	Stage IIIC	Stage III (unspecified)
ECOG 0-1	28/35 (80.0%)	80/97 (82.5%)	7/10 (70.0%)	123/192 (64.1%)	11/24 (45.8%)	0/7 (0%)	5/5 (100.0%)
ECOG ≥2	1/4 (25.0%)	4/10 (40.0%)	0/0 (0%)	4/13 (30.8%)	1/5 (20.0%)	0/1 (0%)	0/0 (0%)
Unknown	5/6 (83.3%)	16/26 (61.5%)	1/1 (100.0%)	27/41 (65.9%)	2/4 (50.0%)	0/ 0 (0%)	2/3 (66.7%)
Overall	34/45 (75.6%)	100/133 (75.2%)	8/11 (72.7%)	154/246 (62.6%)	14/33 (42.4%)	0/8 (0%)	7/8 (87.5%)

8079 Poster Session

Pronounced gender-based and regional disparities in lung cancer mortality in the US: Insights from five decades of nationwide mortality data.

Muhammad Ahmad, Malik W.Z. Khan, Abdul Wali Khan, Shammas Bajwa, Amna Gul, Mustafa Ali Samejo, Fariha Hasan, Hassan Ali, Mariem Galuia; Khyber Medical University, Peshawar, Pakistan; Department of Internal Medicine, University of Missouri, Kansas City, MO; The University of Oklahoma Medical Center, Oklahoma City, OK; Miami Cancer Institute, Miami, FL; Advent Health sebring, Sebring, FL; Department of Internal Medicine, Cooper University Hospital, Camden, NJ; Mercy Catholic Medical Center, Darby, PA; AdventHealth, Orlando, FL

Background: Lung cancer remains the leading cause of cancer-related mortality in the United States, necessitating an understanding of long-term mortality trends to evaluate public health interventions and identify disparities. This study examines lung cancer mortality trends from 1968 to 2016 using data from the CDC WONDER database, stratified by demographic and regional characteristics. **Methods:** The analysis included deaths attributed to lung cancer, identified using International Classification of Disease (ICD) codes across three periods: ICD-8 (1968–1978), ICD-9 (1979–1998), and ICD-10 (1999–2016). Crude and age-adjusted mortality rates (AAMRs) per 100,000 population were calculated. Temporal trends were assessed with Joinpoint regression analysis to estimate annual percentage changes (APC) and average annual percentage changes (AAPC) with 95% confidence intervals (CIs). Data were stratified by gender, race, and U.S. Census regions. **Results:** Between 1968 and 2016, there were 6,289,300 deaths attributed to lung cancer in the U.S. The overall AAMR rose from 53.53 to 59.28, with an AAPC of 0.22 (95% CI: 0.19 to 0.25). Notable trends included a sharp rise from 1968 to 1980 (APC: 3.02; 95% CI: 2.88 to 3.18), a slowdown from 1980 to 1991 (APC: 1.72; 95% CI: 1.60 to 1.83), a decline from 1991 to 2004 (APC: -0.84; 95% CI: -0.92 to -0.75), a steeper drop from 2004 to 2012 (APC: -2.17; 95% CI: -2.36 to -1.96), and an acceleration from 2012 to 2016 (APC: -3.83; 95% CI: -4.40 to -3.40). Of the total, 37.1% of deaths were females (2,333,863) and 62.9% were males (3,955,437). The male AAMR decreased from 97.85 to 72.2 (AAPC: -0.65; 95% CI: -0.69 to -0.62), while the female AAMR rose from 17.96 to 49.24 (AAPC: 2.14; 95% CI: 2.10 to 2.19). Racially, 656,875 deaths (10.4%) involved Black or African Americans, who had higher AAMRs than the 5,534,744 deaths (88%) among Whites. Whites saw a more marked increase in AAMR (AAPC: 0.29; 95% CI: 0.27 to 0.32) compared to Blacks (AAPC: 0.095; 95% CI: 0.055 to 0.14). Regionally, the South had the highest AAMR at 83.2, while the West, with the lowest at 68.58, was the only region to experience an overall decrease from 52.74 in 1968 to 45.64 in 2016. **Conclusions:** The decline in overall mortality rates since 2004 underscores the effectiveness of smoking cessation programs and treatment advancements; yet, rising female mortality and high rates in the South call for a reassessment of outreach efforts to ensure public health strategies. Research Sponsor: None.

Radiomic signatures as predictors of pathological response to neoadjuvant chemoimmunotherapy in surgically resected NSCLC.

Ryan Brown, MohammadHadi Khorrami, Bryan Berube, Sumaiya Alam, Amr Ali, Kübra Canaslan, Fatemeh Ardeshir Larijani, Michael E. Menefee, Marc A. Shapiro, Khaled Aref Hassan, James Stevenson, Alex A. Adjei, Nathan A. Pennell, Anant Madabhushi, Lukas Delasos; Cleveland Clinic, Cleveland, OH; Winship Cancer Institute, Emory University, Atlanta, GA; Emory University School of Medicine, Atlanta, GA; Emory University, Atlanta, GA; Dokuz Eylul University, Faculty of Medicine, Department of Medical Oncology, Izmir, Turkey; Winship Cancer Institute, Atlanta, GA; Cleveland Clinic Foundation, Cleveland, OH; Cleveland Clinic Taussig Cancer Institute, Cleveland, OH; Cleveland Clinic Taussig Cancer Center, Cleveland, OH

Background: Historically, pathological complete response (pCR), a potential early predictor of survival, was achieved by a small fraction of patients with non-small cell lung cancer (NSCLC) receiving neoadjuvant chemotherapy. Now with chemoimmunotherapy (chemo-IO) becoming the cornerstone of perioperative treatment, the rate of pCR has significantly increased to over 15%. Existing factors like PD-L1 expression and circulating tumor DNA clearance have shown limited efficacy in reliably predicting response to neoadjuvant chemo-IO, thus underscoring the need for novel biomarkers. In this study, we aim to investigate the potential of radiomic texture features derived from pre-treatment CT scans to predict pCR in patients with NSCLC undergoing neoadjuvant chemo-IO prior to surgery. **Methods:** The study included 101 patients with surgically resected NSCLC treated at Cleveland Clinic. All patients received neoadjuvant platinum-doublet chemotherapy combined with an anti-PD-1 inhibitor prior to surgery. Tumor stage, histology, PD-L1 expression levels, and treatment details (e.g., chemotherapy regimen, immunotherapy agent, number of treatment cycles) were collected for analysis. Pathological responses were assessed based on the percentage of residual viable tumor in the surgical specimen, with pathological complete response (pCR) defined as 0% viable tumor. Radiomic features were extracted from both intratumoral and peritumoral regions on pre-treatment CT images. Patients were randomly divided into training and validation cohorts, ensuring an equal distribution of pCR and non-pCR cases in the training set. The training cohort (St) comprised 50 patients, while the validation cohort (Sv) included 51 patients. A linear discriminant classifier (LDA) was trained using St and subsequently evaluated on Sv. The predictive performance was assessed using the area under the curve (AUC). **Results:** 37 of 101 patients (37%) achieved a pCR. Utilizing a combination of 5 peritumoral and intratumoral radiomic features extracted from pretreatment CT scans, the AUC for predicting pCR was 0.82 (95% CI: 0.79 – 0.86) in St and 0.78 (95% CI: 0.76 – 0.81) in Sv. In contrast, the predictive capability of PD-L1 expression alone yielded an AUC of 0.57 for pCR prediction. Moreover, no significant difference was observed in pCR rates between patients with low and high PD-L1 expression levels ($P = 0.1$). The integration of radiomic features with clinicopathologic factors, including age, race, tumor stage, and PD-L1 expression, resulted in a modest improvement in predictive performance (AUC = 0.8) but was not statistically significant ($P > 0.5$). **Conclusions:** This analysis suggests that radiomic features extracted from both intra- and peri-tumoral regions on pre-treatment CT images may be indicative of the probability of achieving a pCR in patients with NSCLC receiving neoadjuvant chemo-IO. Research Sponsor: None.

8081 Poster Session

Impact of *MTAP* deletion on immunotherapy outcomes in patients with mesothelioma.

Jessica Ross, Eduardo Ortiz, Gustavo Barraza, Maria Mayoral, Michelle S. Ginsberg, Alexandra Luongo, Andrea Arfe, Marjorie Glass Zauderer, Prasad S. Adusumilli, Scott Eckert, Matteo Repetto, Soo-Ryum Yang, Maelle Saliba, Jennifer L. Sauter, Gregory J. Riely, Kathryn C. Arbour, Mark G. Kris, Marc Ladanyi, Michael Offin; Memorial Sloan Kettering Cancer Center, New York, NY; Westchester Medical Center, Hawthorne, NY

Background: *MTAP* (*methylthioadenosine phosphorylase*) is located on chromosome 9p21 and often co-deleted with *CDKN2A* across a variety of cancers. *MTAP* deletions (del) are found in about 30% of diffuse pleural mesotheliomas (DPM). *MTAP*del has been associated with resistance to immunotherapy (IO) treatment (tx) in multiple tumor types. In patients (pts) with DPM, objective response rate (ORR) on ipilimumab/nivolumab is 40%, disease control rate (DCR) 77%, and median progression-free survival (PFS) 6.8 months (mos): the implications of *MTAP* status on IO outcomes is unclear but represents a potential predictive biomarker. With multiple targeted therapies underway for *MTAP*del tumors, such as PRMT5 inhibitors, this alteration is also of therapeutic importance. **Methods:** We prospectively identified pts with pathologically confirmed DPM whose tumors were sequenced with MSK-IMPACT version 7, a 505-gene next generation sequencing panel that includes *MTAP* and *CDKN2A.* IO regimens included anti-PD(L)1 monotherapy, dual checkpoint blockade with additional anti-CTLA4 tx, and anti-PD(L)1 + chemotherapy. *MTAP*del was defined as low read count and confirmed by FACETS copy number when able. Radiologists reviewed imaging to determine best response and PFS on IO using mRECIST or, when not applicable, RECIST. Overall survival (OS) was compared between *MTAP*del and *MTAP*wildtype (WT) cohorts using Kaplan-Meier curves and log-rank tests. Baseline demographics were compared using Fisher's exact test. **Results:** We examined 156 pts with DPM: 39 had *CDKN2A*del (25%) and 32 had *MTAP*del (21%). 18/32 were treated with IO and available for analysis. 79 pts with *MTAP*WT DPM treated with IO were analyzed as a control. There were more pts treated with dual checkpoint blockade in the *MTAP*del vs *MTAP*WT group (83% vs 56%, single-agent IO 6% vs 39%, single-agent IO + chemo 11% vs 5%, p=0.03) and more men (94% vs 70%, p=0.04); there was no statistically significant difference in age (median 72 vs 69, p=0.5), histology (72% epithelioid vs 79%, p=0.5), or smoking status (current/former 61% vs 57%, p=0.9). All tumors with *MTAP*del also harbored a *CDKN2A*del: 5/79 tumors in the *MTAP*WT cohort had a *CDKN2A*del ($p<0.001$). Among the *MTAP*del cohort, 13 patients had (m)RECIST-evaluable disease. ORR on IO was 15% (2/13), DCR 38% (5/13), and median PFS 2.5 mos. OS was similar between the *MTAP*del and *MTAP*WT cohorts: median 25.4 vs 27.6 mos (HR 0.84, 95% CI 0.36 – 1.94, p=0.98). **Conclusions:** *MTAP*del (co-occurring with *CDKN2A*del) was identified in both epithelioid and non-epithelioid DPM and was associated with a low ORR and short PFS on IO, but OS was similar compared to *MTAP*WT. Larger, multi-institution cohorts are needed to validate this finding. If confirmed, this could have implications for tx selection, particularly among pts with epithelioid DPM, in which the optimal choice between 3 FDA-approved first-line regimens is uncertain. Research Sponsor: None.

Test performance of a DNA methylation–based liquid biopsy biomarker for detection and classification of pleural mesothelioma (PM).

Sabine Schmid, Sami Ul Haq, Luna Jia Zhan, M. Catherine Brown, Devalben Patel, Frances A. Shepherd, Natasha B. Leighl, Adrian G. Sacher, Marc De Perrot, Bc John Cho, Fatemeh Zaeimi, Miguel García-Pardo, Benjamin H. Lok, Scott Victor Bratman, Ming Sound Tsao, Martin Früh, Penelope Ann Bradbury, Geoffrey Liu; Inselspital, Universitätsspital Bern, Bern, Switzerland; University Health Network, Toronto, Canada, Toronto, ON, Canada; University Health Network, Toronto, ON, Canada; Department of Medical Oncology and Hematology, University Health Network, Princess Margaret Cancer Centre, Toronto, ON, Canada; Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada; Division of Thoracic Surgery, University Health Network, University of Toronto, Toronto, ON, Canada; Toronto General Hospital, Toronto, ON, Canada; Hospital Universitario Ramon y Cajal, Madrid, Spain; Princess Margaret Cancer Centre, University Health Network, University of Toronto, Toronto, ON, Canada; Princess Margaret Cancer Centre, Toronto, ON, Canada; Kantonsspital St. Gallen, St. Gallen, Switzerland; Department of Medical Oncology and Hematology, Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada

Background: Circulating tumor DNA (ctDNA) profiling in pleural mesothelioma (PM) is challenging due to its molecular heterogeneity and lack of mesothelioma-specific mutations. Diagnosis can be challenging and may require repeat biopsies. Cell-free methylated DNA immunoprecipitation sequencing (cfMeDIP-seq) of plasma cell-free DNA (cfDNA) offers a non-invasive approach to analyzing differentially methylated regions (DMRs), providing insights into epigenetic changes that could serve as potential biomarkers for diagnosis, histological differentiation, and prognosis in PM. **Methods:** cfMeDIP-seq was performed on plasma samples from 55 PM patients and 24 asbestos-exposed non-cancer controls (NCC). Libraries were sequenced to an average depth of 70 million reads, and chromosomes 1-22 were binned into 300 bp windows for read tallying. For NCCs, bins with a mean beta-value <0.3 and CG density >2 (n = 3,537,691 windows) were analyzed. DMR analysis and pathway enrichment were conducted using R packages (limma, clusterProfiler), and machine learning models were developed with Python modules (pandas, numpy, sklearn). **Results:** Among the 55 PM patients (72% epithelioid, 13% biphasic, 15% sarcomatoid), the median age was 70 years, 85% were male, and 78% had prior asbestos exposure. Using a stringent filter (mean beta-value <0.1; CG density >5), a random forest classifier was developed with 141 windows, distinguishing PM from NCC with 91% accuracy, 88% precision (or positive predictive value, PPV), and an area under the ROC curve (AUC) of 0.94 across 5-fold cross-validation cohorts. DMR analysis of epithelioid vs. sarcomatoid PM revealed 1,585 significantly different windows (adjusted $p < 0.05$), achieving 83% accuracy, 74% precision, and an AUC of 0.98. Gene ontology analysis indicated significant enrichment in RNA processing pathways. Among epithelioid PM patients, distinct DMRs were identified between those with overall survival (OS) $\leq$ 6 months and >6 months (n = 1,824 windows, adjusted $p < 0.05$). Patients with OS $\geq$ 36 months and <36 months showed 37 significantly differential windows (adjusted $p < 0.05$), though test performance assessment was limited by the small sample size. **Conclusions:** If validated, global methylome profiling of ctDNA via cfMeDIP-seq offers a novel, non-invasive method that may enhance accurate diagnosis and histological differentiation. Additionally, identifying epigenetic biomarkers could provide deeper insights into PM biology, paving the way for personalized medicine and improved patient outcomes. Research Sponsor: von Tobel Foundation; Dr. Hans Altschuler Foundation.

Prognostic significance of VISTA expression in patients with malignant pleural mesothelioma treated with nivolumab: Results of a retrospective multi-institutional analysis (HOT1901).

Hiroshi Yokouchi, Hiroshi Nishihara, Yoshiyuki Kenmotsu, Kosuke Tsuji, Takayuki Kishikawa, Hajime Kikuchi, Eisaku Miyauchi, Yutaro Nagano, Kenya Kanazawa, Jun Sugisaka, Yoshinori Minami, Yutaka Yamada, Ryo Morita, Aya Suzuki, Ayumu Takahashi, Yasutaka Kawai, Noriaki Sukoh, Keiki Yokoo, Toshiyuki Harada, Satoshi Oizumi; Department of Respiratory Medicine, NHO Hokkaido Cancer Center, Sapporo, Japan; Center for Cancer Genomics, Keio University Hospital, Shinjuku-Ku, Japan; Department of Internal Medicine, Kin-ikyo Chuo Hospital, Sapporo, Japan; Department of Respiratory Medicine, Faculty of Medicine, Hokkaido University, Sapporo, Japan; Division of Thoracic Oncology, Tochigi Cancer Center, Utsunomiya, Japan; Department of Respiratory Medicine, Obihiro-Kosei General Hospital, Obihiro, Japan; Tohoku University Hospital, Sendai, Japan; Department of Respiratory Medicine, Kushiro City General Hospital, Kushiro, Japan; Department of Pulmonary Medicine, Fukushima Mecical University, Fukushima, Japan; Department of Pulmonary Medicine, Sendai Kousei Hospital, Sendai, Japan; Division of Respiratory Medicine and Neurology, Department of Internal Medicine, Asahikawa Medical University, Asahikawa, Japan; Department of Respiratory Medicine, Ibaraki Prefectural Central Hospital, Ibaraki, Japan; Department of Respiratory Medicine, Akita Kousei Medical Center, Akita, Japan; Department of Respiratory Medicine, Miyagi Cancer Center, Natori, Japan; Department of Respiratory Medicine, NHO Hakodate Medical Center, Hakodate, Japan; Department of Respiratory Medicine, Oji General Hospital, Tomakomai, Japan; Department of Respiratory Medicine, NHO Hokkaido Medical Center, Sapporo, Japan; Department of Respiratory Medicine, Teine Keijinnkai Hospital, Sapporo, Japan; Department of Respiratory Medicine, Japan Community Health Care Organization Hokkaido Hospital, Sapporo, Japan

Background: Nivolumab as a second-line treatment for pleural mesothelioma (PM) has demonstrated efficacy in the MERIT phase 2 trial in Japan and the CONFIRM phase 3 trial in the UK. However, the response rate and survival outcomes were modest. Therefore, the exploration of biomarkers that can determine its efficacy and prognosis is crucial. Recently, V-domain immunoglobulin suppressor of T cell activation (VISTA), and other coinhibitory or costimulatory molecules which are expressed on T cells and tumor cells, have attracted attention as novel therapeutic targets and predictors of clinical outcomes beyond PD-L1 for immunotherapy against various solid tumors. However, few studies have explored the efficacy of nivolumab by examining these molecules, as well as specific gene mutation profiles, in patients with PM. Thus, we aimed to identify biomarkers associated with survival in our cohort. **Methods:** This retrospective, multi-institutional cohort study included patients with PM who received nivolumab monotherapy as a second-line or later treatment at 18 hospitals in Japan between August 2018 and October 2019. We investigated the association of progression-free survival (PFS) and overall survival (OS) with clinical variables, expression of CD4, CD8, OX40, PD-L1, Tim-3, LAG-3, and VISTA in tumor tissues via immunohistochemistry (IHC), and gene expression profiles using next-generation sequencing (NGS). **Results:** Fifty-five patients were enrolled in this study. IHC and NGS were performed in 42 and 33 patients, respectively. The median survival follow-up time for all patients was 12.3 months (range, 0.2–47.0 months). The median PFS was 4.8 months (95% confidence interval [CI], 3.6–6.0), and the median OS was 12.3 months (95% CI, 10.3–14.4). No differences in OS or PFS were observed based on histological type. The IHC analysis revealed that high VISTA expression in tumor cells was significantly associated with improved PFS and OS compared with low VISTA expression (PFS, median: 5.1 months [95% CI, 3.5–6.7] vs. 2.4 months [95% CI, 0.0–5.1], $p = 0.001$; OS, median: 12.8 months [95% CI, 11.0–14.6] vs. 4.3 months [95% CI, 1.2–7.3], $p = 0.007$). Multivariate analysis confirmed that high VISTA expression in tumor cells was an independent predictor of prolonged PFS and OS (PFS: hazard ratio [HR], 0.14; $p < 0.001$; OS: HR, 0.38; $p = 0.044$). NGS data showed that gene alterations commonly reported in PM, such as mutations in *CDKN2A*, *BAP1*, and *NF2*, were not associated with PFS or OS. **Conclusions:** For PM patients with low VISTA expression in tumor cells, nivolumab may not be the optimal treatment choice, and alternative therapies should be considered. These findings provide a basis for further biomarker exploration in combination therapies, such as nivolumab-ipilimumab or chemoimmunotherapy, for patients with PM. Research Sponsor: Research funding from the Department of Respiratory Medicine, Hokkaido Cancer Center.

Digital spatial profiling for identification of prognostic genes and molecular subgroups in pleural mesothelioma.

Mercedes Herrera, David Lora, Melina Peressini, Ramon Yarza, Jose Maria Gracia, Álvaro C. Ucero, Magdalena Molero Abraham, Ana Belén Enguita, David Gómez-Sánchez, Vera Adradas Rodriguez, Esther Conde, Nuria Carrizo, Igor Gómez-Randulfe, Roxana Reyes, Noemi Reguart, Javier Baena, Helena Bote de Cabo, Santiago Ponce Aix, Luis G. Paz-Ares, Jon Zugazagoitia; Hospital Universitario 12 de Octubre, Madrid, Spain; Faculty of Statistics, Complutense University of Madrid, Madrid, Spain; Tumor Microenvironment and Immunotherapy Research Group, Instituto de Investigación Hospital 12 de Octubre (i+12), Madrid, Spain; START Madrid-CIOCC, Centro Integral Oncológico Clara Campal, Madrid, Spain; H12O-CNIO Lung Cancer Clinical Research Unit, Health Research Institute Hospital Universitario 12 de Octubre (i+12), Madrid, Spain; Department of Pathology. Hospital Universitario 12 de Octubre, Madrid, Spain; Pathology Department, Hospital Universitario 12 de Octubre. Universidad Complutense de Madrid. Research Institute Hospital 12 de Octubre (i+12). CIBERONC, Madrid, Spain; Department of Pathology, Hospital Universitario 12 de Octubre, Madrid, Spain; Complexo Hospitalario Universitario de A Coruña (CHUAC), A Coruña, Spain; Hospital Clínic Barcelona, Barcelona, Spain; Hospital Universitario 12 de Octubre, H12O-CNIO Lung Cancer Clinical Research Unit, Universidad Complutense and Ciberonc, Madrid, Spain; Hospital Universitario 12 de Octubre, H12O-CNIO Lung Cancer Unit, Universidad Complutense and Ciberonc, Madrid, Spain

Background: Pleural mesothelioma (PM) is an aggressive malignancy that harbors significant inter- and intra-tumoral heterogeneity. Spatial transcriptomics enables the dissection of the tumor's molecular architecture by facilitating compartment-specific gene expression profiling. We performed high-resolution RNA-seq analysis of tumor (Tm) and stroma (St) compartments in PM samples to identify gene expression patterns and their association with clinical outcomes. **Methods:** Formalin-fixed paraffin-embedded (FFPE) tumor samples from untreated PM patients (pts) across three institutions were analyzed using the NanoString GeoMx Digital Spatial Profiling (DSP) platform. Regions of interest (ROIs) were selected based on histopathological features and fluorescently labeled antibodies for tumor and stromal areas. RNA expression of >1800 genes from selected ROIs was analyzed using GeoMx Cancer Transcriptome Atlas (CTA). Differential gene expression was assessed utilizing R "limma" package. A cutoff of absolute fold change ≥1 and p-value <0.05, with the Benjamini-Hochberg false discovery rate method, was applied to identify significant differentially expressed genes (DEGs). Elastic Net regression optimized through cross-validation methods was employed to identify genes associated with overall survival (OS) outcomes. Data from the TCGA PanCancer Atlas was utilized for external validation. **Results:** A total of 72 pts, 80.3% male, median age of 71y (range: 44-94) were identified for the analysis. Among them, 87.5% (63/72) were epithelioid (Ep) and 12.5% (9/72) non-epithelioid (NEp). After quality control, RNA data was available from 71 and 67 pts in Tm and St compartments, respectively. Across 132 ROIs in the Tm compartment, we identified 4 significantly DEGs between NEp (upregulated *COL5A2, THBS1*; downregulated *CLU, KRT19*) and Ep subgroups. No DEG between Ep and NEp subgroups were identified in 115 ROIs from the St compartment. Unsupervised clustering identified four molecular subgroups with distinct gene expression in the Tm compartment, of which Cluster 1 showed significantly decreased OS (6.3m vs. 16.4m; HR 3.3, p =0.001). Elastic Net regression identified 31 genes predictive of OS (R^2 = 0.43, Harrell's c-index = 0.87), including nine genes (*IFNGR2, FCER1G, MFGE8, CKLF, CBL, HLA-DRB3, HK1, PLAT, CD163*) associated with worse prognosis. Tumors in Cluster 1 demonstrated higher expression of these genes. External validation using the TCGA cohort confirmed four genes *IFNGR2* (p = 0.02), *CBL* (p = 0.01), *HK1* (p <0.001), *PLAT* (p <0.001), as significantly associated with decreased OS in PM. **Conclusions:** Spatially resolved transcriptomic profiling suggests Tm-enriched regions as the primary drivers of PM subtype and aggressiveness, identifying nine genes and a molecular subgroup associated with poorer survival outcomes. Further validation and functional studies are warranted. Research Sponsor: TRANSCAN-3 Consortium; TRNSC18004PAZ.

8086 Poster Session

Multiomics profiling for prediction of immunotherapy response in advanced pleural mesothelioma: Sub-study of the NIPU trial.

Mehrdad Rakaee, Solfrid Thunold, Masoud Tafavvoghi, Åsa Kristina Öjlert, Krinio Giannikou, Elio Adib, Johanna Mattsson, Carina Strell, Patrick Micke, David J. Kwiatkowski, Aslaug Helland, Vilde Drageset Haakensen; University Hospital of North Norway, Oslo, Norway; Oslo University Hospital, Oslo, Norway; Oslo University Hospital, Department of Oncology and Department of Cancer Genetics, Oslo, Norway; Brigham and Women's Hospital, Boston, MA; Brigham and Women's Hospital, Boston, MA; Uppsala University, Department of Immunology, Genetics and Pathology, Uppsala, Sweden; Uppsala University, Uppsala, Sweden; Oslo University Hospital, Division of Cancer Medicine, Oslo, Norway

Background: The combination of ipilimumab and nivolumab (IPI/NIVO) is a standard treatment for unresectable pleural mesothelioma. However, the objective response rate (ORR) is relatively low, and serious toxicity necessitating treatment cessation with or without steroid treatment is seen in 20%. Predictive biomarkers for IPI/NIVO in mesothelioma are needed to personalize treatment decisions. **Methods:** In the NIPU trial, 118 patients progressing after first-line chemotherapy were included in the study and were randomly assigned to IPI/NIVO alone or in combination with the telomerase UV1 vaccine. Whole-slide tumor tissues were available from 99 patients and analyzed using multiplex immunofluorescence (mIF) with a panel including CD8, CD20, CD66b, FoxP3, Granzyme-B, and pan-cytokeratin. Machine learning algorithms (XGBoost) were utilized and trained for immune cell subset classification and tissue subregion segmentation (tumor vs. stroma). Bulk RNA-sequencing (RNA-seq) was performed on 25 matched baseline fresh frozen tissues, followed by differential expression analysis (DESeq2), gene set enrichment analysis (GSEA) and immune cell deconvolution. Radiological evaluation was done by local assessment of immune version of the mesothelioma modified RECIST criteria. Disease control rate (DCR) was defined as the fraction of patients with partial response (PR) or stable disease (SD) compared to those with progressive disease (PD). **Results:** The DCR and ORR were 69% and 20%, respectively. From mIF analysis, stromal CD66b, CD20, and tumoral CD66b showed the highest area under the curve (AUC = 0.60 $\pm$ 0.1) for differentiating DCR groups. For ORR, tumoral CD8+FoxP3+ T-cells demonstrated the highest AUC (0.58) for identifying PR. Patients with tumoral CD66b% scores above the median (>0) had significantly longer progression-free survival (6.2 vs. 4.2 months; HR: 0.63, 95% CI: 0.42–0.97, P = 0.04) and showed a trend toward improved overall survival (HR: 0.65, 95% CI: 0.41–1.0, P = 0.07). These findings were consistent with RNA-seq-derived immune fraction scores. Lasso Cox regression identified natural killer cells, neutrophils, and CD4+ T cells as top predictive features for DCR groups. Additionally, GSEA hallmark analysis revealed significant enrichment of interferon-γ and -α pathways in the DCR PR/SD group ($Q < 0.001$) compared to PD. **Conclusions:** High/positive levels of tumoral CD66b+ neutrophils show promise as predictive biomarkers for immunotherapy efficacy in advanced pleural mesothelioma. Larger, independent studies are needed to confirm these findings and validate their clinical utility. Clinical trial information: NCT04300244. Research Sponsor: Bristol Myers Squibb; South-Eastern Norway Regional Health Authority; Ultimovacs.

Phase III study on atezolizumab versus placebo in adjuvant therapy of pleural mesothelioma patients after pleurectomy/decortication: Preliminary results of the AtezoMeso study.

Maria Pagano, Massimiliano Paci, Giulia Pasello, Federico Rea, Federica Grosso, Paolo Bironzo, Francesco Leo, Federica Bertolini, Pier Luigi Filosso, Armando Santoro, Francesco Agustoni, Giulio Melloni, Alessandra Guglielmi, Annamaria Catino, Salvatore Pisconti, Marcello Tiseo, Luca Ampollini, Paola Taveggia, Giamaica Ciardiello, Carmine Pinto; Medical Oncology, Comprehensive Cancer Centre, AUSL-IRCCS, Reggio Emilia, Italy; Unit of Thoracic Surgery, AUSL Reggio Emilia, Reggio Emilia, Italy; Department of Surgery, Oncology and Gastroenterology, University of Padova Medical School; Medical Oncology 2, Veneto Institute of Oncology IOV-IRCCS, Padua, Italy; Thoracic Surgery Unit, Department of Cardiac, Thoracic and Vascular Sciences and Public Health, University of Padua, Padua, Italy; SSD Mesotelioma, Melanoma e Tumori Rari, Aou SS Antonio e Biagio e Cesare Arrigo, Alessandria, Italy; Department of Oncology, University of Torino, Torino, Italy; SCDU Chirurgia Toracica, Ospedale S Luigi, Regione Gonzole 10, Orbassano, Torino, Italy; Department of Oncology, Modena University Hospital, Modena, Italy; Dipartimento di Scienze Mediche e Chirurgiche Materno-Infantili e dell'Adulto, Modena, Italy; Medical Oncology and Hematology Unit, IRCCS Humanitas Research Hospital, Milan, Italy; Department of Medical Oncology Fondazione IRCCS Istituto Nazionale Tumori, Monza, MI, Italy; Struttura complessa Chirurgia Toracica Fondazione IRCCS Policlinico San Matteo di Pavia, Pavia, Italy; Department of Medical Oncology, ASUGI, Maggiore Hospital, Trieste, Italy; IRCCS Istituto Tumori "Giovanni Paolo II", Bari, Italy; Unit of Medical Oncology, Ospedale S.G. Moscati, Taranto, Italy; Department of Medicine and Surgery, University of Parma and Medical Oncology Unit, University Hospital of Parma, Parma, Italy; Thoracic Surgery, Surgical Unit, Dept of Medicine and Surgery, University Hospital of Parma, Parma, Italy; AZ Ospedaliera Villa Scassi, Genova, Italy; Medical Oncology Unit, Comprehensive Cancer Centre, AUSL-IRCCS di Reggio Emilia, Reggio Emilia, Italy; Medical Oncology Unit, Comprehensive Cancer Centre, AUSL-IRCCS, Reggio Emilia, Italy

Background: AtezoMeso Study is a multicentric double-blind, placebo-controlled, Phase III trial, that aims to evaluation the efficacy of adjuvant atezolizumab therapy versus placebo in patients with pleural mesothelioma (PM), who have undergone pleurectomy/decortication (P/D) and peri-operative chemotherapy. Here, we report preliminary data on disease recurrence and Next Generation Sequencing (NGS) testing. **Methods:** Patients with PM who have undergone P/D and perioperative platinum-pemetrexed chemotherapy are randomized 2:1 to receive atezolizumab or placebo for up to 12 months, or until unacceptable toxicity or patients'/physicians' decision. The primary objective of the study is disease free survival (DFS), with a sample size of 90 patients. Surgical specimens are analyzed centrally to determine the genomic profile using FoundationOne CDx Platform. **Results:** Between December 2021 and January 2025, 64 patients were randomized in 14 Italian centers. The characteristics of patients included 46 (71.88%) males and 18 (28.12%) females. %), with a median age of 67 years (range 48-79). Sixty (93.75%) patients had epithelioid histotype, and 4 (6.25%) non-epithelioid. Sixteen (25%) patients are ongoing the adjuvant treatment. At the median follow up of 8.3 months (1-30 months), 25 (53.19%) of 47 evaluable patients experienced a disease recurrence. Sixteen (64%) of 25 patients had a local recurrence of disease, 5 (20%) patients an extra-thoracic recurrence, and 4 (16%) patients both. The median DFS of all evaluable patients was 12 months (7.4 - 16.6 months). The histotype of all relapsed patients was epithelioid. NGS testing was performed in 43 (67.19%) of 64 patients. Median Tumor Mutational Burden (TMB) was 2 mutations/megabase (0-13). The most frequent genomic alteration detected were BAP1 found in 21 (48.83%) patients, CDKNA2A-B in 18 (41.86%), NF2 in 8 (18.60%), SETD2 and TP53 in 5 (11.63 %). One (2.32%) patient had a mutation of BRCA2. The co-occurrence of BAP1 and CDKNA2A-B mutations was detected in 7 (16.27%) patients, all of whom had a disease recurrence. **Conclusions:** These preliminary dataof AtezoMeso Study, regarding all randomized patients, show a median DFS longer than expected in control arm according with the study design hypothesis (9 months). The TMB of MPM patients is low. BAP1 mutations were identified as the most frequent molecular alterations. Furthermore the co-occurrence of BAP1 and CDKNA2A-B mutations was found in patients with disease relapse. Clinical trial information: NCT04996017. Research Sponsor: None.

Real-world efficacy and safety of tarlatamab in patients with relapsed extensive-stage small cell lung cancer.

Mitchell Parma, Eric Kumar Singhi, Luisa Maren Solis, Wei-Lien Wang, Mehmet Altan, Maria Cecilia Franco-Vega, Alexa J. Halliday, Joshua Jacome, Jianjun Zhang, John Heymach, Lauren Averett Byers, Carl Michael Gay, Bingnan Zhang; Department of Hematopoietic Biology and Malignancy, The University of Texas MD Anderson Cancer Center, Houston, TX; The University of Texas MD Anderson Cancer Center, Houston, TX; Department of Translational Molecular Pathology, The University of Texas MD Anderson Cancer Center, Houston, TX; Department of Pathology, The University of Texas MD Anderson Cancer Center, Houston, TX; Department of Thoracic Head and Neck Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX; Department of Thoracic/Head and Neck Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX; University of Texas MD Anderson Cancer Center, Houston, TX; Department of Thoracic/Head and Neck Medical Oncology, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Tarlatamab, a bispecific T cell engager targeting Delta-Like ligand 3, received FDA approval in May 2024 for patients with relapsed extensive-stage small cell lung cancer (SCLC). While the clinical trials leading to its approval demonstrated impressive objective response, it has unique toxicities including cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS). Here, we report a real-world case series of safety and efficacy data for patients treated with standard of care tarlatamab at MD Anderson Cancer Center. **Methods:** We queried the MD Anderson Lung Cancer GEMINI database for patients treated with tarlatamab and retrospectively collected demographic, clinical, and outcome data. From 7/1/2024-1/15/2025, a total of 39 patients received tarlatamab. 8 patients were excluded from analysis either due to diagnosis of extrapulmonary small cell cancer or rapid clinical deterioration due to disease progression around the time of the first tarlatamab infusion. The final cohort consisted of 31 patients. **Results:** The average age of our cohort was 66 years, 36% of patients were of non-white race, and their median lines of prior treatment was 2. 4 patients had transformed SCLC from classical EGFR-mutant lung adenocarcinoma (EGFR transformed), and 12 patients had untreated brain metastases (BM) prior to tarlatamab initiation. Safety data is summarized in the Table. At the cutoff, 17 patients had their first repeat systemic imaging: 59% had tumor shrinkage, 12% had stable or mixed tumor response, and 29% experienced tumor growth. Of the 3 EGFR transformed cases that had a repeat imaging on treatment, 2 had tumor growth. 18 patients underwent a repeat brain magnetic resonance imaging (MRI) after tarlatamab treatment. Out of 11 patients with untreated BM, 82% (9) had intracranial tumor shrinkage or stability, and 2 patients had mixed response, one of which was an EGFR transformed case. Of the 7 patients who either had no prior BM or had BM treated with radiation, only 1 had developed new BM (EGFR transformed). **Conclusions:** Preliminary data from this cohort show efficacy comparable to that observed in clinical trials. Notably, we report impressive intracranial response in patients with untreated BM. The toxicity profile reveals similar CRS but higher ICANS rates compared to those reported in the clinical trials. Additional data collection and analyses are ongoing at this time. Research Sponsor: None.

Safety data from C1D1 and C1D8 of Tarlatamab.

Adverse Event	Hospitalization for C1D1 of Tarlatamab 1 mg IV (N=31)	Hospitalization for C1D8 of Tarlatamab 10 mg IV (N=28)
Cytokine-release syndrome — no. (%)		
Overall	12 (39)	11 (39)
Grade 3 or more	1 (3)	1 (4)
Tocilizumab Administration	8 (26)	4 (14)
ICANS — no. (%)		
Overall	8 (26)	4 (14)
Grade 3 or more	3 (10)	0 (0)
Adverse event leading to ICU stay — no. (%)	4 (13)	1 (4)

8089 Poster Session

A phase 1 dose escalation and expansion study of ZG006, a trispecific T cell engager targeting CD3/DLL3/DLL3, as monotherapy in patients with refractory small cell lung cancer or neuroendocrine carcinoma.

Qiming Wang, Jianhua Shi, Xiaoli Chai, Li Zheng, Lihua Wu, Haibo Mou, Rongbo Lin, Xiujuan Qu, Linlin Liu, Qi Xu, Dan Cao, Yu Yao, Jason Jisheng Wu; The Affiliated Cancer Hospital of Zhengzhou University & Henan Cancer Hospital, Zhengzhou, Henan, China; Department II of Medical Oncology, Linyi Cancer Hospital, Linyi, China; ChangSha TaiHe Hospital, Changsha, Hunan, China; Clinical Trial Center, West China Hospital, Sichuan University, Chengdu, China; Shulan (Hangzhou) Hospital, Hangzhou, Zhejiang, China; Shu Lan (Hang Zhou) Hospital, Hangzhou, China; Fujian Cancer Hospital, Fuzhou, China; Department of Oncology, the First Hospital of China Medical University, Shenyang, China; China-Japan Union Hospital of Jilin University, Changchun, China; Department of Hepato-Pancreato-Biliary & Gastric Medical Oncology, Zhejiang Cancer Hospital, Hangzhou, China; West China Hospital of Sichuan University, Chengdu, China; The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China; Suzhou Zelgen Biopharmaceuticals Co., Ltd., Suzhou, China

Background: ZG006 is a unique designed T cell engager, targeting CD3 and Delta-like ligand 3 (DLL3) with two distinct DLL3 epitopes, and bridges tumor cells and T cells by strongly binding to DLL3 on tumor cells and CD3 on T cells, thereby mediating T cell-specific killing of DLL3-expressing tumor cells such as small cell lung cancer (SCLC) or neuroendocrine carcinoma (NEC). Here, we report the complete results for the phase 1 study of ZG006 for the treatment of patients (pts) with refractory SCLC or NEC. **Methods:** This is a multi-center, open-label, phase 1 clinical study of ZG006 as monotherapy in pts with SCLC or NEC who failed or were intolerant to the standard therapies. A standard "3+3" design, with an accelerated approach for the first two lower dose levels was used during the dose escalation stage. Patients were treated with doses from 0.1 to 100 mg, intravenous infusion, once every 2 weeks. Tumor response was assessed by RECIST1.1. DLL3 expression was retrospectively evaluated by IHC. **Results:** As of data cut-off in Dec 2024, a total of 45 pts (41 SCLC pts and 4 NEC pts) were enrolled and received≥1 dose of ZG006, 4 at the dose group of 0.1 mg, 3 at 0.3 mg, 3 at 1 mg, 3 at 3 mg, 5 at 10 mg, 12 at 30 mg, 11 at 60 mg and 3 at 100 mg. Patients included 35 males and 10 females, with median age 59 years (range: 43-72). The majority (86.6%) had received ≥2 lines of prior treatments and 44.4% received ≥3 lines. Twenty-six pts (57.8%) had prior anti-PD-(L)1 treatment. Only one patient in 100 mg group experienced DLT events (grade 3 cytokine release syndrome and grade 4 pneumonia). Treatment-related adverse events (TRAEs) occurred in all 45 pts; most commonly: cytokine release syndrome (CRS), pyrexia, anemia, white blood cell count decreased, pruritus, decreased appetite, hyponatraemia, asthenia, neutrophil count decreased, nausea, hypoalbuminaemia, alanine aminotransferase increased and constipation. CRS occurred mostly after the first two doses and usually recovered within 2 days. Eleven pts (24.4%) experienced serious TRAEs. There was no TRAE leading to treatment discontinuation or death and no ICANS was reported. Twenty-three SCLC patients receiving ZG006 10-60 mg were efficacy-evaluable with at least one post-baseline tumor assessment, and the ORR was 60.9% (14/23, 10 confirmed) and the DCR was 78.3% (18/23). Among the 18 pts who had low/medium DLL3 expressions, 12 pts achieved PRs with an ORR of 66.7%, which demonstrated that ZG006 had a great anti-tumor activity in SCLC pts. ZG006 demonstrated a nearly dose-proportional increase in concentration with a half life of approximately 4 days after multiple doses. **Conclusions:** ZG006 exhibited a promising antitumor activity with acceptable safety profiles. Phase 2 dose expansion studies have been initiated to further investigate the efficacy and safety of ZG006 in pts with SCLC or NEC. Clinical trial information: NCT05978284. Research Sponsor: None.

Efficacy and safety of envafolimab plus carboplatin and etoposide as first-line treatment for extensive-stage small-cell lung cancer: A prospective, single-arm, phase II trial.

Shengjie Sun, Xiao Zhao, Jing Zhang, Lupeng Qiu, Quanli Han, Xiang Yan, Yanyun Zhu, Jinliang Wang, Xiaoling Zhang, Shunchang Jiao; Senior Department of Oncology, the Fifth Medical Center of PLA General Hospital, Beijing, China

Background: Extensive-stage small cell lung cancer (ES-SCLC) is related to high malignancy and the poor prognosis. At present, immunotherapy combined with chemotherapy resulted in favorable therapeutic efficacy, and had been established as the standard treatment regimen for first-line treatment of ES-SCLC. However, some patients may still experience intolerable AEs over the course of treatment, such as immune-related pneumonitis and enteritis. Additionally, currently marketed ICIs were administered by continuous intravenous infusion, which is inconvenient for patients. This trial aimed to evaluate the efficacy and safety of envafolimab, which is a subcutaneously administered fusion protein of humanized anti-PD-L1 monodomain antibody, plus chemotherapy as a first-line treatment for ES-SCLC. **Methods:** This prospective, single-arm, phase II trial was conducted at the Fifth Medical Center of Chinese PLA General Hospital. Eligible patients with histologically or cytologically confirmed ES-SCLC were consecutively enrolled. Patients were given four cycles of carboplatin (5-6 mg/mL/min, day 1 of each cycle) and etoposide (80-100 mg/m^2, days 1-3 of each cycle) with envafolimab (300 mg, Q3W, day 3 post-chemotherapy of each cycle), followed by envafolimab maintenance until disease progression or intolerable toxicity. The primary endpoint was progression-free survival (PFS), and the secondary endpoint included objective response rate (ORR), disease control rate (DCR), and safety. **Results:** Between October 2021 and November 2022, a total of 32 patients were enrolled in this study. 32 patients were included for safety analysis, and 31 patients were included for efficacy analysis. As of the data cutoff (September 15, 2024), the median follow-up was 27.7 months. The ORR was 87.1% (95% CI, 70.2-96.4%), and the DCR was 100% (95% CI, 88.8-100%). The median DoR was 5.47 months (95% CI, 3.43-10 months). The median PFS was 6.43 months (95% CI, 4.83-7.67 months), and median OS was 20 months (95% CI, 14.7-NA). Treatment-related adverse events (TRAEs) of any grade were reported in 59.4% of patients, with grade $\geq$ 3 TRAEs in 15.6% patients. No treatment-related deaths occurred. **Conclusions:** First-line envafolimab in combination with carboplatin and etoposide yielded favorable clinical efficacy with a manageable safety profile for patients with ES-SCLC, representing a promising treatment modality. Clinical trial information: ChiCTR2100044981. Research Sponsor: None.

8091 Poster Session

Unveiling drivers of MHC repression and therapeutic strategies to counter immune evasion in small cell lung cancer.

Triparna Sen, Subhamoy Chakraborty, Andrew Elliott, Vrinda Jethalia, Ari Vanderwalde, Balazs Halmos, Deniz Demircioglu, Dan Hasson; Icahn School of Medicine at Mount Sinai, New York, NY; Icahn School of Medicine, New York, NY; Caris Life Sciences, Pheonix, AZ; Caris Life Sciences, Phoenix, AZ; Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, NY

Background: Small cell lung cancer (SCLC) is a highly aggressive neuroendocrine malignancy with a median survival of 9–11 months. Despite the addition of immune checkpoint blockade (ICB) to frontline chemotherapy, improvements remain limited. SCLC evades anti-tumor immunity by suppressing major histocompatibility complex class I (MHC-I) and antigen presentation (AP). The variability of MHC repression across molecular subtypes of SCLC and high-grade neuroendocrine tumors is not fully understood. This study analyzed clinical SCLC and neuroendocrine tumor samples to identify molecular subtypes and regulators of MHC repression, enhancing the understanding of immune evasion. **Methods:** Molecular profiling was conducted on 944 SCLC and 5056 non-small cell lung cancer (NSCLC) tumors using next-generation DNA (592-gene panel/whole exome), RNA (whole transcriptome) sequencing, and immunohistochemistry. Transcriptomic profiling of 40 SCLC cell lines and genetically engineered mouse models (GEMMs) was also performed. **Results:** Key regulators and gene networks driving MHC-I suppression in SCLC and other high-grade neuroendocrine tumors were identified. Canonical (MHC-I and II) and non-canonical AP expression scores characterized the spectrum of MHC-I repression across subtypes. Low MHC-I scores correlated with reduced immune signatures (e.g., T cell-inflamed, NK cell, and STING pathway signatures; Spearman = 0.87, 0.58, 0.62, respectively) and predicted poor OS and PFS to immunotherapy. Enhancer network and gene expression analyses identified actionable regulators of MHC-I repression, including interferon signaling. Knockout studies of top MHC-I regulators and single cell analyses revealed non-homologous end-joining (NHEJ) genes (like DNAPKCs) inversely correlated with HLA-A/B/C expression. DNAPKCs inhibition upregulated MHC-I, TAP1, and TAP2, enhanced antigen-specific T-cell-mediated cytolysis in SCLC. This inhibition activated the STING pathway, increased CD8+ T-cell infiltration, and enhanced MHC Class-I. Combining DNAPKCs inhibitor NU1774 with anti-PD-L1 reactivated MHC-I and led to significant tumor regression in aggressive murine SCLC models, supporting new combination therapies. **Conclusions:** We identified molecular subtypes and actionable pathways to restore MHC-I expression in SCLC, advancing understanding of immune evasion mechanisms. DNAPKCs is established as a key therapeutic target, enhancing PD-L1 blockade by reactivating antigen presentation. The developed MHC-I expression scores and associated biomarkers offer predictive tools for identifying patients likely to benefit from immunotherapy. These findings support biomarker-driven, personalized approaches to improve treatment for SCLC, addressing a critical unmet need in this devastating cancer. Research Sponsor: None.

8093 Poster Session

Serplulimab versus placebo plus chemotherapy as first-line treatment for extensive-stage small-cell lung cancer: Efficacy and safety from the end-of-study analysis of the international phase 3 ASTRUM-005 study.

Ying Cheng, Liang Han, Lin Wu, Jun Chen, Hongmei Sun, Guilan Wen, Yinghua Ji, Anastasia V. Zimina, Jianhua Shi, Zhijie Pan, Jinsheng Shi, Xicheng Wang, Yuansong Bai, Tamar Melkadze, Yueyin Pan, Xuhong Min, Maksym Viguro, Jing Li, Qingyu Wang, Jun Zhu, ASTRUM-005 Study Group; Department of Oncology, Jilin Cancer Hospital, Changchun, China; Department of Oncology, Xuzhou Central Hospital, Xuzhou, China; Department of Thoracic Medical Oncology, Hunan Cancer Hospital, The Affiliated Cancer Hospital of Xiangya School of Medicine, Central South University, Changsha, China; Department of Lung Cancer Surgery, Tianjin Medical University General Hospital, Tianjin, China; Department of Oncology, Jiamusi Cancer Hospital, Jiamusi, China; Department of Respiratory Medicine, The First Affiliated Hospital of Nanchang University, Nanchang, China; Department of Oncology, The First Affiliated Hospital of Xinxiang Medical University, Xinxiang, China; Budgetary Healthcare Institution of Omsk Region "Clinical Oncology Dispensary", Omsk, Russian Federation; Department II of Medical Oncology, Linyi Cancer Hospital, Linyi, China; Department of Respiratory Medicine, The First Affiliated Hospital of Zhejiang University School of Medicine, Hangzhou, China; Department of Oncology, Cangzhou People's Hospital, Cangzhou, China; Department of Oncology, The First Affiliated Hospital of Guangdong Pharmaceutical University, Guangzhou, China; Department of Oncology and Hematology, China-Japan Union Hospital of Jilin University, Changchun, China; Research Institute of Clinical Medicine, Tbilisi, Georgia; Anhui Provincial Hospital, Hefei, China; Department of Interventional Radiology, Anhui Chest Hospital, Hefei, China; Clinical Research Department, Medical Center "Mriya Med-Service", Kryvyi Rih, Ukraine; Shanghai Henlius Biotech, Inc., Shanghai, China

Background: ASTRUM-005 is a randomized, double-blind, phase 3 trial comparing the efficacy and safety of anti-PD-1 antibody serplulimab plus chemotherapy (chemo) versus (vs) placebo plus chemo as first-line therapy for extensive-stage small-cell lung cancer (ES-SCLC). Significantly prolonged overall survival (OS) in the serplulimab arm was observed at interim analysis and sustained OS improvement at extended follow-up (2024 ASCO Annual Meeting No. 8100). Here we present end-of-study analysis of ASTRUM-005 at a median follow-up of 42.4 months. **Methods:** Patients with ES-SCLC who had not received prior systemic therapy were randomized 2:1 to receive serplulimab plus chemo (carboplatin and etoposide) or placebo plus chemo. Serpluliamb or placebo were administered intravenously at 4.5 mg/kg every 3 weeks. Up to 4 cycles of intravenous carboplatin and etoposide were given every 3 weeks. Stratification factors included PD-L1 expression level, brain metastases, and age. The primary endpoint was OS. Secondary endpoints included progression-free survival (PFS), objective response rate, duration of response, and safety. **Results:** Between Sep 12, 2019 and Apr 27, 2021, 585 patients were randomized (serplulimab group, n = 389; placebo group, n = 196) and received at least one dose of study treatment. All 585 patients were included in efficacy and safety analyses. As of data cutoff on May 7, 2024, consistent with previous reports, marked improvement in OS, PFS, ORR, and DOR were achieved by patients receiving serplulimab plus chemo than those receiving placebo plus chemo. Median OS was 15.8 vs.11.1 months (stratified HR 0.60, 95% CI 0.49–0.73) for respective arms; estimated 4-year OS rate (95% CI) was 21.9% (17.6–26.6) and 7.2% (3.8–12.1). Subgroup analysis of OS by age, sex, race, ethnicity, ECOG PS, smoking history, brain metastasis, or PD-L1 expression level revealed similar trends of improvement in the serplulimab arm. Median PFS according to independent radiology review committee (IRRC) assessment per RECIST v1.1 was 5.8 vs 4.3 months (stratified HR 0.47, 95% CI 0.38–0.57), respectively. The safety profile was consistent with previous findings. Serplulimab/placebo-related treatment-emergent adverse events of grade 3 or higher occurred in 136 (35.0%) and 57 (29.1%) patients in respective arms. No new safety signals were identified in this study. **Conclusions:** This end-of-study analysis showed that addition of serplulimab to chemo continued to confer survival benefit to previously untreated patients with ES-SCLC along with manageable safety. These results support serplulimab plus chemo for first-line treatment of ES-SCLC. Clinical trial information: NCT04063163. Research Sponsor: Shanghai Henlius Biotech, Inc.

DAREONTM-9, a phase Ib study of obrixtamig plus topotecan in patients (pts) with advanced small cell lung cancer (SCLC): Interim analysis results.

Martin Wermke, Juergen Alt, Farastuk Bozorgmehr, Florian Fuchs, Pauline du Rusquec, Anas Gazzah, Sean Dulloo, Ewa Kalinka, Aman Chauhan, Anna Mosikian, Sabine Kirner, Dian Yang, Cyrus Sayehli; TU Dresden University of Technology, NCT/UCC Early Clinical Trial Unit, Dresden, Germany; Department of Internal Medicine III (Hematology, Oncology, Pneumology), University Medical Center Mainz, Mainz, Germany; Department of Thoracic Oncology, Thoraxklinik, Heidelberg University; Translational Lung Research Centre Heidelberg (TLRC-H), Heidelberg, Germany; Department of Medicine, University Hospital Erlangen, Friedrich-Alexander-University of Erlangen-Nuremberg, Erlangen, Germany; Thoracic Oncology, Hôpital Institut Curie, Paris, France; Department of Drug Development (DITEP), Gustave Roussy, Université Paris-Saclay, Villejuif, France; Department of Oncology, University Hospitals of Leicester NHS Trust, Leicester, United Kingdom; Instytut Centrum Zdrowia Matki Polki, Department of Oncology, Łódź, Poland; Division of Medical Oncology, Department of Internal Medicine, Sylvester Comprehensive Cancer Center, University of Miami, Miami, FL; Boehringer Ingelheim International GmbH, Ingelheim Am Rhein, Germany; Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach an Der Riss, Germany; Boehringer Ingelheim (China) Investment Co., Ltd., Shanghai, China; Interdisciplinary Study Center with ECTU, Medical Clinic and Polyclinic II of the University Hospital Würzburg, Würzburg, Germany

Background: Delta-like ligand 3 (DLL3) is highly expressed on SCLC cells and is a promising target for new therapeutic drugs. Obrixtamig (BI 764532) is a DLL3/CD3 IgG-like bispecific T-cell engager that binds simultaneously to DLL3 on tumor cells and CD3 on T-cells leading to tumor cell lysis. We report the first safety and preliminary efficacy data for the dose escalation part of the Dareon-9 trial, investigating the combination of obrixtamig and topotecan in pts with advanced SCLC (NCT05990738). **Methods:** Pts who progressed on or relapsed after ≥1 line of platinum-based treatment (Tx) ± anti-programmed cell death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1) were eligible for the trial. Obrixtamig was given as step-up dosing followed by target dose (3 dose levels). Topotecan was given per label. Dose escalation of obrixtamig was guided by a Bayesian Logistic Regression Model with overdose control. Antitumor activity was assessed using RECIST 1.1. The ongoing dose confirmation part will assess obrixtamig at the dose selected at the end of dose escalation. **Results:** As of January 2, 2025, 25 pts had received ≥1 cycle of Tx. Median number of cycles for both obrixtamig and topotecan was 4 (range 1–13); median Tx exposure was 2.6 months (range ≤1–8.5). Median age was 65 years (range 38–78); ECOG PS was 0 in 13 pts (52%), 1 in 12 pts (48%); median number of prior lines of Tx was 1 (range 1–3), 92% had received prior anti-PD-1/PD-L1. Obrixtamig-related adverse events (AEs; any grade/grade ≥3) occurred in 23 (92%) and 7 (28%) pts, with no grade 5 AEs. Topotecan-related AEs (any grade/grade ≥3) occurred in 25 (100%) and 21 (84%) of pts, with no grade 5 AEs. No pts discontinued obrixtamig due to Tx-related AEs. No obrixtamig- or topotecan-related grade ≥2 neurologic events occurred. All cytokine release syndrome cases were low grade: grade 1 (44%) and grade 2 (4%). The most frequent (≥10%) Tx-emergent grade 3/4 AEs were: neutropenia and/or decreased neutrophil count in 15 pts (60%); thrombocytopenia and/or decreased platelet count in 13 pts (52%); decreased lymphocyte count in 8 pts (32%); anemia in 6 pts (24%); and fatigue in 4 pts (16%). Grade 3 febrile neutropenia was reported in 1 pt (4%). Preliminary efficacy data from evaluable pts (n=23) showed an unconfirmed ORR of 70% (95% CI 47–87); 1 pt (4%) had a CR and 15 (65%) pts had a PR. Disease control rate was 87% (95% CI 66–97). In the 13 pts with ≥2 post-baseline tumor assessments (follow-up >13 weeks), the confirmed ORR was 69%. Median duration of response was not reached. **Conclusions:** The obrixtamig plus topotecan combination was tolerable with no unexpected toxicities. AE frequency and severity reported for the combination were consistent with the expected safety findings for obrixtamig and topotecan as monotherapy. Preliminary efficacy data for the combination are encouraging and indicate an improvement on top of topotecan monotherapy. Clinical trial information: NCT05990738. Research Sponsor: Boehringer Ingelheim.

Lung cancer enrollment of demographic subgroups in US clinical trial sites.

Evon Okidi, Caroline Der-Nigoghossian, Kevin Blum, Keith Fleming, Cameron E. McClure, Kimberly Doggett; Dassault Systemes, New York, NY; BeOne Medicines Ltd, Long Beach, CA; BeOne Medicines Ltd, Durham, NC

Background: Most clinical trials globally are not representative of a diverse patient population and 78% of trial participants remain White. This may limit the generalizability of trial results to the broader population, create an insufficient understanding of drugs' safety and efficacy between different patient populations, and hinder equitable access to investigational drugs. We compare the racial and ethnic composition of US clinical trials sites for lung cancer to epidemiology data. **Methods:** The de-identified data was sourced from Medidata's clinical trial database. The cohort included clinical trial participants enrolled in US sites in phase 1-3 interventional lung cancer studies conducted between 2016 and 2022. Lung cancer incidence estimates were taken from the National Cancer Institute's incidence data. Sites were classified as at/above or below expected demographic composition based on a relative ratio calculation, RR = proportion of trial patients/proportion of population with lung cancer. RR $\geq$1 means site recruited at/above expected ratio for the demographic group and vice versa. A 10% tolerance was used to capture minor deviations. A Mann-Whitney U test was used to determine if the two site types have statistically different enrollment rates, with a p-value of 0.05 for significance. **Results:** The analysis cohort consisted of 6,988 lung cancer patients from 85 studies and 876 US sites. Most sites enrolled White non-Hispanic patients at/above the epidemiological threshold. Conversely, the majority of sites enrolled non-White patients below the threshold (Table 1). The overall enrollment performance of sites enrolling a representative cohort of Black, American Indian and White patients did not differ from their counterparts. However, sites enrolling at or above the epidemiological threshold of Asian non-Hispanic and Hispanic patients had a higher enrollment rate than sites underrepresenting these patient populations. **Conclusions:** The majority of US clinical trial sites underrepresent demographic subgroups except White non-Hispanic patients. Sites enrolling a representative pool of racial and ethnic demographic subgroups did not have a lower overall enrollment performance. Research Sponsor: None.

Enrollment rate of sites recruiting at/above vs. below epidemiological threshold.

	Enrollment Rate (pts/site/month) Median (IQR)				
	Sites Enrolling At or Above Epidemiological Threshold		Sites Enrolling Below Epidemiological Threshold		
Race/Ethnicity Sub-group	N (%) sites	Enrollment Rate	N (%) sites	Enrollment Rate	P-value
Asian (non-Hispanic)	67 (13%)	0.11 (0.03 - 0.23)	439 (87%)	0.04 (0.02 - 0.08)	<0.0001
Black (non-Hispanic)	96 (15%)	0.04 (0.02 - 0.08)	553 (85%)	0.04 (0.02 - 0.09)	0.99
American Indian (non-Hispanic)	6 (4%)	0.08 (0.06 - 0.12)	137 (96%)	0.04 (0.01 - 0.07)	0.19
White (non-Hispanic)	461 (59%)	0.04 (0.01 - 0.09)	326 (41%)	0.04 (0.02 - 0.07)	0.64
Hispanic	76 (14%)	0.07 (0.03 - 0.14)	447 (86%)	0.04 (0.02 - 0.08)	0.002

8096 Poster Session

Comprehensive longitudinal immune cell monitoring in patients with extensive-stage small-cell lung cancer patients treated with chemo-immunotherapy to predict early relapse.

Seren Durer, Patricia A. Rayman, Peronne Joseph, Jennifer Powers, C. Marcela Diaz-Montero, Afshin Dowlati; University Hospitals Seidman Cancer Center, Case Western Reserve University, Cleveland, OH; Center for Immunotherapy and Precision Immuno-Oncology (CITI), Lerner Research Institute, Cleveland Clinic, Cleveland, OH

Background: Small cell lung cancer (SCLC) is characterized by rapid growth, and although initial chemo-immunotherapy achieves high response rates, relapse typically occurs within 6–12 months. Emerging data suggest that myeloid-derived suppressor cells (MDSCs) and lymphocyte subsets influence immunotherapy response and relapse kinetics. We conducted a detailed immune profiling study to characterize circulating myeloid and lymphoid populations in SCLC patients, comparing those with early vs. late (>200 days) relapse. **Methods:** Purified PBMCs collected at baseline and relapse were analyzed by high-parameter flow cytometry using panels containing myeloid and lymphocytic markers. **Results:** Patients with ES-SCLC treated with chemo-immunotherapy were prospectively enrolled in this biomarker trial. A total of 32 were accrued. Among patients with early (<200 days) vs. late (≥200 days) relapse, baseline frequencies of CD33+ myeloid cells were similar. At relapse, however, a marked decrease in activated CD15+/CD16+ neutrophils was observed in both groups. PMN-MDSCs showed distinct kinetics: early-relapse patients had elevated MDSCs at baseline, whereas late-relapse patients exhibited significant MDSC expansion only at relapse. Additionally, a P-selectin–high monocytic subpopulation (M-MDSC) emerged more prominently in the late-relapse cohort, potentially reflecting a protective or anti-tumor phenotype. On lymphocyte analysis, a significant decline in CD8+ cytotoxic T-cell frequencies was observed at relapse across all patients, indicating a potential mechanism of immune evasion. The analysis of CD107 expression further supported the decrease in cytotoxic T-cell activity at relapse. Notably, higher baseline frequencies of CD57+ T-cell correlated with relapse-free intervals greater than 200 days. Lastly, lower baseline frequencies of activated B cells were associated with longer relapse-free survival. **Conclusions:** Our results reveal novel findings, suggesting that unique kinetics of myeloid and lymphoid immunophenotype levels are associated with relapse timing in SCLC treated with chemo-immunotherapy. These findings suggest potential predictive biomarkers and inform the development of targeted immunomodulatory strategies. Research Sponsor: None.

Efficacy and safety of HTMC0435 combination with temozolomide in relapsed extensive-stage small-cell lung cancer (ES-SCLC): A phase Ib/II study.

Yun Fan, Hui Li, Zhiyu Huang, Sizhe Yu, Kaiyan Chen, Lei Gong, Yanjun Xu, Hongyang Lu, Xiaoling Xu, Na Han, Jing Qin, Cuiping Gu; Zhejiang Cancer Hospital, Hangzhou, China; Zhejing Cancer Hospital, Hangzhou, China

Background: Treatment options for ES-SCLC in second-line setting are limited. HTMC0435, an oral PARP inhibitor, significantly reduced the ability of PARP to repair DNA damage and inhibited tumor cell proliferation when combined with temozolomide (TMZ) in preclinical studies. We investigated the safety and activity of this regimen in relapsed SCLC. **Methods:** This was a phase Ib/II dose-escalation (3+3 design) and dose-expansion study. ES-SCLC patients who had progressed after first- or second-line therapy were eligible. Pts were administered with HTMC0435 6 mg or 8 mg bid on days 1-21 in combination with TMZ 75 mg/m^2 on days 1-7 of each 21-day cycle. The study objectives were to evaluate safety, pharmacokinetics and preliminary efficacy of the combination regimen. **Results:** From Feb-2023 to Nov-2023, 59 eligible pts were enrolled, with 7 pts in dose escalation and 52 pts in dose expansion. No dose-limiting toxicity (DLT) occurred, and HTMC0435 8mg bid combination with TMZ was selected as recommended phase 2 dose (RP2D). As of 31 October 2024, the median follow-up time was 10.3 months. 55 pts received HTMC0435 8mg bid and TMZ. Among these patients, brain and liver metastases were in 41.8% (23/55) and 23.6% (13/55) pts, respectively. 61.8% (34/55) pts had received prior platinum-based and anti–PD-(L)1 therapy as first line therapy. Among 49 efficacy evaluable patients, the objective response rate (ORR) and disease control rate (DCR) were 24.5% (12/49, 95%CI: 12.0%-37.0%) and 63.3% (31/49, 95%CI: 49.3%-77.3%). The median duration of response (DoR) was 6.9 mos (95%CI: 1.22-12.58). The median progression-free survival (PFS) and overall survival (OS) were 2.8 mos (95%CI: 1.16-4.44) and 12.0 mos (95%CI: 7.85-14.75). 23 pts were platinum-resistant (chemotherapy-free interval $<$ 90 days), with ORR of 25.0% (5/20, 95%CI: 8.7%-49.1%), DCR of 55.0% (11/20, 95%CI: 31.5%-76.9%), mDoR not reached, mPFS of 2.5 mos (95%CI: 1.38-5.03) and mOS of 12.6 mos(95%CI: 5.78-NC). Among the 29 platinum-sensitive pts (chemotherapy-free interval $\geq$ 90 days), ORR and DCR were 26.9% (7/26, 95%CI: 11.6%-47.8%) and 73.1% (19/26, 95%CI: 52.2%-88.4%), and the mDoR was 4.2 mos (95%CI: 4.14-NC). The mPFS and mOS were 4.2 mos (95%CI: 2.69-5.52) and 11.2 mos (95%CI: 8.38-NC). 96.6% (57/59) pts experienced treatment-related adverse events (TRAEs) and 55.9% (33/59) pts experienced grade 3-4 TRAEs. Most common TRAEs (grade 3-4) were neutropenia (35.6%), leukopenia (28.8%), thrombocytopenia (13.6%), anemia (8.5%). Six (10.2%) pts experienced TRAEs led to dose reduction of HTMC0435 and no TRAEs led to discontinuation of HTMC0435 were reported. **Conclusions:** This combination of HTMC0435 and TMZ showed promising anti-tumor activity and manageable safety both in platinum-sensitive and platinum-resistant SCLC patients. Clinical trial information: NCT05728619. Research Sponsor: Shanghai Yidian Pharma.

Debio 0123, a highly selective WEE1 inhibitor, in combination with carboplatin (C) and etoposide (E), in patients (pts) with recurrent small cell lung cancer (SCLC): Determination of recommended dose (RD) from a phase 1 escalation.

Valentina Gambardella, Alejandro Navarro, Prantesh Jain, José María López-Picazo, Gonzalo Fernandez Hinojal, Jon Zugazagoitia, Maria J. de Miguel, Shirish M. Gadgeel, Sajjad Akbar Bhatti, Pedro Rocha, Anna Vilalta-Lacarra, Esteban Rodrigo Imedio, Sandrine Micallef, Jonathan Wessen, Vito Dozio, Rikke Frederiksen Franzen, Anne Bellon, Luis G. Paz-Ares; Department of Medical Oncology, Hospital Clínico Universitario, INCLIVA Biomedical Research Institute, University of Valencia, Valencia, Spain; Vall d'Hebron University Hospital, Barcelona, Spain; Roswell Park Comprehensive Cancer Center, Buffalo, NY; Clinica Universidad de Navarra, Pamplona, Spain; Clinica Universidad de Navarra, Madrid, Spain; Hospital Universitario 12 de Octubre, Madrid, Spain; START Madrid-CIOCC, Centro Integral Oncológico Clara Campal, Madrid, Spain; Henry Ford Cancer, Henry Ford Health, Detroit, MI; University of Arkansas for Medical Sciences, Little Rock, AR; Vall d'Hebron University Hospital, Barcelona, Spain; Department of Medical Oncology, Clínica Universidad de Navarra, Pamplona, Spain; Debiopharm International SA, Lausanne, Switzerland; Debiopharm International, Lausanne, Switzerland

Background: Debio 0123 is an oral, brain-penetrant, highly selective WEE1 inhibitor. WEE1 inhibition leads to S phase and G2/M cell cycle checkpoint abrogation, allowing mitosis without DNA repair, leading to mitotic catastrophe and subsequent cell death. Debio 0123 is in clinical development in solid tumors, as monotherapy and in combination with different therapeutic agents. Debio 0123 has shown manageable safety profile and initial signals of antitumor activity. SCLC is an aggressive disease that carries a high mutational burden and genomic instability. Debio 0123 has shown to significantly improve the antitumor activity of DNA damaging agents, C + E, in preclinical SCLC models. **Methods:** This Phase 1 study (NCT05815160) is evaluating Debio 0123 in combination with C + E in pts with recurrent SCLC after first line of platinum-based chemotherapy. Of note, pts with stable brain metastasis were eligible. In the dose escalation, pts who had a chemotherapy-free interval (CFI)>45 days since the last dose of platinum chemotherapy, received escalating doses of Debio 0123 (D1–3 and D8–10) in combination with standard C (AUC5) on D1 and E (100 mg/m2) on D1-3 in 21-day cycles. **Results:** Dose escalation data (cut-off date Oct 24th, 2024) are presented. Overall, 16 pts were treated (44% female, mean age 63.3 years). Using a Bayesian Logistic model-guided dose escalation, tested doses of Debio 0123 ranged from 200-400 mg. The RD was selected at 200 mg. At this dose level, 3/10 pts experienced a dose-limiting toxicity. The treatment was considered well tolerated with a manageable overall safety profile, in line with that expected for the chemotherapy combination. Most frequent Debio 0123 -related toxicities are shown in Table 1. PK data showed Debio 0123 plasma levels increasing proportionally with the dose. Debio 0123 CSF/plasma ratio was ~40%, suggesting that Debio 0123 crosses the blood brain barrier. At 200 mg, confirmed partial responses (PR) occurred in 4/9 evaluable pts overall, and in 4/7 pts in the subgroup with CFI>90 days, including pt with intracranial response; 4 pts had SD of which 2 had tumor shrinkage of > 20 %. mPFS at the RD (n=10) was 7.2 months. **Conclusions:** Debio 0123 combined with C + E is well tolerated, with a manageable safety profile, up to 200 mg; this combination led to promising antitumor activity in pts with recurrent SCLC after prior platinum-based therapy with CFI > 45 days. Further investigation of Debio 0123 at 200 mg in pts with a CFI > 90 days is ongoing. Clinical trial information: NCT05815160. Research Sponsor: Debiopharm International.

Summary of treatment-emergent adverse events (TEAEs) related to Debio 0123 in ≥ 2 pts at the RD (200 mg).

TEAE	Any grade (N=10) n (%)	Grade ≥3 (N=10) n (%)
Neutropenia/neutrophil count decreased	4 (40)	3 (30)
Nausea	3 (30)	0
Diarrhea	2 (20)	1 (10)
Thrombocytopenia/platelet count decreased	2 (20)	1 (10)

Does early versus late initiation of immunotherapy in extensive-stage small cell lung cancer affect survival outcomes?

Paresh Kumar, Weston He, Ahmad Karkash, Yan Han, Justin Wang Shi, Julian A. Marin-Acevedo, Mya Tran, Misty Dawn Shields; Indiana University School of Medicine, Indianapolis, IN; Indiana University Simon Comprehensive Cancer Center, Indianapolis, IN; Indiana University, Indianapolis, IN; IU Health, Indianapolis, IN; Indiana University Melvin and Simon Comprehensive Cancer Center, Indianapolis, IN; IU Simon Cancer Center, Indianapolis, IN; Indiana University Melvin and Bren Simon Comprehensive Cancer Center, Indianapolis, IN

Background: Small cell lung cancer (SCLC) is an aggressive malignancy characterized by a rapid doubling time, high metastatic potential, and risk for relapse, prompting urgent treatment. Chemoimmunotherapy is the standard of care for first line treatment of extensive-stage SCLC (ES-SCLC). A study evaluating the National Cancer Database reported improvement in overall survival (OS) with initiation of chemotherapy after 28 days from a SCLC diagnosis. However, the optimal timing for initiation of immunotherapy for SCLC remains unclear. Here, we seek to understand if the timing of immunotherapy impacts outcomes for ES-SCLC. **Methods:** We retrospectively reviewed 149 charts of patients diagnosed with ES-SCLC treated at Indiana University (IU) Health and IU Simon Comprehensive Cancer Center from January 2018 to August 2024. Patients who received platinum-based chemotherapy combined with immune checkpoint inhibitor (ICI) as first line therapy were included. Patients were categorized into two groups based on ICI timing: (1) with the first cycle and (2) after the first cycle of chemotherapy. Additionally, patients were stratified by time-to-ICI-initiation from diagnosis (TII), ≤21 days vs >21 days. **Results:** A total of 75 patients diagnosed with ES-SCLC who received chemotherapy with either durvalumab (18.7%) or atezolizumab (81.3%) were identified. Across the entire cohort, median OS and progression-free survival (PFS) were 12.2 and 5 months, respectively. Patients with TII of ≤21 days had a median OS of 16.8 months, compared to 11.8 months for those with TII >21 days (P = .26). Median OS was 16 months for patients who received ICI with the first cycle of chemotherapy and 10 months for those who received it later (P = .43). Median PFS was similar between these groups. For univariate analysis, we used median OS for the entire cohort (i.e., 12.2 months) to define responders (OS ≥12.2 months, n=30) and non-responders (OS <12.2 months, n=42). In responders group, 60% received ICI with the first cycle of chemotherapy, compared to 53.3% in non-responders (P = .57). **Conclusions:** The timing of initiation of immunotherapy, either with first cycle of chemotherapy or within 21 days of diagnosis, does not significantly improve outcomes in patients diagnosed with ES-SCLC. At our institution, atezolizumab is more commonly utilized for ES-SCLC. Recent real-world data suggests a survival benefit with use of durvalumab. Further prospective investigation is warranted to understand if ICI selection and timing can impact outcomes in ES-SCLC. Research Sponsor: None.

Patients' clinical and demographic characteristics.

		Receipt of ICI with Cycle 1		
Variable	**Overall N=75**	**No N=33**	**Yes N=42**	***P* Value**
Age	62.7 ± 9	61.5 ± 9.1	63.6 ± 8.9	0.299
ECOG PS ≥ 2	17 (25%)	9 (30%)	8 (21.1%)	0.679
Female	48 (64%)	22 (66.7%)	26 (61.9%)	0.670
Active tobacco use	43 (57.3%)	**25 (75.8%)**	**18 (42.9%)**	**0.007**
Presence of brain metastases	19 (25.3%)	6 (18.2%)	13 (31%)	0.207

Predictive and prognostic impacts of SCLC comprehensive index (SCI) in extensive-stage small-cell lung cancer (ES-SCLC) treated with chemo-immunotherapy.

Songji Oh, Changhee Park, Soyeon Kim, Jaemoon Koh, Taekeun Park, Jeonghwan Youk, Miso Kim, Bhumsuk Keam, Yoon Kyung Jeon, Dong-Wan Kim, Tae Min Kim; Cancer Research Institute, Seoul National University, Seoul, Korea, Republic of; Department of Internal Medicine, Seoul National University Hospital, Seoul, South Korea; Cancer Research Institute, Seoul National University, Seoul, Korea, Republic of (South); Department of Pathology, Seoul National University College of Medicine, Seoul, South Korea; Department of Internal Medicine, Seoul National University Hospital, Seoul National University College of Medicine, Seoul, South Korea; Seoul National University Hospital, Seoul, South Korea

Background: First-line (1L) chemo-immunotherapy is standard of care for ES-SCLC with improved survival outcomes (IMpower133 and CASPIAN). However, there were no reliable biomarkers associated with survival outcomes in these patients (pts). This study aimed to develop a SCI signature using RNA profiling with the nCounter system to predict chemo-immunotherapy outcomes. **Methods:** The SCI genes were selected based on IMpower133 transcriptomic data (Cancer Cell 2024;42:429) by K-means clustering to determine optimal cut-offs and risk grouping. A gene scoring system was developed with weights being assigned to genes linked to better survival rates. The validation cohort consisted of 93 ES-SCLC pts who received 1L chemo-immunotherapy (etoposide, carboplatin, and atezolizumab) at Seoul National University Hospital (SNUH). NanoString nCounter analysis was performed on all FFPE samples and RNA-seq was validated on 40 samples. Cox proportional hazards models were used for univariable and multivariable analyses. **Results:** The SCI was developed using genes related to neural (N=7), epithelial-to-mesenchymal transition (N=5), tumor-associated macrophages (N=5), and the T-cell inflamed signature (TIS) (N=18). The SCI signature also included molecular subtypes (N=3), targetable genes (N=4) and 5 housekeeping genes. Our validation cohort included 93 pts with mean age of 69 years and male-to-female ratio of 7.5:1. The median progression-free survival (PFS) and overall survival (OS) were 5.7 months and 12.9 months, respectively. SCLC molecular subtypes were as follows: SCLC-ASCL1 (39%) -NEUROD1 (24%) -POU2F3 (3%) -YAP1 (32%) and -Inflamed (TIS) (9%). The SCI model using 47 genes stratified pts into high- (N=29), intermediate- (N=48), and low- (N=16) risk groups with median PFSs of 4.8, 5.9, and 9.9 months and median OSs of 8.1, 14.3, and 24.4 months, respectively. In this cohort, the high-risk group showed significantly worse PFS (HR=4.68, $P < 0.001$) and OS (HR=5.03, $P < 0.001$) compared to the low-risk group. Similarly, in the IMpower133 cohort, the high-risk group demonstrated poorer outcomes with PFS (HR=2.33, $P = 0.001$) and OS (HR=3.47, $P < 0.001$) compared to the low-risk group. **Conclusions:** The SCI 47-gene panel based on IMpower133 transcriptome was validated through nCounter analysis system and effectively stratified ES-SCLC pts into distinct risk groups with strong predictive and prognostic capacities. It provides a practical biomarker for guiding immunotherapy in pts with ES-SCLC. Correlative analyses of nCounter with RNA-seq and AI-powered TIL will be presented.
Research Sponsor: None.

8101 Poster Session

Multi-omic analysis and overall survival update of phase II TRIDENT study: Durvalumab plus olaparib in extensive-stage small-cell lung cancer (ES-SCLC).

Yuanyuan Zhao, Yan Huang, Hong Liu, Bijing Xiao, Li Zhang; Department of Medical Oncology, State Key Laboratory of Oncology in South China, Guangdong Provincial Clinical Research Center for Cancer, Sun Yat-Sen University Cancer Center, Guangzhou, China; Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center of Cancer Medicine, Guangdong Key Laboratory of Nasopharyngeal Carcinoma Diagnosis and Therapy, Sun Yat-sen University, Guangzhou, China

Background: Chemotherapy plus anti-PD1/PD-L1 therapy has revolutionized the standard first-line treatment for patients with ES-SCLC. Durvalumab plus Olaparib as maintenance therapy showed encouraging anti-tumor activity in TRIDENT study as previous report. Here, we aim to identify molecular biomarkers of ES-SCLC through multi-omic analysis. **Methods:** 60 treatment-naïve ES-SCLC patients were enrolled in the TRIDENT study (NCT05245994), receiving Durvalumab plus Olaparib as maintenance therapy after Durvalumab plus chemotherapy as first line treatment. Frozen tumor tissues were collected before treatment to employ transcriptome sequencing and high-resolution quantitative DNA methylation. Next-Generation Sequencing (NGS) and Proximity Extension Assay (PEA) of cytokine were conducted using baseline plasma. **Results:** At the data cutoff on December 31, 2024, the median duration of follow-up was 13.0 months. The median PFS was 6.77 months (95% CI, 5.75-8.97), median overall survival was 14.59 months (95% CI 12.98–22.34). The 1-2-3 survival rate was 61.7%, 21.7% and 1.7%. For DNA methylation analysis, unsupervised clustering was performed based on Non-negative Matrix Factorization (NMF) and samples were classified into two clusters, with a clear difference in methylation levels. Patients in DNA hypomethylation group demonstrated better survival outcomes. Differentially methylated genes in pathway enrichment analysis revealed that immune-related and antigen processing and presentation signaling pathways were activated, while glycolysis and oxidative phosphorylation, DNA damage and repair signaling pathways were suppressed in the hypomethylation group. Moreover, transcriptome data further indicated a significant suppression in pathways related to epithelial-mesenchymal transition (EMT), extracellular matrix (ECM) remodeling, and cell adhesion in the hypomethylation group. As for cytokine analysis, high serum levels of IL6, IL8, Gal-9, CCL23, CSF-1 and HO-1 were significantly associated with poorer OS, while pro-inflammatory cytokines MCP-2 was correlated with better survival outcomes. **Conclusions:** Our findings indicated that DNA hypomethylation levels may be associated with better efficacy and survival outcomes in ES-SCLC treated with the combination of Olaparib and Durvalumab. Clinical trial information: NCT05245994. Research Sponsor: AstraZeneca.

Impact of immunotherapy on small cell lung cancer survival: A focus on treatment setting, race, and socioeconomics.

Pranali Santhoshini Pachika, Shreyas Kalantri, Zhanxu Liu, Tyler Jones, Borna Amir-Kabirian, Maiying Kong, Goetz Hans Kloecker; University of Louisville, Louisville, KY; Brown Cancer Center, Louisville, KY

Background: Immunotherapy has transformed the treatment landscape for many cancers, but its benefit in small cell lung cancer (SCLC) has remained modest. Trials like IMpower133 and CASPIAN demonstrated survival gains of only 2 to 2.7 months in patients with extensive-stage SCLC. However, the ADRIATIC trial highlighted significant survival benefits with durvalumab in limited-stage SCLC. Our study examines survival trends in SCLC across the pre-immunotherapy (PIE) and immunotherapy eras (IE) using National Cancer Database data, though it does not account for the recent advances in limited-stage SCLC due to the dataset being capped at 2021. **Methods:** Kaplan-Meier plots estimate survival probabilities, and log-rank tests compare survival between the IE (2016-2021) and PIE (2010-2015). Median overall survival (OS) and 5-year OS are reported with 95% CI, using a p-value threshold of <0.05. Cox regression analyzes the impact of demographic, clinical, and socioeconomic factors on survival, with hazard ratios (HR) indicating mortality risk. **Results:** This study analyzed 244,973 SCLC patients, divided into IE (n = 124,774) and PIE (n = 120,199). The majority were White (85%), with a median age of 68 years and a near-equal sex distribution (48% male, 52% female). Most patients were diagnosed at Stage IV (63%), and only 5% at Stage I. Survival rates were better in the IE ($p < 0.001$) except for stage IV disease. Patients treated at academic centers and Asian/Pacific Islander patients had better outcomes. Cox regression identified disease stage, immunotherapy use, facility type, insurance, and socioeconomic factors as key survival determinants. Immunotherapy improved survival, while lower income, lack of insurance, and non-academic centers worsened outcomes, highlighting the need for accessible care and financial support. **Conclusions:** Immunotherapy has modest improvement in survival outcomes for SCLC, but disparities in treatment access and outcomes persist across different populations. Ensuring equitable access to specialized care and financial support is essential to further improving survival rates. Research Sponsor: None.

Category	Group	N	Median Survival (months)	5yr OS (%)	P value
All stages	IE	124,774	8.74	11.2	<0.001
	PIE	120,199	8.48	8.3	
Stage I and II	IE	12,146	27.76	31	<0.001
	PIE	10,559	22.01	26	
Stage III	IE	28,347	15.18	19	<0.001
	PIE	29,288	13.67	15	
Stage IV	IE	79,005	6.24	5	<0.001
	PIE	74,714	6.24	3	
Facility	Academic	33,883	9.69	13.3	<0.001
	Non-Academic	90,655	8.38	10.3	
Race	Hispanic	3,169	9.30	14.2	<0.001
	Non-Hispanic - Asian/Pacific Islander	2,242	9.86	14.5	
	Non-Hispanic - Black	9,786	9.95	13.8	
	Non-Hispanic - White	106,464	8.57	10.7	
Income	< $46,277	22,397	8.31	10.5	<0.001
	$46,277 - $57,856	27,868	8.51	10.2	
	$57,857 - $74,062	25,949	8.87	10.9	
	$74,063+	28,283	9.20	12.8	
Insurance	Medicaid	11,677	9.49	13.2	<0.001
	Medicare	79,039	7.89	9.3	
	Not Insured	3,083	7.16	10.4	
	Other Government	2,730	9.56	11.5	
	Private	26,732	11.20	15.6	

Safety, tolerability, and preliminary efficacy results of a phase 1 study of LB2102, a dnTGFβRII armored DLL3-targeted autologous CAR-T cell therapy, in patients with relapsed or refractory small cell lung cancer (SCLC) and large cell neuroendocrine carcinoma (LCNEC).

Jacob Sands, Alberto Chiappori, Ben C. Creelan, Paul Otto Schwarzenberger, Mythili Koneru, Sahista Vahora, Christian Davis, Da Xu, Chuan Wang, Reinhold Munker, Zhonglin Hao, Adam Jacob Schoenfeld; Dana-Farber Cancer Institute, Boston, MA; Moffitt Cancer Center and Research Institute, Tampa, FL; Legend Biotech USA, Inc., Somerset, NJ; Markey Cancer Center, Lexington, KY; Memorial Sloan Kettering Cancer Center, New York, NY

Background: Delta-like- ligand 3 (DLL3) is a promising therapeutic target for SCLC and other neuroendocrine tumors. Here, we present preliminary results from the ongoing dose-escalation study of LB2102, an autologous CAR-T cell therapy engineered to target DLL3 and armored with a TGF-β receptor blockade to overcome the immunosuppressive tumor microenvironment. **Methods**: This ongoing, open-label, multicenter, phase 1 study evaluates LB2102 in patients with SCLC/LCNEC who are relapsed/refractory to ≥1 prior line of therapy. Dose escalation follows a modified 3+3 design, with planned dose levels of 0.3, 1.0, 2.0, 4.0, 8.0, 12.0, 16.0 x 10^6 CAR+ T cells/kg. All subjects undergo 3-day lymphodepletion (LD) with fludarabine (30 mg/m^2), and cyclophosphamide (300 mg/m^2). The primary objective is to assess safety, tolerability and determine the recommended phase 2 dose (RP2D). **Results**: As of December 13, 2024, 9 patients were treated with LB2102 across dose-level (DL) 1 at 0.3x10^6 (n=3), DL2 at 1x10^6 (n=3), and DL3 at 2x10^6 CAR+ T cells/kg (n=3). Eight subjects had SCLC and one subject on DL2 had LCNEC. The median age was 54 (range 20-61), and the median prior lines of therapy was 2 (range 1-7). Bridging therapy was administered in all patients. No Dose-limiting toxicities (DLT) and no neurotoxicity was observed. One subject in DL3 experienced grade 1 CRS. Grade >3 treatment-emergent adverse events (TEAEs) attributed to LB2102 included anemia (n=2), leukopenia (n=2) and neutropenia (n=2); none were classified as serious, and all were deemed related to lymphodepletion. At DL3, best observed response per RECIST1.1 was 1 partial response (with deepening of response over time) and 2 stable disease (SD). The best overall response for subjects at DL1 was progressive disease (n=3) and at DL2 was SD (n=3) (with increased tumor shrinkage in 1 subject). Significant CAR-T expansion in peripheral blood was observed as measured by qPCR at DL3 (n=3) with a median C_{max} of 694.4 copies/μg genomic DNA (range, 45.6-2256.7) and a median T_{max} of 15 days (range, 10-29). **Conclusions**: LB2102 has been well tolerated with no DLT observed up to DL3 (2 x 10^6 CAR+ T cells/kg). There appears to be a dose-dependent efficacy signal observed at higher doses with responses correlating to CAR-T expansion, although the data is limited. Given no DLTs and preliminary efficacy signal up to DL3, further exploration of higher dose levels is warranted. Clinical trial information: NCT05680922. Research Sponsor: Legend Biotech USA Inc.

Dose levels (CAR+ T cells/kg)	Subject No.	Best Overall Change in Sum of Tumor Size (%)
DL1: 0.3 x 10^6	1	+22.8%
	2	Non-evaluable*
	3	+57.1%
DL2: 1 x 10^6	4	-31.6%
	5	-22.6%
	6	-4.8%
DL3: 2 x 10^6	7	-14.3%
	8	-69.8%
	9	-20.6%

*Subject had non-measurable disease at baseline and progressed during study period.

Association of IFITM3 with the efficacy of anti-PD1/PD-L1 therapy and regulation of immunosensitivity via MHC-I regulation in SCLC.

Shengxiang Ren, Yanan Cui, Tianyu Qiu, Jiale Wang, Gaohua Feng, Chunyan Wu, Fengying Wu, Fei Li, Hua Zhang; Department of Oncology, Shanghai Pulmonary Hospital & Thoracic Cancer Institute, Tongji University School of Medicine, Shanghai, China; Department of Pulmonary and Critical Care Medicine, Zhangjiagang Hospital of Traditional Chinese Medicine, Suzhou, China; Department of Pathology, Shanghai Pulmonary Hospital, Tongji University School of Medicine, Shanghai, China; Department of Pathology, Frontier Innovation Center, School of Basic Medical Sciences, Fudan University, Shanghai, China; Department of Medicine, Division of Hematology/Oncology, University of Pittsburgh School of Medicine, Pittsburgh, PA

Background: Majority of small cell lung cancer (SCLC) patients exhibit resistance to immune checkpoint inhibitors (ICIs), which is associated with the downregulation of major histocompatibility complex class I (MHC-I) molecules. This study investigates the regulatory mechanisms underlying MHC-I expression and explores potential therapeutic strategies to enhance ICI efficacy. **Methods:** Single-cell and bulk RNA sequencing data from SCLC patient tumors were analyzed to identify key regulators of MHC-I expression. The IMpower133 cohort (116 patients treated with chemotherapy plus anti-PD-L1 therapy and 131 patients treated with chemotherapy alone) and an in-house cohort (39 patients treated with chemotherapy and anti-PD-1 therapy) were utilized to assess the association between IFITM3 expression and immunotherapy outcomes. Additionally, tumor samples from 42 extensive-stage SCLC patients receiving first-line chemotherapy plus anti-PD1/PD-L1 were evaluated via immunohistochemistry (IHC) to determine IFITM3 expression as a predictive biomarker. *In vitro* and *in vivo* functional studies were conducted to elucidate the role and mechanisms of IFITM3 in modulating tumor sensitivity to PD-1 inhibitors. **Results:** Integrative analysis of multiple real-world cohorts of SCLC confirmed a significant positive association between *IFITM3* and MHC-I expression. IFITM3 overexpression elevated MHC-I-related genes, activated antigen presentation pathways, and enhanced $CD8^+$ T cell activity. In the IMpower133 cohort, high IFITM3 expression was significantly associated with prolonged progression-free survival (PFS) in patients receiving chemoimmunotherapy (HR 0.65,95% CI 0.44-0.96, p=0.014) but not in those treated with chemotherapy alone (HR 1.97,95%CI 1.19-3.25, p=0.0069). Similarly, in the in-house cohort, high IFITM3 expression conferred a PFS advantage in patients receiving chemoimmunotherapy (HR 0.42,95% CI 0.19-0.90, p=0.023). Furthermore, patients with elevated IFITM3 protein levels, as determined by IHC H-scores, exhibited improved clinical outcomes following chemoimmunotherapy. Importantly, inducing IFITM3 expression directly or through treatment with Ethyl gallate (EG), an IFITM3 activator, effectively sensitized tumors to PD-1 blockade in SCLC mouse models. **Conclusions:** IFITM3 positively regulates MHC-I expression and predicts response to ICIs in SCLC. Combining EG with PD-1 inhibitors represents a promising strategy to improve immunotherapy efficacy in SCLC patients. Research Sponsor: None.

Implementation of tarlatamab treatment for small cell lung cancer using an outpatient care program.

Jennifer W. Carlisle, Katherine O'Reilly, Kübra Canaslan, Xiyuan (Angel) Ji, Jeffrey M. Switchenko, Conor Ernst Steuer, Fatemeh Ardeshir Larijani, Suresh S. Ramalingam, Ticiana Leal; Winship Cancer Institute, Emory University, Atlanta, GA; Emory University, Atlanta, GA; Dokuz Eylul University, Faculty of Medicine, Department of Medical Oncology, Izmir, Turkey; Department of Biostatistics and Bioinformatics, Emory University, Atlanta, GA; Emory University, Winship Cancer Institute, Atlanta, GA; Winship Cancer Institute, Emory School of Medicine, Atlanta, GA; Winship Cancer Institute at Emory University, Atlanta, GA

Background: Tarlatamab, a bispecific T-cell engager targeting DLL3, was FDA approved for relapsed small cell lung cancer (SCLC) in May 2024. It requires observation for 24 hours for the first two doses due to the risk of Cytokine Release Syndrome (CRS). We developed an outpatient program to administer tarlatamab at the Winship Cancer Institute and describe the initial experience in this report. **Methods:** Patients received tarlatamab in the outpatient infusion center then were observed in an outpatient oncology Immediate Care Center (ICC) onsite, staffed by advanced practice providers, to complete the 24-hour monitoring for CRS and immune effector cell-associated neurotoxicity (ICANS). Vital signs and ICE scores were monitored, and patients were hospitalized with > grade 2 CRS or grade 1 ICANS based on American Society for Transplantation and Cellular Therapy Consensus Grading. Patients were prescribed dexamethasone 8mg to be taken at physician direction for later-onset symptoms prior to return to a health care facility. Demographics, disease characteristics, treatment history, toxicities, and outcomes were abstracted from the electronic medical record. **Results:** From June 2024 to January 2025, 29 patients with SCLC were treated, 27 of whom completed cycle 2 at data cut-off and were evaluated for safety and efficacy. Baseline demographics and clinical characteristics are shown in Table 1. Four patients were admitted prophylactically based on limited home support, distance from home, or location of administration; 6 patients required admission from the ICC during the first two cycles due to CRS/ICANS (CRS: 1, ICANS:1, both: 4) and one patient was admitted 48 hours after C1D8 for grade 1 CRS and nausea. CRS was observed 14 patients (grade 1: 7, grade 2: 4, grade 3: 3) and ICANS was observed in 10 patients (grade 1: 3, grade 2: 4, grade 3: 3). Eight patients required dose holds, with two who reinitiated step up dosing. Investigator-assessed radiographic responses included 9 partial response, 7 stable disease, 6 progressive disease, and 5 not evaluable. With a median duration of follow-up of 133 days (95% CI 91,168), the estimated median progression free survival was 101 days (95% CI 78, NA). **Conclusions:** Outpatient administration of tarlatamab is safe and feasible with appropriate monitoring, including for patients with an ECOG performance status of 2. Research Sponsor: None.

Baseline demographics and clinical characteristics.

	n (%)
Age (median, range)	64, 35-80
Gender	Male: 11 (38%); Female:18 (62%)
Primary site and histology	SCLC: 25; Transformed EGFR mutant NSCLC: 3; Unknown primary site: 1
Race:	Black: 14 (48%); White: 14 (48%); Unreported: 1 (3%)
ECOG Performance status:	0: 4 (14%); 1: 20 (69%); 2: 5 (17%)
Prior Lines of Therapy:	1: 9 (31%); 2: 9 (31%); 3: 7 (24%); 4: 4 (14%)
Metastatic sites:	Liver: 12 (41%); Brain: 17 (58%); Bone: 7 (24%)
Duration of platinum sensitivity:	< 90 days: 6 (21%); 90-180 days: 12 (41%); > 180 days: 11 (38%)

8107 Poster Session

Cataloging genomic and transcriptomic features of relapsed SCLC.

Sid Devarakonda, Sumithra Sankararaman, My Hoang, Zach L. Skidmore, Brett H. Herzog, Kymberlie Pepin, Joshua McMichael, Jeffrey Ward, Daniel Morgensztern, Saiama Naheed Waqar, Malachi Griffith, Obi Griffith, Trudy G. Oliver, Ramaswamy Govindan; Swedish Cancer Institute, Seattle, WA; Washington University School of Medicine, St. Louis, MO; Washington University, St. Louis, MO; Washington University in St. Louis, St. Louis, MO; Washington University School of Medicine in St. Louis, St. Louis, MO; Washington University in St. Louis Department of Biomedical Engineering, Saint Louis, MO; Duke Cancer Institute, Durham, NC

Background: Relapsed small cell lung cancer (R-SCLC) is characterized by poor outcomes and treatment resistance. The mechanisms driving treatment resistance in R-SCLC remain poorly understood. We comprehensively profiled R-SCLC samples along with patient-matched treatment-naive samples (TN-SCLC) using whole-exome (WES), whole-genome (WGS), and RNA-sequencing (RNA-seq) to catalog mechanisms of treatment resistance and identify actionable alterations. **Methods:** We analyzed 54 R-SCLC and 27 TN-SCLC samples (with 26 patient-matched TN-R pairs) using WES. At presentation, 31 patients were diagnosed with extensive and 23 with limited stage SCLC. R-SCLC samples were also analyzed by WGS (n = 28, including 18 TN-R pairs) and RNA-seq (n = 31, including 12 TN-R pairs). Differences in mutational signatures, structural variations, gene expression, alternative splicing, and neo-antigen profiles were investigated between TN and R-SCLC samples. **Results:** R-SCLC samples contained mutation signatures characteristic of platinum exposure and APOBEC mutagenesis, which were absent in TN-SCLC. MYC family genes (MYC, MYCL, MYCN) were frequently amplified at relapse. Transcriptomic analyses revealed dysregulation of WNT signaling and IDO1. Extensive differences in alternative splicing, especially intron retention (IR), were observed (96% of all IR events were in TN-SCLC). IR in TN-SCLC affected genes involved in DNA repair, RNA metabolism, WNT and MYC pathways. TN-SCLC showed a median of 86 neoantigens, and R-SCLC 90 neoantigens per sample. *TP53* was the most frequently altered gene to result in a neo-antigen (48% of analyzed samples). Immune evasion mechanisms, including upregulation of CD24 and downregulation of MHC-I, were observed in R-SCLC samples. **Conclusions:** This study highlights the heterogeneity of treatment resistance in SCLC, driven by genomic instability, WNT and MYC dysregulation, and splicing aberrations. Potential therapeutic strategies for R-SCLC include targeting splicing machinery, WNT signaling, and immune evasion pathways. These findings advance our understanding of SCLC biology and provide a foundation for biomarker-driven drug development. Research Sponsor: None.

8109 Poster Session

A prospective, single-arm, phase II trial of adebrelimab plus nab-paclitaxel and carboplatin in patients with unresectable advanced metastatic or recurrent thymic carcinomas.

Ning Xu, Zhiqiang Gao, Changlu Wang, Feng Pan, Yan Shen, Lei Zhu, Jiajia Yuan, Changhong Zhao, Zhitao Gu, Teng Mao, Wentao Fang; School of Medicine, Shanghai Jiao Tong University, Shanghai Chest Hospital, Shanghai, China; Shanghai Chest Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China; Jiangsu Hengrui Pharmaceuticals Co., Ltd., Shanghai, China

Background: With the limited efficacy of chemotherapy (carboplatin/paclitaxel) for advanced thymic carcinomas (TCs), better treatments are in need. In this study (ChiCTR2300072705), we evaluated the efficacy and safety of adebrelimab in combination with nab-paclitaxel and carboplatin as first-line treatment for unresectable advanced metastatic or recurrent TCs. **Methods:** In this study, patients with unresectable UICC stage III or IV, recurrent, or metastatic TCs without any previous anti-tumor therapy were enrolled. Patients were treated with adebrelimab (20 mg/kg) plus nab-paclitaxel (260 mg/m^2) and carboplatin (AUC 5) every 3 weeks for up to 4-6 cycles, followed by adebrelimab (20 mg/kg) every 3 weeks for up to 2 years until progression or unacceptable toxicity. The primary endpoint was the objective response rate (ORR). Secondary endpoints included progression free survival (PFS), disease control rate (DCR), overall survival (OS), and safety. A Simon two-stage design was applied. If more than 4 out of the first 18 pts achieved a response, the cohort would expand to include 33 pts, and the outcome would be considered positive if more than 10 pts achieved a response. **Results:** Between August 2023 and September 2024, 18 pts were enrolled in the first stage. All pts were included in the efficacy and safety analysis. The median age was 58.0 years old (range 29-71). At data cutoff (Dec 1, 2024), 9 pts (50.0%) were undergoing treatment. Discontinuations occurred in 5 pts (27.8%) primarily due to disease progression, 2 (11.1%) due to adverse events (AEs), 2 (11.1%) due to patient's decision. Three (16.7%) of 18 pts had complete response, 9 (50.0%) had partial response, and 6 (33.3%) had stable disease. The ORR was 66.7% (12/18) and DCR was 100%. The median PFS was 10.2 months (95% CI, 8.8 - 11.6 months). AEs of any grade and of grade ≥3 severity occurred in 100% (18/18) and 61.1% (11/18) of pts, respectively. The most common treatment related AEs were white blood cell count decreased, neutrophil count decreased, and lymphocyte count decreased. The immune-related AEs of grade ≥3 severity occurred in 16.7% (3/18) of pts, including immune-mediated myositis, rash and lipase increased. None of the pts died from the treatment. **Conclusions:** In previously untreated advanced TCs, preliminary results showed that adebrelimab plus nab-paclitaxel and carboplatin is effective and safe. It provides a new treatment option in pts with advanced TCs. Clinical trial information: ChiCTR2300072705. Research Sponsor: None.

Combining SBRT with GM-CSF and peg-IFNα to induce abscopal effects in previously treated patients with stage IV thymic tumors: A single arm, single center, phase II trial.

Min Fan, Boyan Wang, Huiting Li, Junmiao Wen, Jiayan Chen; Fudan University Shanghai Cancer Center, Shanghai, China

Background: After the failure of first-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 single center, 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 27 patients were enrolled in the trial from March 2021 to September 2024. One patient died of cardiac arrest before ORR evaluation during COVID-19 pandemic and was excluded, leaving 26 patients in the analysis, with 1 (3.8%) type A thymoma, 1 (3.8%) type AB thymoma,4 (15.4%) type B1 thymoma, 3 (11.5%) type B2 thymoma, 1 (3.8%) type B3 thymoma, 1 (3.8%) type B2+B3 thymoma, 13 (50.0%) thymic squamous cell carcinoma and 2 (7.7%) thymic neuroendocrine tumor. At a median follow-up of 26.4 months, 8 (30.8%) out of 26 patients had abscopal effects, and the ORR was 38.5%. The median OS for patients with abscopal effect has not been attained yet. The median PFS was 13.0 months. We observed that patients with abscopal effects tended to have longer OS and PFS than those without abscopal effects. 5 patients (19.2%) experienced Grade 3 treatment-related adverse events (CTCAE version 5.0). **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.

Association of immune-related adverse events with survival and treatment outcomes in thymic tumors treated with immune checkpoint inhibitors.

Harold Nathan C. Tan, Khaoula Ben Haj Frej, Lei Kang, Hung Le, Elad Sharon, Stephane Champiat, Funda Meric-Bernstam, Frank V. Fossella, Aung Naing, Mehmet Altan, Ecaterina Elena Dumbrava; Department of Investigational Cancer Therapeutics, Division of Cancer Medicine, MD Anderson Cancer Center, Houston, TX; UConn School of Medicine, Avon, CT; Department of Investigational Cancer Therapeutics, The University of Texas MD Anderson Cancer Center, Houston, TX; Dana-Farber Cancer Institute/ Harvard Cancer Center, Boston, MA; Department of Thoracic Head and Neck Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Thymic tumors are rare cancers with limited therapeutic options, particularly in refractory cases. Immune checkpoint inhibitors (ICIs) such as anti-PD1 and anti-PD-L1 antibodies have transformed cancer treatment, but data in thymic tumors remain scarce. We investigated the safety, efficacy, and biomarkers of ICIs in thymic tumors, focusing on immune-related adverse events (irAEs) and clinical outcomes. **Methods:** This study included patients (pts) with thymic tumors treated with ICIs at the University of Texas MD Anderson Cancer Center. The primary objective was to assess the occurrence, type, and severity of irAEs. Secondary objectives included evaluating clinical response using RECIST 1.1 and analyzing overall survival (OS) and progression-free survival (PFS) through Kaplan-Meier analysis. Cox regression was used to identify predictors of OS. **Results:** Forty-two pts (median age 58.5 years, 55% male) were analyzed: 29 (69%) had thymic carcinoma, 8 (19%) thymoma, and 5 (12%) thymic malignancy with neuroendocrine features. Pts had a median of one prior line of therapy (range 1-6) and received ICIs as monotherapy (n=23, 55%) or in combination with chemotherapy (n=9, 21%), other immunotherapies (n=6, 14%), targeted therapies (n=2, 5%), or other agents (n=2, 5%). irAEs occurred in 60% of pts (100% of pts with thymoma), with 9 pts (21%) experiencing severe irAEs (≥G3). Median time to develop ≥G3 irAEs was 42 days. Common all-grade irAEs included fatigue (19%), musculoskeletal toxicities (17%), and rash (17%), while the most frequent ≥G3 irAEs were musculoskeletal, myasthenia gravis (MG)-like, myocarditis, and hepatobiliary toxicities. Among the three pts with thymoma who developed MG-like symptoms, only one pt had a pre-existing diagnosis of MG. Two thymoma patients developed concurrent myocarditis and MG. One treatment-related death occurred due to pneumonitis in a patient with thymoma. Clinical benefit was observed in 69% of pts, including 9 partial responses (PR) (21%) and 10 with stable disease. Most pts (84%) with any-grade irAEs had SD or PR as best response with ICI. Median PFS was 195 days, with a 1-year PFS rate of 45%, while median OS was 274 days, with a 1-year OS rate of 44%. Pts with any-grade irAEs had improved OS (HR 0.3, 95% CI 0.11 -0.98, p = 0.04). Other OS predictors included *TP53* mutations (HR 7.8, 95% CI 2.2 – 27.8, p = 0.002), *CDKN2A* alterations (HR 0.2, 95% CI 0.04-0.54, p = 0.004), African-American race (HR 10.9, 95% CI 3.7-32.3, $p < 0.001$), and lung metastases (HR 6.9, 95% CI 2.4 -19.8, $p < 0.001$). **Conclusions:** ICIs demonstrate promising efficacy in thymic malignancies, with higher toxicity rates in thymoma pts. The incidence of irAEs may serve as a prognostic marker for survival and treatment outcomes. Factors such as *TP53, CDKN2A* alterations, and lung metastases could guide patient selection for future ICI trials in thymic tumors.
Research Sponsor: None.

8112 Poster Session

Pathomics-based prediction of thymic epithelial tumor subtypes within the French RYTHMIC network.

Lodovica Zullo, Mathilde Bateson, Jose Carlos Benitez-Montanez, Audrey Mansuet-Lupo, Damien Sizaret, Juan Florez-Arango, Alvaro Lopez-Gutierrez, Daniela Miliziano, Pascale Missy, Vincent Thomas De Montpreville, Olaf Mercier, Jordi Remon Masip, David Planchard, Nicolas Girard, Thierry Molina, Benjamin Besse; Department of Cancer Medicine, Gustave Roussy, Villejuif, France; Owkin France, Paris, France; Medical Oncology Department, Virgen de la Victoria University Hospital, Malaga, Spain; Department of Pathology, Cochin Hospital, AP-HP centre, Université Paris Cité, Paris, France; Department of Pathology, CHRU Tours - Hôpital Trousseau, Chambray-Lès-Tours, France; Clinica Las Américas – AUNA, Medellin, Colombia; The French Cooperative Thoracic Intergroup, Paris, France; Marie Lannelongue Hospital, Le Plessis-Robinson, France; Department of Thoracic Surgery and Heart-Lung Transplantation, Hôpital Marie-Lannelongue, Le Plessis-Robinson, France; Department of Medical Oncology, Institut Curie, Paris, France; Department of Pathology, Hôpital Necker-Enfants Malades, Paris, France; Gustave Roussy, Villejuif, France

Background: Thymic epithelial tumors (TETs) are classified into primary subtypes (A, AB, B1, B2, B3, C) and mixed classes, determined by varying proportions of tumoral and non-tumoral components, and different subtypes have different prognosis. This heterogeneity, combined with their rarity, poses significant diagnostic challenges that impact tumor treatment. We aim to develop and test a multiple-instance learning (MIL) model capable of classifying TETs major histological subtypes from hematoxylin-eosin/hematoxylin-eosin-saffron (HE/HES)-stained slides. **Methods:** Cases who underwent central revision by a panel of expert pathologist between 2012 and 2016 in the context of the French national RYTHMIC network were retrospectively collected, and their HE/HES slides were digitized in whole slide images (WSIs), forming the training cohort. A MIL model was trained exclusively on digitized WSIs, without clinical features, and internally validated using 3-repeated 2-fold cross-validation for the classification of major TET subtypes: A, AB, B1, B2, B3, C. Prospectively digitized WSIs from the RYTHMIC network (2022–2024) served as the testing cohort. Class predictions were assessed using AUC scores and ROC curves. Interpretability was explored through Shapley values and heatmaps. **Results:** A total of 456 WSIs from unique histological samples formed the training cohort, with 243 (53%) samples obtained via thymectomy. The most represented subtype was AB (n=129, 28%), followed by B2 (n=110, 24%). Internal validation achieved a mean AUC of 0.94 [sd 0.005] for histological subtypes classification. High-attention regions identified on the slides featured varying proportions of epithelial cells and lymphocytes, consistent with the biological characteristics of each subtype. The test set comprised 75 WSIs from unique histological samples, with 63 (84%) obtained via thymectomy. The most represented subtype was AB (n=35, 47%), followed by B2 (n=19, 25%). In the test set, the model achieved a mean AUC of 0.89 [95%CI 0.83–0.93] for histological subtypes classification. **Conclusions:** Our model shows promise for diagnosing TET major subtypes, emphasizing the value of digital pathology in identifying and classifying rare entities. We are currently reviewing discrepancies between MIL and pathologists' diagnoses in subtype classification within the test set to evaluate the potential of artificial intelligence in aiding the diagnosis of complex cases. The final results will be presented at the congress. Research Sponsor: None.

TPS8113 **Poster Session**

Comparing impact of treatment before or after surgery in patients with stage II-IIIb resectable non-small cell lung cancer (NSCLC; Alliance A082304-SWOG S2402).

Raid Aljumaily, Sumithra J. Mandrekar, Yingqi Zhao, Linda W Martin, David E. Kozono, Shauna Hillman, Anne C. Chiang, Raymond U. Osarogiagbon, Tom Stinchcombe, Jhanelle E. Gray, Daniel Morgensztern; Stephenson Cancer Center at The University of Oklahoma Health Sciences Center, Oklahoma City, OK; Alliance Statistics and Data Management Center, Mayo Clinic, Rochester, MN; SWOG Statistics and Data Management Center, Fred Hutchinson Cancer Center, Seattle, WA; University of Virginia, Charlottesville, VA; Brigham and Women's Hospital/Dana-Farber Cancer Institute, Boston, MA; Mayo Clinic, Rochester, MN; Yale School of Medicine, New Haven, CT; Baptist Cancer Center, Multidisciplinary Thoracic Oncology Program, Memphis, TN; Duke Cancer Institute, Durham, NC; H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL; Washington University School of Medicine in St. Louis, St. Louis, MO

Background: There are currently three approved approaches for patients with resectable NSCLC including neoadjuvant chemoimmunotherapy, adjuvant chemoimmunotherapy and perioperative treatment with neoadjuvant chemoimmunotherapy followed by adjuvant immunotherapy. All regimens were approved after showing event-free survival (EFS) or disease-free survival (DFS) benefit with the addition of immunotherapy to chemotherapy compared to chemotherapy alone. Each approach has its benefits and risks. Starting immunotherapy prior to surgery may improve treatment compliance and efficacy of immunotherapy. Nevertheless, neoadjuvant chemoimmunotherapy may result in missing an opportunity for curative surgery and increase the complexity of tumor resection. PROSPECT-LUNG (NCT06632327) is a randomized study evaluating whether starting chemoimmunotherapy before or after surgery leads to better outcomes. **Methods:** This is a randomized phase 3 trial in which patients will be randomized 1:1 to surgery followed by chemoimmunotherapy (adjuvant arm) or neoadjuvant chemoimmunotherapy followed by surgery and adjuvant therapy (perioperative arm). Patients with histologic or cytologic confirmation of surgically resectable stage IIA-IIIB NSCLC (per AJCC 9th edition) or stage IIA to IIIB per AJCC 8th edition up to single ipsilateral mediastinal station (N2a), ECOG PS $\leq$ 2 (or Karnofsky $\geq$ 60%), no prior treatment for NSCLC and no previous malignancy within 3 years are eligible. The dual primary endpoints are real-world event free survival (rwEFS) defined as date from randomization to date of the first of the following events: failure to undergo resection for any reason, progression prior to surgery that precludes resection, recurrence or progression at any time after surgery or death from any cause, and overall survival (OS) defined as time from randomization to death from any cause. The target accrual is 1,100 patients assuming one-sided type I error of 0.03 for OS endpoint and 0.02 for rwEFS endpoint. This sample size will enable the detection of a 3-year rwEFS improvement from 55% in the adjuvant therapy arm to 64% in the perioperative arm with an 84% power. This sample size would detect an HR of 0.73 (improvement in median OS from 8.1 to 11 years in favor of the perioperative arm, 5-year OS from 65% in the adjuvant arm to 73% in the perioperative arm, assuming exponential survival) with 83.6% power. The study has a pragmatic design with minimal data collection, reporting of adverse events that lead to discontinuation of therapy, hospitalization or death only. It allows providers to choose therapy per standard of care (FDA approved or on NCCN), includes patients with ECOG performance status 2, permits use of local laboratory testing and imaging studies and determination of recurrence/progression will be done by local treating physicians with no use of RECIST. Clinical trial information: NCT06632327. Research Sponsor: National Cancer Institute; U10CA180821.

TPS8114 **Poster Session**

GEMINI-NSCLC study: Integrated longitudinal multi-omic biomarker profiling study of non-small cell lung cancer (NSCLC) patients.

Douglas C. Palmer, Virginia Ann Rhodes, Fred R. Hirsch, Asrar Alahmadi, Amy Lauren Cummings, Christine M. Lovly, Raymond U. Osarogiagbon, Christopher Gilbert, Vincenzo Graziano, Jorge M Blando, Ezra E.W. Cohen, Melissa Nicole Maggart; AstraZeneca, Gaithersburg, MD; Tempus, AI, Inc., Chicago, IL; Mount Sinai Medical Center, New York, NY; The Ohio State University Wexner Medical Center, Columbus, OH; University of California Los Angeles Translational Oncology Research, Santa Monica, CA; Vanderbilt University Medical Center, Nashville, TN; Baptist Cancer Center, Multidisciplinary Thoracic Oncology Program, Memphis, TN; The Medical University of South Carolina, Charleston, SC; AstraZeneca, Inc., Gaithersburg, MD; AstraZeneca, Waltham, MA; Tempus AI, Inc., Chicago, IL

Background: Lung cancer is the global leading cause of cancer deaths. Despite treatment advances, NSCLC outcomes remain poor. The molecular landscape of NSCLC has identified various subtypes allowing targeted therapies, but some tumors lack a biomarker-directed therapy. Identifying improved surrogates of immunotherapy (IO) response is key to stopping ineffective treatments and empowering patients to switch therapies more rapidly. Combining next-generation sequencing (NGS) and circulating tumor DNA (ctDNA) technologies with high-resolution multi-omic data may revolutionize NSCLC management by enabling non-invasive monitoring, personalized treatment strategies, and the development of next-generation therapies to improve patient outcomes. **Methods:** The Gemini-NSCLC study is a multicenter, real-world observational study profiling patients with NSCLC undergoing IO standard-of-care (SOC) therapy. Cohort 1 (C1) includes patients with early-stage disease treated with curative intent therapies. Cohort 2 (C2) includes patients with late-stage disease receiving first-line IO, excluding those with targetable genomic drivers. Patients will have blood and tissue collected at study entry and longitudinally. They will undergo testing with DNA and RNA sequencing and novel assays, including baseline spatial transcriptomic profiling, serial tumor-informed ctDNA profiling, and scRNA sequencing with T-Cell receptor seq of peripheral immune cells. All patients will be assessed with cohort-relevant real-world endpoints, allowing correlation with longitudinal multi-omic data for biomarker discovery. Information from novel multi-omic assays will be descriptive and hypothesis-generating. For C1, the primary endpoint is real-world disease-free survival (rwDFS). Secondary endpoints include pathologic complete response (pCR) rate and real-world overall survival (rwOS) stratified by ctDNA status. Molecular endpoints include sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of minimal residual disease (MRD) assay vs. conventional imaging. Patients are followed until recurrence or five years post-therapy. Patients in whom disease recurs may roll over to C2 for continued data collection. For C2, the primary endpoint is rwOS, with rwPFS as a secondary endpoint. Molecular endpoints include ctDNA dynamics with IO and correlation with rwOS. Exploratory endpoints include evolving genomic variants as resistance mechanisms. As of 01/2025, the study is enrolling and active at 49 of 60 planned sites, with accruals of 48/500 in C1, 20/700 in C2. Clinical trial information: NCT05236114. Research Sponsor: Tempus, AI, Inc.; AstraZeneca.

TPS8115 **Poster Session**

KEYMAKER-U01E: A phase 2 umbrella study with rolling arms of investigational agents with or without chemotherapy plus pembrolizumab for resectable stage II–IIIB (N2) non–small-cell lung cancer (NSCLC).

Konstantin H. Dragnev, Mustafa Erman, Emilio Bria, Jay M. Lee, Cole Manschot, Jeffrey Thompson, Ayman Samkari, Jonathan Spicer; Dartmouth Cancer Center, Lebanon, NH; Department of Medical Oncology, Hacettepe University Cancer Institute, Ankara, Turkey; Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Università Cattolica del Sacro Cuore, Rome, Italy; Division of Thoracic Surgery, David Geffen School of Medicine at UCLA, Los Angeles, CA; Merck & Co., Inc., Rahway, NJ; Division of Thoracic Surgery, Department of Surgery, McGill University Health Centre, Montreal, QC, Canada

Background: Neoadjuvantpembrolizumab (pembro) + chemotherapy (CT) followed by adjuvant pembro significantly improved event-free survival (EFS), pathological complete response (pCR), major pathological response, and overall survival (OS) in early-stage NSCLC. Despite the expanding number of therapeutic options for early-stage NSCLC, there remains an unmet need to improve outcomes. Sacituzumab tirumotecan (sac-TMT/MK-2870/SKB264) is an antibody-drug conjugate composed of an anti-trophoblast cell surface antigen 2 antibody, a hydrolytically cleavable linker, and a belotecan-derivative topoisomerase I inhibitor payload (average drug-to-antibody ratio, 7.4). Sac-TMT monotherapy demonstrated encouraging antitumor activity in a phase 1/2 study in heavily pretreated, advanced NSCLC. The phase 2 KEYMAKER-U01E study (NCT06788912) is evaluating the addition of multiple investigational agents ± CT to pembro followed by surgery and adjuvant pembro in resectable stage II–IIIB (N2) NSCLC; the treatment arm presented here includes sac-TMT + pembro. **Methods:** This open-label, adaptive design study is enrolling participants (pts) aged ≥18 years with previously untreated, pathologically confirmed, resectable stage II, IIIA, or IIIB (N2) NSCLC (AJCC v8) with no *EGFR* mutations, and measurable disease per RECIST v1.1. Pts must be able to undergo surgery, have ECOG PS 0 or 1, and provide a tumor sample for biomarker analysis. Approximately 60 pts will be randomized 1:1 to Arm 1 or 2. In Arm 1 (reference arm), pts will receive neoadjuvant therapy of 4 cycles of pembro 200 mg intravenously (IV) + CT IV Q3W (cisplatin 75 mg/m^2 or carboplatin area under the curve 5 or 6 mg/mL/min on day 1 with gemcitabine 1000 mg/m^2 on days 1 and 8 for squamous histology, with pemetrexed 500 mg/m^2 on day 1 for nonsquamous, or with paclitaxel 175 or 200 mg/m^2 on day 1 for any histology). Pts in Arm 2 will receive 4 cycles of pembro 200 mg IV Q3W + 6 cycles of sac-TMT 4 mg/kg IV Q2W (treatment arm). Following surgery, all pts will receive up to 13 cycles of adjuvant pembro 200 mg IV Q3W. Additional agents may be included when available. Randomization will be stratified by histology (squamous vs nonsquamous) and tumor stage (II vs III). Dual primary endpoints are pCR (ypT0/ypN0) and percentage of residual viable tumor, assessed by blinded independent pathology review. Secondary endpoints are EFS and distant metastasis-free survival per investigator review, OS, objective response rate during neoadjuvant therapy, and safety. Postoperative tumor imaging occurs ≤4 weeks before the start of adjuvant therapy, with pts followed per study protocol until disease recurrence, development of new primary NSCLC, pregnancy, death, pt withdrawal, or end of study. AEs will be graded per NCI CTCAE v5.0. Enrollment is scheduled to begin in March 2025 at 34 sites globally. Clinical trial information: NCT06788912. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

TPS8116 **Poster Session**

A randomized study of neoadjuvant REGN7075 + cemiplimab + chemotherapy (chemo) vs cemiplimab + chemo in patients (pts) with resectable non-small cell lung cancer (NSCLC).

Ardy Davarifar, Craig Gordon, Ira Oliff, Ting Huang, Wenjun Zheng, Bei Wang, Dimitris Skokos, Frank A. Seebach, Israel Lowy, Melissa Divya Mathias, Michael David Kinnaman, Eric Kim, Elizabeth Miller, Matthew Ingham; University of Tennessee Medical Center, Knoxville, TN; Corewell Health Farmington Hills Hospital, Farmington Hills, MI; Orchard Healthcare Research Inc., Skokie, IL; Regeneron Pharmaceuticals, Inc., Tarrytown, NY

Background: Neoadjuvant chemo + anti–PD-1 checkpoint blockade, with/without adjuvant anti–PD-1, represents a new standard of care for pts with resectable NSCLC. However, most pts do not achieve major pathologic response (MPR) or pathologic complete response (pCR), and event-free survival (EFS) remains suboptimal; therefore, novel perioperative approaches are needed. REGN7075, a first-in-class costimulatory bispecific antibody, aims to bridge CD28+ T cells with EGFR-expressing tumor cells, facilitating T-cell activation through endogenous tumor antigens. Early efficacy and pharmacodynamic evidence suggest that REGN7075 can enhance immune responses and antitumor immunity even in "cold" tumors. In a first-in-human, open-label, Phase 1/2 study (NCT04626635), REGN7075 + cemiplimab (anti–PD-1) demonstrated clinical activity in PD-1–refractory, microsatellite stable colorectal cancer (Segal NH, et al. 2024). The addition of REGN7075 to cemiplimab + chemo may deepen antitumor responses in resectable NSCLC where EGFR is highly expressed, potentially representing a novel immunotherapy-based treatment (Tx) approach in this setting. In this perioperative platform study, multiple novel Tx approaches for resectable NSCLC will be evaluated in comparison to a control arm (cemiplimab + chemo). **Methods:** In this Phase 2, open-label, perioperative platform trial (NCT06465329), pts with resectable NSCLC will be randomized to an investigational arm (a novel antitumor agent + cemiplimab + chemo) or control arm (cemiplimab + chemo), stratified by tumor stage and PD-L1 expression. Here, we focus on the first investigational arm with REGN7075. The study will consist of neoadjuvant, surgical, and adjuvant periods. During the neoadjuvant period, pts assigned to the control arm will receive cemiplimab + chemo for up to 3 cycles before surgery. Pts in the investigational arm will receive REGN7075 with cemiplimab + chemo. Pts from both arms who proceed to surgery and undergo R0/R1 resection will then receive adjuvant cemiplimab. Eligibility criteria: histologically confirmed stage II–IIIB (N2) NSCLC considered resectable with curative intent (appropriate candidate for surgery), Tx naïve, no known *EGFR/ALK* alterations, ECOG PS ≤1. Primary endpoint: MPR. Secondary endpoints: safety, feasibility of surgery, pCR, and EFS. Pre-Tx and surgical tissue will be used for translational analysis and biomarker development. Up to 40 pts will be enrolled in each investigational arm, and the control arm will be open to enrollment throughout the study. A Bayesian statistical design will be used to evaluate the posterior probability of at least 15% improvement in MPR for investigational arms vs the control arm. This study is currently enrolling. Clinical trial information: NCT06465329. Research Sponsor: Regeneron Pharmaceuticals, Inc.

TPS8117 **Poster Session**

Phase 2 peri-operative study of fianlimab + cemiplimab + chemotherapy versus cemiplimab + chemotherapy in resectable early-stage non-small cell lung cancer (NSCLC).

Ekaterine Arkania, Tamta Makharadze, Gopal Kunta, Tamar Melkadze, Ana Baramidze, Alexander I. Spira, Luis G. Paz-Ares, Nicolas Girard, Ji Sun Park, Maria Ghattas, Yuntong Li, Siyu Li, Mark Salvati, Israel Lowy, Matthew G. Fury, Luca Paoluzzi; LTD Israeli-Georgian Medical Research Clinic "Helsicore", Tbilisi, Georgia; LTD High Technology Hospital Medical Center, Batumi, Georgia; Clermont Oncology Center, Clermont, FL; Todua Clinic, Tbilisi, Georgia; NEXT Oncology Virginia, Fairfax, VA; Complutense University of Madrid, Madrid, Spain; Curie-Montsouris Thorax Institute, Paris, France; Regeneron Pharmaceuticals, Inc., Tarrytown, NY

Background: Co-blockade of lymphocyte activation gene 3 (LAG-3) and programmed cell death-1 (PD-1) may enhance the efficacy of anti–PD-1 therapies. Fianlimab (anti–LAG-3) and cemiplimab (anti–PD-1) are high-affinity, fully human, immunoglobulin G4 monoclonal antibodies. In a Phase 1 study (NCT03005782), fianlimab + cemiplimab showed promising clinical activity with durable responses and an acceptable risk–benefit profile in patients with programmed death-ligand 1 (PD-L1)-naïve, advanced NSCLC. Immuno-oncology + chemotherapy is a new standard of care in the perioperative setting, but potential improvements to outcomes in early-stage disease remain under investigation. **Methods:** This is a randomized, multicenter, double-blind, Phase 2 peri-operative study (NCT06161441) in patients with fully resectable stage II–IIIB (N2), operable, and treatment-naïve NSCLC with squamous or non-squamous histology. The aim of this study is to investigate the efficacy and safety of fianlimab + cemiplimab + chemotherapy versus cemiplimab + chemotherapy as peri-operative treatment. The study will be conducted globally at ~130 sites. Key inclusion criteria: age ≥18 years; newly diagnosed, histologically confirmed, fully resectable stage II–IIIB (N2) NSCLC; no distant metastases; evaluable PD-L1 immunohistochemistry results; no cancer treatment in the past 3 years, except adjuvant hormone therapy for hormone-sensitive cancers in long-term remission; Eastern Cooperative Oncology Group performance status ≤1; no known *EGFR* mutations or *ALK* aberrations; and adequate organ and bone marrow function. Mediastinal lymph node sampling is required for patients with mediastinal adenopathy. Enrolled patients (n=~180) will be stratified by clinical TNM stage (II vs III), histology (nonsquamous vs squamous), and PD-L1 expression (<1%, 1–49%, ≥50%), and randomized (1:1:1) to the following study arms for the neoadjuvant period (≤4 cycles; each cycle is every 3 weeks): arm A, placebo + cemiplimab 350 mg + platinum doublet chemotherapy; arm B, fianlimab dose 1 + cemiplimab 350 mg + platinum doublet chemotherapy; arm C, fianlimab dose 2 + cemiplimab 350 mg + platinum doublet chemotherapy. After surgery, in the adjuvant period (≤14 cycles), patients in all arms will continue the same IO regimen with approved maintenance chemotherapy. Treatment will last ~12 months (12 weeks' neoadjuvant therapy + 42 weeks' adjuvant therapy), or until disease recurrence, unacceptable toxicity, or a decision from the patient or investigator. Primary endpoint: pathological complete response as determined by blinded independent pathological review (BIPR). Key secondary endpoints: event-free survival and tumor response by investigator assessment, major pathological response by BIPR, safety, pharmacokinetics, immunogenicity, and patient-reported outcomes. Clinical trial information: NCT06161441. Research Sponsor: Regeneron Pharmaceuticals, Inc.

TPS8118 **Poster Session**

Safety, efficacy, and tumor immune microenvironment changes with neoadjuvant chemotherapy and cemiplimab with or without alirocumab in stage 1B-3A non-small cell lung cancer.

Eziafa Oduah, Scott Joseph Antonia, Jeffrey J. Clarke, Tom Stinchcombe, Joel Rivera Concepcion, Laura Alder, Cameron Oswalt, Thomas A. D'Amico, David H. Harpole, Betty Caroline Tong, Hai Salfity, Kunal Patel, Kaitlin Bevers, Matthew Galen Hartwig, Xiaofei F. Wang, Neal E. Ready; Duke University, Durham, NC; Duke Cancer Institute, Durham, NC; Duke University Medical Center, Durham, NC; Department of Surgery, Duke University Medical Center, Durham, NC; Duke University Trent Center for Bioethics Humanities and History of Medicine, Durham, NC

Background: The addition of immune checkpoint blockade to neoadjuvant and adjuvant therapy is now standard of care in early-stage surgically resectable non-small cell lung cancer (NSCLC). However, resistance to immunotherapy limit their benefit for most patients. The pathological complete response (pCR) rate, a surrogate for long term survival, remains close to 20%, leaving many patients at a high risk of recurrence and death. Thus, there is a need to apply strategies to overcome immunotherapy resistance in earlier stages of NSCLC to improve cure. Proprotein convertase subtilisin/kexin type 9 (PCSK9), a major cholesterol regulator, has emerged as an inhibitory modulator of anti-tumor immunity. Preclinical evidence showed that PCSK9 downregulated MHC class I antigen expression on tumor cells. This effect was reversed by genetic or pharmacologic inhibition of PCSK9. PCSK9 inhibitor synergized with immune checkpoint blockade to increase cytotoxic T-cell mediated tumor death. Retrospective clinical analyses of NSCLC patients treated with immune checkpoint inhibitors also showed a correlation between higher PCSK9 levels and poorer survival. **Methods:** TOP 2301 is a multi-center, open label, two-arm, randomized, phase 2 trial of chemotherapy and cemiplimab (350mg IV every 3 weeks) with or without the PCSK-9 inhibitor, alirocumab (150 mg SC every 4 weeks), prior to surgery. Eligible patients will have stage IB-3A NSCLC, deemed surgical candidates, and have no EGFR or ALK mutations. One hundred and twenty-six patients will be randomized 1:1 to receive neoadjuvant SOC chemotherapy and cemiplimab versus SOC chemotherapy, cemiplimab and alirocumab. Approximately 64 participants are required in each arm to have 90% power to reject the null hypothesis. The primary objective is to compare the pCR rates for neoadjuvant chemotherapy plus cemiplimab versus chemotherapy, cemiplimab, and alirocumab. Secondary efficacy objectives for the experimental arm include: the objective response rate (ORR), disease free survival (DFS), and overall survival (OS). A secondary safety objective is to determine the safety and tolerability of neoadjuvant chemotherapy and cemiplimab with alirocumab in early-stage NSCLC. The correlative science objective will evaluate the difference in tumor infiltrating lymphocytes and dendritic cells through IHC, FACs analysis, and bulk RNA-seq with CIBERSORT from postsurgical specimens of patients treated with neoadjuvant chemotherapy and cemiplimab with or without alirocumab. The trial was open to enrollment on 12/15/2024. Clinical trial information: NCT06385262. Research Sponsor: None.

TPS8119 **Poster Session**

Neoadjuvant lazertinib with or without chemotherapy for patients with epidermal growth factor receptor (*EGFR*)-mutated resectable non-small cell lung cancer (NSCLC): NeoLazer trial.

Hye Ryun Kim, Se-Hoon Lee, Se Hyun Kim, Min Hee Hong, Chang Gon Kim, Byung Jo Park, Ha Eun Kim, Young Ho Yang, Tae Hee Hong, Myung-Ju Ahn, Jin Seok Ahn, Sehhoon Park, Seong Yong Park, Jong Ho Cho, Junghee Lee, Yeong Jeong Jeon, Yu Jung Kim, Sukki Cho, Hong Kwan Kim, Chang Young Lee; Division of Medical Oncology, Department of Internal Medicine, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, South Korea; Division of Hematology-Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea; Division of Hematology-Oncology, Department of Internal Medicine, Seoul National University Bundang Hospital, Seongnam, South Korea; Department of Thoracic and Cardiovascular Surgery, Severance Hospital, Yonsei University College of Medicine, Seoul, South Korea; Department of Thoracic and Cardiovascular Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea; Department of Internal Medicine, Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seongnam, South Korea; Department of Thoracic and Cardiovascular Surgery, Seoul National University Bundang Hospital, Seongnam, South Korea

Background: While perioperative systemic treatment with checkpoint inhibitors plus chemotherapy has become a standard approach for resectable NSCLC, the benefit of systemic treatment in *EGFR*-mutated NSCLC remains unclear. In resectable *EGFR*-mutated NSCLC, adjuvant osimertinib has been shown to significantly improve disease-free survival and overall survival. However, neoadjuvant osimertinib alone has demonstrated limited efficacy, with a major pathologic response rate of less than 15% (NCT03433469). These data altogether highlight an unmet clinical need for optimizing perioperative systemic approach in resectable *EGFR*-mutated NSCLC. Lazertinib, a third-generation, central nervous system-penetrating EGFR tyrosine kinase inhibitor, has demonstrated superior efficacy compared to comparator EGFR tyrosine kinase inhibitor in treatment-naïve *EGFR*-mutated advanced NSCLC (NCT04248829). The NeoLazer trial (NCT06268210) is a phase II, randomized, controlled study designed to evaluate the efficacy and safety of neoadjuvant lazertinib with or without chemotherapy in patients with *EGFR*-mutated resectable NSCLC. **Methods:** Eligible patients must be ≥19 years of age, have an ECOG performance status of 0 or 1, non-squamous histology, stage IB–IIIB NSCLC based on the AJCC 8th edition, have confirmed sensitizing *EGFR* mutations (exon 19 deletion or L858R mutation), be deemed completely resectable by a multidisciplinary team, and demonstrate adequate organ and bone marrow function. The trial will enroll approximately 160 patients, who will be randomized 1:1 to receive either lazertinib (240 mg once daily) with chemotherapy (pemetrexed 500 mg/m^2 and carboplatin AUC5 every 3 weeks) or lazertinib alone (240 mg once daily) for three cycles before surgical resection. Randomization will be stratified by disease stage (IB–II vs. III) and *EGFR* mutation type (exon 19 deletion vs. L858R mutation). Following surgery, all patients will receive adjuvant lazertinib for three years. Neoadjuvant and adjuvant treatments will continue until unacceptable toxicity, disease progression or relapse, or patient withdrawal. The primary endpoint is major pathologic response, defined as ≤10% residual viable cancer cells in the surgical specimen. Secondary endpoints include safety based on CTCAE 5.0, type of surgical resection (segmentectomy vs. lobectomy), pathologic complete response, objective response rate based on RECIST 1.1, event-free survival, disease-free survival, and overall survival. In addition, the trial incorporates exploratory analyses, including whole-genome sequencing of tumor tissue and monitoring the dynamics of minimal residual disease through serial blood sampling. Clinical trial information: NCT06268210. Research Sponsor: None.

TPS8120 **Poster Session**

Neotrace: A multicenter phase II study of neoadjuvant sacituzumab govitecan plus zimberelimab followed by adjuvant zimberelimab with or without sacituzumab govitecan in patients with resectable non-small cell lung cancer.

Friederike C. Althoff, Fabian Acker, Sebastian Koschade, Sophie Heinzen, Lukas Aguinarte, Maximilian Rost, Hanna Schulte, Gernot Rohde, Melanie Demes, Waldemar Schreiner, Katrin Krause, Viktor Grünwald, Hubert Serve, Thomas Oellerich, Martin Sebastian; Goethe University Frankfurt, Frankfurt Am Main, Hessen, Germany; Goethe-Universität Hospital Frankfurt, Frankfurt, Germany; Goethe University Frankfurt, Frankfurt, Germany; Department of Medicine II, Hematology, Oncology, University Hospital Frankfurt, Frankfurt, Germany; AIO-Studien-gGmbH, Berlin, Germany; Essen University Hospital, Essen, Germany; Goethe University Frankfurt, Frankfurt Am Main, Germany

Background: Phase III trials, including KEYNOTE-671, have established combined neoadjuvant chemoimmunotherapy followed by adjuvant immunotherapy (IO) as the standard of care for resectable NSCLC. However, a notable challenge in KEYNOTE-671 and similar studies was that ~17-22% of patients did not proceed to surgery following neoadjuvant chemoimmunotherapy, highlighting the need for more tolerable regimens. Recent data from studies such as NEOpredict (which demonstrated a 100% surgical completion rate with neoadjuvant nivolumab with/without relatlimab), NeoCOAST-2 (which reported a 34% pathological complete response [pCR] rate using a neoadjuvant combination of an anti-TROP2 antibody drug conjugate [ADC], IO, and single-agent platinum, thereby surpassing the ~20% pCR rates achieved with neoadjuvant chemoimmunotherapy), and EVOKE-02 (which showed promising objective response rates of 69% and 44% with the anti-TROP2 ADC sacituzumab govitecan plus pembrolizumab in first-line metastatic NSCLC patients with PD-L1 ≥50% and PD-L1 0-49%, respectively) demonstrate that chemotherapy-sparing approaches may reduce toxicity while maintaining or enhancing efficacy. These findings highlight the potential synergistic effect of ADC plus IO, suggesting this strategy may also be an effective treatment option in the perioperative setting with potentially lower toxicity compared to chemoimmunotherapy. Additionally, long-term adverse events associated with platinum-based chemotherapy, such as neuropathy, may be lower or avoided altogether. This study aims to improve the pCR rate, reduce toxicity, enhance surgical eligibility, and personalize adjuvant treatment. **Methods:** NeoTRACE is a phase II, multicenter, open-label, single-arm study evaluating the neoadjuvant combination of sacituzumab govitecan (SG) and the PD-1 inhibitor zimberelimab (ZIM) in patients with resectable stage II to IIIB (N2) NSCLC with no known EGFR or ALK alterations. Patients will receive neoadjuvant SG 10 mg/kg IV on days 1 and 8, and ZIM 360 mg IV on day 1, every 3 weeks for 4 cycles, followed by definitive surgery as per local standards. In the adjuvant phase, patients will either continue adjuvant SG plus ZIM for up to 4 cycles, followed by ZIM only for a total of up to 13 cycles, or receive adjuvant ZIM monotherapy (as per physicians' choice). The primary endpoint is the rate of pCR in tumor and lymph nodes. Secondary endpoints include major pathological response, surgical resection rate, time to surgery, DFS, OS, safety, and quality of life. The study also explores circulating tumor DNA dynamics, TROP2 expression, and spatial transcriptomics and proteomics to identify potential biomarkers. As of June 2025, the NeoTRACE study is recruiting 50 patients across 15 sites in Germany. EudraCT: 2024-517561-16. Clinical trial information: 2024-517561-16 (EudraCT). Research Sponsor: None.

TPS8121 **Poster Session**

Efficacy of low-dose nivolumab combined with chemotherapy as neoadjuvant treatment for lung cancer.

Aline Fusco Fares, Joao Antonio Soler, Isaac Rodrigues, Eduardo Constantino, Thais Fares, Bruno Cezar de Mendonça Uchôa Jr., Maira Abreu, Henrique Nietmann, Luciana Vargas, Adriana Joaquim, Celso Murilo Nálio Matias de Faria, Daniel Vilarim Araujo; University of Florida, Gainesville, FL; Hospital de Base de Sao Jose do Rio Preto, Sao Paulo, Brazil; Hospital de Base de Sao Jose do Rio Preto, Sao Jose Do Rio Preto, Brazil; FAMERP, Sao Jose Do Rio Preto, Brazil

Background: Immune checkpoint inhibitors have revolutionized cancer treatment, providing durable responses in a substantial subset of patients. However, their high costs remain a significant barrier to access, especially in low- and middle-income countries (LMICs). Evidence from pharmacodynamic studies suggests that lower doses (LD) of anti-PD-(L)1 agents can achieve comparable receptor saturation and therapeutic efficacy without compromising outcomes. Mounting data supports the concept of treating patients with LD anti-PD(L)1 agents. For instance, the use of LD nivolumab (0.3 mg/kg) has demonstrated equivalent PD-L1 receptor occupancy and similar survival outcomes to standard doses, offering a more cost-effective alternative. Notably, at 0.3 mg/kg, up to 10 patients can be treated for the cost of treating a single patient with standard doses. While most supporting evidence pertains to advanced disease settings, data on the use of LD in curative-intent applications, such as neoadjuvant therapy for resectable non-small cell lung cancer (NSCLC), remain limited. This study investigates the efficacy and safety of LD nivolumab combined with platinum-based chemotherapy as a neoadjuvant treatment for resectable NSCLC, addressing the urgent need for affordable treatment options in LMICs. **Methods:** This is an ongoing investigator-initiated, single-arm, phase II trial conducted at Hospital de Base, São José do Rio Preto, Brazil. Eligible participants are adults with histologically confirmed stage IB-IIIA NSCLC, with known PD-L1 expression, and no actionable genomic alterations in EGFR, ALK, or ROS1. All patients will receive three cycles of nivolumab (0.3 mg/kg IV every three weeks) combined with carboplatin (AUC 5-6) and either pemetrexed or paclitaxel, selected based on tumor histology and physician preference. Surgery will be scheduled 9-12 weeks after initiating therapy. The co-primary endpoints are major pathologic response rate (MPR), defined as ≤10% viable tumor cells in the resected surgical specimen, and complete pathologic response. Secondary endpoints include disease-free survival, overall survival, and treatment-related adverse events (AEs) graded per CTCAE v5.0. Exploratory analyses will evaluate outcomes based on disease stage, PD-L1 levels, and smoking history. The trial employs a Simon two-stage design with an initial cohort of 17 patients to assess futility. If at least one MPR is observed, enrollment will expand to a total of 33 patients. This design aims to detect an improvement in MPR from 12% (null hypothesis) to 24% (alternative hypothesis), with a significance level of 0.1 and 80% power. All specimens will undergo pathological review, and blood samples will be collected for exploratory biomarker analyses, including circulating tumor DNA. Study enrollment began in January 2024, and as of December 2024, 5 patients have been screened, with 3 enrolled. Clinical trial information: NCT06667154. Research Sponsor: Hospital de Base de Sao Jose do Rio Preto.

TPS8122 **Poster Session**

Phase II study of pembrolizumab in combination with cisplatin or carboplatin and pemetrexed as induction chemoimmunotherapy in resectable epithelioid and biphasic pleural mesothelioma (CHIMERA study).

Giulia Pasello, Daniela Scattolin, Fabiana Letizia Cecere, Luana Calabrò, Federica Grosso, Giovanni Luca Ceresoli, Marcello Tiseo, Alessandra Bearz, Paolo Andrea Zucali, Francesco Callegarin, Giuseppe Marulli, Gian Luca De Salvo, Antonio Rosato, Loredana Urso, Stefano Indraccolo, Eleonora Faccioli, Laura Bonanno, Fiorella Calabrese, Federico Rea, Valentina Guarneri; Oncology Unit 2, Istituto Oncologico Veneto (IOV-IRCCS), Padova, Italy; Istituto Oncologico Veneto IRCCS, Padova, Italy; Istituti Fisioterapici Ospitalieri (IFO) Regina Elena IRCCS, Roma, Italy; University of Ferrara, Ferrara, Italy; Mesothelioma Unit, SS Antonio e Biagio e Cesare Arrigo, Alessandria, AL, Italy; Department of Medical Oncology, Humanitas Gavazzeni Clinic, Bergamo, Italy; Medical Oncology Unit, University Hospital of Parma, Parma, Italy; Department of Medical Oncology, CRO-IRCCS National Cancer Institute Aviano, Aviano, Italy; Department of Biomedical Science, Humanitas University, Pieve Emanuele, Milan, Italy; Thoracic Surgery Unit Humanitas Cancer Center Thoracic Surgery Unit, Rozzano Milan, Italy; Clinical Research Unit, Veneto Institute of Oncology IOV-IRCCS, Padua, Italy; Department of Surgery, Oncology and Gastroenterology - University of Padova, Padova, Italy; Basic and Translational Oncology Unit, Istituto Oncologico Veneto (IOV)-IRCCS, Padua, Italy; Thoracic Surgery Unit Azienda Ospedaliera-Universitaria Padova, Padova, Italy; Istituto Oncologico Veneto IOV, IRCCS, Padova, Italy; Department of CardioThoracic and Vascular Sciences and Public Health, University of Padova, Padova, Italy; Thoracic Surgery Unit, Department of Cardiac, Thoracic and Vascular Sciences and Public Health, University of Padua, Padua, Italy; Department of Surgery, Oncology and Gastroenterology, University of Padua, Veneto Institute of Oncology-IOV-IRCCS, Padua, Italy

Background: Pleural mesothelioma (PM) is a rare cancer related to asbestos exposure, marked by complex histopathological diagnosis and dismal prognosis. Patients' survival is strongly influenced by the histological subtype and by the eligibility to a multimodal approach, which is reserved to very selected patients. Platinum-pemetrexed chemo-regimen or the immunotherapy combination ipilimumab+nivolumab are the available first-line treatment options for unresectable PM patients. In this setting, pembrolizumab in combination with platinum-pemetrexed showed an improved overall and progression free survival (IND227/Keynote483 trial). In patients with resectable PM, the multimodality approach with platinum-pemetrexed chemotherapy and surgery is usually preferred, achieving pathological complete response (pCR) in 5% of cases. To date, the role of perioperative immunotherapy for PM has not yet been extensively investigated. **Methods:** This is a phase II single arm trial enrolling patients with resectable PM from 8 high volume Italian centers, with 18 months of enrollment and 12 months of follow-up. Inclusion criteria will be the histologically confirmed diagnosis of surgical resectable stage I-IIIA treatment-naïve epithelioid/biphasic PM. Patients will receive 3 cycles of pembrolizumab 200 mg plus cisplatin (75 mg/sm) or carboplatin (AUC 5) and pemetrexed (500 mg/sm) every 3 weeks. The surgical procedure of pleurectomy/decortication will be centralized in 2 centers and will be performed within 6 weeks after the last neoadjuvant cycle. The adjuvant treatment will start within 10 weeks from surgery and will be based on 14 cycles of pembrolizumab 200 mg every 3 weeks. The primary endpoint will be the pCR; secondary endpoints will include: major pathological response, objective response rate, event free survival, OS, surgery feasibility, safety. Translational analysis on tissue and blood samples will also be performed. In order to investigate an improvement of pCR from 5% to 18%, 36 patients and a minimum number of 4 pCR are needed to verify this hypothesis with a least 80% power and a probability of type I error of 0.05. Considering a 10% patients dropped-out because of disease progression precluding surgery, a total number of 40 patients will be included in the study. The trial is currently ongoing since November 2024; 5 patients have been enrolled so far. This is the first clinical trial assessing the activity and safety of pembrolizumab in combination with platinum-pemetrexed for resectable PM patients. Clinical trial information: NCT06155279. Research Sponsor: MSD.

TPS8123 **Poster Session**

Trial in progress: Sacituzumab govitecan for the treatment of patients with diffuse pleural mesothelioma.

Michael Offin, Esther Redin, Prashasti Agrawal, Parvathy Manoj, Sarah Ryan, Khadeja A. Moses, Robert Michael Daly, Charles B. Simone II, Jennifer L. Sauter, Mara Monetti, Elizabeth McMahon, Erica Stumpf, Clare Wilhelm, Michelle S. Ginsberg, Valerie W. Rusch MD, Alvaro Quintanal-Villalonga, Andrea Arfe, Marjorie Glass Zauderer, Prasad S. Adusumilli, Charles M Rudin; Memorial Sloan Kettering Cancer Center, New York, NY; New York Proton Center and Memorial Sloan Kettering Cancer Center, New York City, NY; Memorial Sloan Kettering, New York City, NY; Westchester Medical Center, Hawthorne, NY

Background: Diffuse pleural mesothelioma (DPM) is an aggressive malignancy with poor outcomes and only three FDA-approved treatments (all first-line). Even when first-line treatment is effective, most patients experience progression within a year, and there are no approved, nor accepted, second-line approaches. Analysis of our novel library of DPM patient derived xenografts (PDXs) nominated TROP-2 as a candidate target for therapy. The role of TROP-2 expression in proliferation, colony formation, migration, and invasion was determined along with the antitumor efficacy of a TROP-2 targeting antibody-drug conjugate (ADC). Exogenous TROP-2 expression increased tumorigenicity *in vitro* and *in vivo* across multiple DPM models and induced upregulation of pro-oncogenic pathways. Treatment of PDXs with the TROP-2 ADC sacituzumab govitecan-hziy (SG) inhibited tumor growth with higher efficacy than gemcitabine (a standard of care later-line treatment) or the cytotoxic payload alone (irinotecan; results previously presented at WCLC 2024). These data identified TROP-2 as a promising therapeutic target in DPM leading to the development of an investigator-initiated trial with Department of Defense support (HT9425-24-1-0754). **Methods:** A single arm phase 2 unblinded Simon two-stage single-institution study recently commenced at Memorial Sloan Kettering Cancer Center (MSK) assessing the primary endpoint of overall response rate to SG by modified (m)RECIST v1.1 in patients with recurrent and/or unresectable/metastatic pathologically confirmed DPM (NCT06477419). Secondary endpoints include overall survival, progression-free survival, and safety. Key eligibility criteria include receipt of at least one prior line of standard systemic therapy and agreement to undergo study biopsies at screening, prior to cycle 3, and end of treatment (optional) if safe and feasible. SG will be administered intravenously at the FDA-approved dose/schedule established in breast cancer (10 mg/kg on days 1 and 8 of a 21-day cycle). Patients will undergo imaging after the first 2 cycles and subsequently every 3 cycles until progression. In the first stage, 19 patients will be treated. If at least 4 responses are observed, then an additional 14 patients will be accrued. To date, 4 patients have been enrolled. Tumor material will undergo 1) routine histologic subtyping, TROP-2 immunohistochemistry, and next-generation sequencing (MSK-IMPACT), 2) flow cytometry, 3) proteomic analyses/mass-spectrometry, and 4) RNA sequencing/methylation analysis. These studies will characterize how SG alters tumoral expression of TROP-2 and signaling pathways supporting cancer growth and survival. Clinical trial information: NCT06477419. Research Sponsor: U.S. Department of Defense; HT9425-24-1-0754; Gilead Science.

TPS8124 **Poster Session**

TIGOS-LS, an open-label, randomized study of BMS-986489 vs durvalumab as consolidation therapy following chemoradiotherapy in limited-stage small-cell lung cancer.

Melissa Lynne Johnson, Ticiana Leal, Jerome H. Goldschmidt, Sarah Yue Wang, William E Brady, Maen A. Hussein, Caressa Lietman, Hillarie Windish, Christophe Y. Calvet, Lola Dosunmu, Alisha Maniar, LaRee Tracy, Neal E. Ready; Sarah Cannon Research Institute, Nashville, TN; Winship Cancer Institute at Emory University, Atlanta, GA; Blue Ridge Cancer Care/Sarah Cannon Research Institute, Blacksburg, VA; Texas Oncology-Northeast Texas/Sarah Cannon Research Institute, Tyler, TX; Florida Cancer Specialists/Sarah Cannon Research Institute, Leesburg, FL; Bristol Myers Squibb, Princeton, NJ; Duke Cancer Institute, Durham, NC

Background: Standard treatment for limited-stage small-cell lung cancer (LS-SCLC) has recently changed to add durvalumab consolidation after concurrent chemoradiotherapy. Although durvalumab consolidation increases overall survival (OS; Cheng et al. 2024), other therapeutic agents may be able to provide further improvement. BMS-986489 is a potential first-in-class fixed-dose combination of atigotatug (BMS-986012) and nivolumab. Atigotatug binds to fucosyl-monosialoganglioside-1 (fuc-GM1), which is highly expressed on SCLC cells and is largely absent in normal tissues. This binding results in tumor cell death by antibody-dependent cellular cytotoxicity, antibody-dependent cellular phagocytosis, or complement-dependent cytotoxicity. The immune effects initiated by atigotatug may further enhance T cell activation by nivolumab, thereby improving outcomes after chemoradiotherapy. In a randomized phase II study in extensive-stage SCLC, atigotatug improved median OS when added to carboplatin, etoposide, and nivolumab (CE/NIVO): 15.6 months (95% confidence interval [CI]: 11.3-NE) vs 11.4 months (95% CI: 9.3-16.5) with CE/NIVO alone (Kalinka et al. 2024). **Methods:** TIGOS-LS is an open-label, randomized study to evaluate the safety and efficacy of BMS-986489 as consolidation therapy vs the new standard durvalumab following chemoradiotherapy in LS-SCLC. Approximately 250 participants will be enrolled at 80 sites within the US. Eligible participants will be adults (≥18 years) with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 and histologically or cytologically confirmed LS-SCLC. All participants must have completed concurrent chemoradiotherapy for LS-SCLC without progression; prophylactic cranial irradiation (PCI) will be permitted before initiation of study treatment. Confirmation of fuc-GM1 expression will not be required. Participants will be stratified based on disease stage (I/II vs III) and receipt of PCI and will be randomly allocated in a 1:1 ratio to either the BMS-986489 or durvalumab arms. BMS-986489 or durvalumab will be administered intravenously at a fixed dose once every 4 weeks for up to 2 years or until other discontinuation criteria are met. Response will be evaluated by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. Survival follow-up will occur every 12 weeks for up to 3 years. The primary endpoint is OS. Key secondary endpoints include progression-free survival, objective response rate, clinical benefit rate, disease control rate, duration of response, and safety parameters. Enrollment is projected to start in April 2025. Clinical trial information: NCT06773910. Research Sponsor: Bristol Myers Squibb.

TPS8125 **Poster Session**

Radiotherapy integration strategy for small-cell lung cancer in extensive stage (RISE) with up to 10 metastases: A study protocol of a randomized phase II trial.

Łukasz Kuncman, Jacek Fijuth, Damian Tworek, Ewa Sierko, Paweł Cisek, Michał Masłowski, Maja Lisik-Habib, Magdalena Orzechowska, Katarzyna Galwas-Kliber, Adam Antczak, Izabela Chmielewska, Barbara Ziółkowska, Marta Kurczewska-Michalak, Wojciech Kuźnicki, Nina Jędrzejczak, Kinga Ranoszek, Mateusz Bilski; Department of External Beam Radiotherapy, Copernicus Memorial Hospital in Lodz Comprehensive Cancer Center and Traumatology, Lodz, Poland; Department of Radiotherapy, Medical University of Lodz, Poland., Łódź, Poland; Department of General and Oncological Pulmonology, Medical University of Lodz, Łódź, Poland; Department of Oncology, Medical University of Bialystok, Białystok, Poland; Department of Radiotherapy, Medical University of Lublin, Lublin, Poland; Department of External Beam Radiotherapy, Copernicus Memorial Hospital in Lodz Comprehensive Cancer Center and Traumatology, Łódź, Poland; Department of Proliferative Diseases, Copernicus Memorial Hospital in Lodz Comprehensive Cancer Center and Traumatology, Lodz, Poland; Department of Molecular Carcinogenesis, Medical University of Łódź, Łódź, Poland; II Clinic of Radiotherapy & Chemotherapy, Maria Sklodowska-Curie National Research Institute of Oncology, Gliwice Branch, Gliwice, Poland; Department of General and Oncological Pulmonology, Łódź, Poland; Department of Pneumonology, Oncology and Allergology, Medical University of Lublin, Lublin, Poland; II Clinic of Radiotherapy and Chemotherapy, Maria Sklodowska-Curie National Research Institute of Oncology, Gliwice, Poland; Department of Clinical Oncology, Copernicus Memorial Hospital in Lodz Comprehensive Cancer Center and Traumatology, Łódź, Poland

Background: The standard of care (SoC) for patients with extensive-disease small-cell lung cancer (ED-SCLC) currently involves chemo-immunotherapy. Radiotherapy (RT) has proven effective as a chest consolidation therapy in ED-SCLC patients who respond to chemotherapy. However, there is limited evidence regarding the role of RT in both chest consolidation and metastasis-directed therapy for ED-SCLC patients undergoing chemo-immunotherapy. The RISE (Radiotherapy for Extensive-Stage Small-Cell Lung Cancer) study aims to evaluate the efficacy of various RT strategies targeting residual lesions in this patient population. **Methods:** A total of 165 patients with ED-SCLC will be recruited, with 55 patients assigned to each of the three study arms. Patients with stabilization or partial regression, according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, during chemo-immunotherapy will be included. Arm I will serve as the control group, comprising patients who continue SoC of programmed death-ligand 1 (PD-L1)/programmed death-1 (PD-1) immunotherapy (durvalumab or atezolizumab) following platinum-based chemo-immunotherapy. Arm II will receive the SoC with consolidative RT to the chest area and potentially, according to palliative indications to metastatic lesions, delivered in 30 Gy in 3-Gy fractions. Arm III will receive SoC with RT of 45 Gy in 3-Gy fractions to the chest area and stereotactic body radiotherapy (SBRT) with 24 Gy in 8-Gy fractions to the metastatic lesions. Blood samples for circulating tumor DNA (ctDNA) will be collected before RT, during each week of treatment, and at the time of disease progression. The primary endpoint is progression-free survival (PFS) based on RECIST 1.1 or patient death. 1. Secondary endpoints are OS, treatment toxicity (frequency of G3 toxicity according to CTCAE v.5.0), area of progression (primary tumor localization/new lesions), Overall response rate (ORR), and the response rate in non-irradiated lesions. The study population of patients with ED-SCLC has a poor prognosis. Dose-escalated chest RT and SBRT (for up to 10 metastases) administered with modern techniques offer the possibility to improve OS and PFS. Trial registration: Clinicaltrials.gov NCT06529081 (Registered 26th Jul 2024). Clinical trial information: NCT06529081. Research Sponsor: Medical Research Agency; 2023/ABM/01/00040.

TPS8126 **Poster Session**

A phase 1/2 clinical trial of quaratusugene ozeplasmid gene therapy and atezolizumab maintenance therapy in patients with extensive stage small cell lung cancer (ES-SCLC).

Bo Wang, Kartik Konduri, Robert M. Jotte, Donald A. Richards, Rachel E. Sanborn, Alexander I. Spira, David Michael Waterhouse, Katherin Combs, Jacqueline Opiola, Mark S. Berger, Daniel Morgensztern; Willamette Valley Cancer Institute and Research Center, Eugene, OR; Texas Oncology PA, Dallas, TX; Rocky Mountain Cancer Centers, Lone Tree, CO; Texas Oncology, Tyler, TX; Earle A. Chiles Research Institute, Providence Cancer Institute, Portland, OR; NEXT Oncology Virginia, Fairfax, VA; Oncology Hematology Care, Cincinnati, OH; Genprex, Inc., Austin, TX; Washington University School of Medicine, St. Louis, MO

Background: The addition of atezolizumab (atezo) to both induction therapy and maintenance therapy for patients with ES-SCLC has improved median progression free survival (PFS) and overall survival (New Eng J Med. 2018;379:2220-9). However, the median PFS from starting atezo maintenance was only 2.6 months (J Thoracic Onc. 2022;17:1122-9). Expression of TUSC2, a tumor suppressor gene, is absent in 41% of SCLC patients and is decreased in 100% of SCLC patients (Clin Cancer Res 2008;14(1):41–47). Quaratusugene ozeplasmid (QuarOze) gene therapy consists of a DNA plasmid expressing the *TUSC2* gene encapsulated in a positively charged lipoplex which delivers the *TUSC2* gene to cancer cells, restoring TUSC2 expression. Xenograft studies using a SCLC cell line in a humanized mouse model treated with a combination of QuarOze and atezo demonstrated significantly increased tumor cell killing compared to that of atezo alone. In addition, infiltration of immune cells was increased in the tumor tissue, whereas myeloid derived suppressor cells were decreased (Meraz IM et al, AACR/NCI/EORTC 2023). Thus, in this study QuarOze is added to atezo maintenance therapy with the aim of improving PFS after the start of maintenance therapy. **Methods:** Eligible patients have ES-SCLC and have completed 3-4 cycles of induction therapy with etoposide, a platinum agent, and atezo without disease progression, and are thus eligible for maintenance therapy. QuarOze is administered IV every 21 days in escalating dose cohorts in Phase 1 and atezo 1200 mg is also administered IV every 21 days. Dexamethasone, acetaminophen, and diphenhydramine are given prior to each treatment to prevent delayed infusion-related reactions. Efficacy is evaluated after every even cycle of treatment using RECIST 1.1 criteria. Safety is evaluated using CTCAE v5, with dose limiting toxicities generally defined as ≥Gr 3 adverse events (AEs). TUSC2 protein expression is measured by a validated immunohistochemistry assay in paraffin sections to determine if PFS is related to pretreatment TUSC2 levels. A validated assay measures pharmacokinetics in all patients. In Phase 1, two planned dose levels (0.09, and 0.12 mg/kg) of QuarOze were administered, and a standard dose escalation with 3-6 patients/dose level was used. The Phase 2 portion of the trial will enroll 50 patients which provides 80% power at a one-sided alpha level of 0.05 to detect an 18-week PFS rate of 52% compared to a historical 18-week PFS rate of 34% with atezo alone. This corresponds to a median PFS of approximately 4.3 months compared to a historical median PFS of 2.6 months with atezo alone. A Safety Review Committee (SRC) reviewed safety data at the end of each dose level of Phase 1 to make recommendations about dose escalation. The Phase 2 portion of the trial opened for enrollment in December, 2024. Clinical trial information: NCT05703971. Research Sponsor: Genprex, Inc.

TPS8127 **Poster Session**

The TIGOS trial: A randomized, double-blind phase 3 trial of atigotatug + nivolumab fixed-dose combination with chemotherapy vs atezolizumab with chemotherapy in patients with 1L extensive-stage small cell lung cancer (ES-SCLC).

Luis G. Paz-Ares, Kenneth John O'Byrne, Melissa Lynne Johnson, Martin Reck, Nicolas Girard, Hidetoshi Hayashi, Caicun Zhou, Vishwanath Suresh Gharpure, Radhika Pisupati, Misena Pacius, Neal E. Ready; Hospital Universitario 12 de Octubre, Universidad Complutense de Madrid, Madrid, Spain; Gallipoli Medical Research, Greenslopes Private Hospital, Brisbane, QLD, Australia; Tennessee Oncology, Nashville, TN; Lungen Clinic Grosshansdorf GmbH, Grosshansdorf, Germany; Institut du Thorax Curie-Montsouris, Institut Curie, Paris, France; Department of Medical Oncology, Kindai University, Faculty of Medicine, Osaka, Japan; Shanghai Pulmonary Hospital, Tongji University School of Medicine, Shanghai, China; Bristol Myers Squibb, Princeton, NJ; Duke Cancer Institute, Durham, NC

Background: Atigotatug is an innate immune inducer monoclonal antibody that binds fucosyl-monosialoganglioside-1 (fuc-GM1) with high affinity and specificity, thereby inducing immune-mediated tumor cell death. Fuc-GM1, a cell surface target, is expressed in 50%–90% of SCLC tumors. In a randomized, open-label phase 2 study, atigotatug combined with nivolumab and chemotherapy vs nivolumab and chemotherapy alone has shown a promising trend in overall survival (OS) with median OS of 15.6 mo vs 11.4 mo, respectively (HR 0.71; 95% CI 0.44–1.16), as a first-line treatment in ES-SCLC. Based on these results, a confirmatory trial comparing this regimen to the standard of care is warranted. TIGOS (NCT06646276) is a randomized, double-blind, multicenter phase 3 trial to compare the efficacy and safety of atigotatug + nivolumab fixed-dose combination with chemotherapy vs atezolizumab with chemotherapy. **Methods:** Approximately 530 eligible patients will be randomized 1:1 to receive either atigotatug + nivolumab fixed-dose combination with carboplatin and etoposide Q3W (induction) followed by atigotatug + nivolumab fixed dose combination (maintenance) Q4W or atezolizumab with carboplatin and etoposide Q3W (induction) followed by atezolizumab (maintenance) Q4W. Patients will be stratified by ECOG performance status (PS) 0–1, presence of liver metastases, and presence of brain metastases at baseline. Treatment will continue until disease progression, unacceptable toxicity, death, or withdrawal of consent. Eligible patients must be ≥18 years old, have histologically or cytologically documented SCLC, ≥1 measurable lesion outside the central nervous system (CNS), any previous limited-stage SCLC treatment completed ≥6 months prior to study treatment initiation, and an ECOG PS of 0–1. Key exclusion criteria include prior treatment for ES-SCLC, untreated symptomatic CNS metastases, and prior treatment targeting T-cell co-stimulation, checkpoint pathways, and/or fuc-GM1. The primary endpoint is OS, and the secondary endpoints are time to definitive deterioration, safety, objective response, duration of response, and progression-free survival, as assessed by the investigator. Assessment of pre- and on-treatment changes in biomarkers will be part of an exploratory analysis. This study will be conducted in 180 locations, with a primary completion date expected in April 2028. Clinical trial information: NCT06646276. Research Sponsor: Bristol Myers Squibb.

TPS8128 **Poster Session**

An open-label, multicenter, phase 1/2 study of peluntamig (PT217), an anti-DLL3/anti-CD47 bispecific antibody, in patients with DLL3-expressing cancers such as SCLC, LCNEC and EP-NEC (SKYBRIDGE study).

Jacob Sands, Jason Timothy Henry, Alexander I. Spira, Daruka Mahadevan, Catherine Belle Meador, Jared Weiss, Abdul Rafeh Naqash, Jennifer A. Chan, Himisha Beltran, Grace H McGregor, Rita Laeufle, Hui Zou; Dana-Farber Cancer Institute and Harvard Medical School, Boston, MA; Sarah Cannon Research Institute at HealthONE, Denver, CO; Next Oncology Virginia and Virginia Cancer Specialists Research Institute, Fairfax, VA; UT Health San Antonio, San Antonio, TX; Massachusetts General Hospital Cancer Center, Boston, MA; The University of North Carolina at Chapel Hill, Chapel Hill, NC; Stephenson Cancer Center, Oklahoma City, OK; Dana-Farber Cancer Institute, Boston, MA; Phanes Therapeutics, San Diego, CA; Phanes Therapeutics, Inc, San Diego

Background: Neuroendocrine carcinomas (NECs) are aggressive cancers with limited median survival. Over 90% of the NEC cases originate from the lung, including small cell lung cancer (SCLC) and large cell neuroendocrine carcinoma (LCNEC) of the lung. The rest of the cases are extra-pulmonary NECs (EP-NECs), including gastroenteropancreatic neuroendocrine carcinoma (GEP-NEC) and neuroendocrine prostate cancer (NEPC). Despite the initial impressive responses to platinum-based chemotherapy with or without an immune checkpoint inhibitor (ICI), at progression, resistance and clinical deterioration are common. High mortality rates and limited treatment options with durability highlight a significant unmet medical need. NECs are known to be heterogeneous. One unifying feature is the consistent surface expression of DLL3, making targeting DLL3 an attractive treatment approach. Peluntamig (PT217) is an IgG1 based anti-DLL3/anti-CD47 bispecific antibody that activates both innate and adaptive immunity to target cells that express DLL3 and/or overexpress CD47. **Methods:** The study consists of 4 parts: Monotherapy Dose Escalation (Part A), Dose Expansion (Part B), Chemotherapy Combination Therapy (Part C), and ICI Combination Therapy (Part D). Each part includes multiple cohorts. The study is designed to evaluate the safety, tolerability, pharmacokinetic (PK), pharmacodynamic (PD), and preliminary efficacy of peluntamig. Parts A, C and D are ongoing. Cohort C1 will enroll patients with first-line (1L) LCNEC of the lung and EP-NEC and patients with second-line (2L) SCLC who have (defined as progression $\geq$ 90 days after last dose of platinum therapy). Patients will receive peluntamig and SOC CE. Cohort C2 will enroll SCLC, LCNEC of the lung and EP-NEC patients eligible for 2L paclitaxel therapy. Patients will receive peluntamig and SOC paclitaxel. Cohort D1 will enroll 2L LCNEC of the lung, EP-NEC and ES-SCLC patients who have progressed/relapsed from their 1L treatment that may have included an ICI. Patients will receive peluntamig + atezolizumab. Cohort D2 will enroll 1L patients with ES-SCLC who have completed their induction therapy with CE plus atezolizumab and are eligible to continue with atezolizumab treatment. Patients will receive peluntamig + atezolizumab as maintenance therapy. Cohort D3 will enroll 1L patients with ES-SCLC who are treatment-naïve. Patients will receive peluntamig + CE + atezolizumab. Dose escalation, guided by a 3+3 design, will be conducted independently for each cohort. Patients will be backfilled to DLT-cleared dose levels to further evaluate safety, tolerability, PK and efficacy. Potentially active cohorts will be further investigated in dose randomization studies in Part B. Clinical trial information: NCT05652686. Research Sponsor: None.

TPS8129 **Poster Session**

A global phase III, double-blind, randomized trial of BNT327/PM8002 plus chemotherapy (chemo) compared to atezolizumab plus chemo in patients (pts) with first-line (1L) extensive-stage small cell lung cancer (ES-SCLC).

Martin Reck, John Heymach, Kevin Franks, Carl Michael Gay, Vinod Ganju, Ina Nordman, Ying Cheng, Nicolas Girard, Mehmet Ali Nahit Sendur, Ilhan Celik, Isaac Dai, Secil Koseoglu, Sarita Koride, Qiong Wang, Silke Günther, Guoqiang Hu, Özlem Türeci, Ugur Sahin; Thoracic Oncology Department, LungenClinic Grosshansdorf, Grosshansdorf, Germany; The University of Texas MD Anderson Cancer Center, Houston, TX; Leeds Cancer Centre, St James's University Hospital, Leeds, United Kingdom; Peninsula & South Eastern Haematology and Oncology Group, Frankston, Australia; Calvary Mater Newcastle, Waratah, NSW, Australia; Jilin Cancer Hospital, Changchun, China; Institut Curie - Centre de Recherche, Paris, France; Ankara Yıldırım Beyazıt University and Ankara City Hospital, Cankaya/Ankara, Turkey; BioNTech SE, Mainz, Germany; BioNTech US Inc., Cambridge, MA; Biotheus Inc., Shanghai, China

Background: SCLC is an aggressive form of lung cancer. Incorporating immunotherapy for ES-SCLC pts in the frontline has improved outcomes, but long-term benefit is still lacking. There is an urgent need for efficacious treatments that can extend the duration of response and improve survival in SCLC. BNT327 is an investigational bispecific antibody, targeting both PD-L1 and VEGF-A in the tumor and tumor microenvironment (TME). By binding to PD-L1 on tumor cells it is designed to restore effector T-cell function and by binding to VEGF-A within the TME it also reverses the negative impact of VEGF signaling on immune cell infiltration and activation. In addition, via VEGF-A neutralization, it normalizes tumor vasculature. This dual targeting of PD-L1 and VEGF-A aims to deliver better efficacy and safety. Preliminary results from a Phase II trial showed encouraging efficacy results and a manageable safety profile for BNT327 with paclitaxel as second-line (2L) treatment of pts with SCLC (1992P, ESMO 2023). Combining BNT327 with chemo is being investigated in several Phase II and III trials in both 1L and 2L, including a global dose optimization trial. This Phase III trial will further assess the efficacy and safety of BNT327 in combination with chemo for previously untreated pts with ES-SCLC in a global population. **Methods:** Thisglobal, randomized, double-blind, Phase 3 trial (NCT06712355) will enroll ~439 pts with histologically or cytologically confirmed SCLC, who have not received prior systemic therapy for ES-SCLC. Pts will be initially randomized 1:1:1 to receive combination therapy of atezolizumab (1,200 mg IV) plus chemo (etoposide + carboplatin) (Arm 1), BNT327 (2,000 mg IV) plus chemo (Arm 2), or BNT327 (1,400 mg IV) plus chemo (Arm 3) administered Q3W for four cycles, followed by maintenance therapy with atezolizumab (Arm 1) or BNT327 (Arm 2 and Arm 3) Q3W until confirmed disease progression, intolerable toxicity, participant withdrawal, trial termination or up to two years, whichever occurs first. Chemo will be dosed per local treatment guidelines. One of the BNT327 arms (Arm 2 or 3) is expected to be closed upon evolving insights on the optimal dose. Further pts will then be randomized (1:1) into Arm 1 or the remaining BNT327 arm. Stratification includes brain metastasis, liver metastasis, and geography. The primary endpoint is overall survival (OS). Secondary endpoints include progression-free survival (PFS), objective response rate, PFS rates and OS rates at defined timepoints, patient-reported outcomes, occurrence of treatment emergent adverse event (TEAEs) and occurrence of dose delay, infusion interruption, and discontinuation due to TEAEs; with efficacy endpoints per RECIST 1.1; safety per CTCAE v5.0. The Phase III trial is currently recruiting pts. Clinical trial information: NCT06712355. Research Sponsor: BioNTech SE.

TPS8130 **Poster Session**

IMMUNORARE^{5}: A national platform of 5 academic phase II trials coordinated by Lyon University Hospital to assess the safety and the efficacy of the immunotherapy with domvanalimab + zimberelimab combination in patients with advanced rare cancers—The B3 Thymomas and Thymic Carcinomas Cohort.

Michaël Duruisseaux, Benjamin Besse, Nicolas Girard, Eric Dansin, Sophie Cousin, Julien Mazieres, Ludovic Doucet, Anne Madroszyk, Laurent Greillier, Charles Ricordel, Sarah Cavaillon, Celine Mascaux, Cécile Vicier, Diego Tosi, Sara Calattini, Vérane Schwiertz, Sylvie Bin, Fabien Subtil, Benoit You, Thomas Pierret; Louis Pradel Hospital, Hospices Civils de Lyon Cancer Institute, Cancer Research Center of Lyon (INSERM 1052, CNRS 5286), Université Claude Bernard Lyon 1, Université de Lyon, Lyon, France; Paris-Saclay University, Gustave Roussy Cancer Campus, Villejuif, France; Institut Curie, Paris, France; Centre Oscar Lambret, Lille, France; Institut Bergonié, Bordeaux, NA, France; CHU de Toulouse, Université Paul Sabatier, Toulouse, France; L'Institut De Cancérologie De l'Ouest, Saint-Herblain, France; Department of Medical Oncology, Institut Paoli Calmettes, Marseille, France; Assistance Publique Hôpitaux de Marseille (AP-HM), Marseille, France; CHU Rennes, Rennes, France; Institut du Cancer de Montpellier, Montpellier, France; Pulmonology Department, Strasbourg University Hospitals; Regenerative Nanomedicine, INSERM U1260, Strasbourg University, Strasbourg, NA, France; Institut Paoli Calmettes, Marseille, France; Institut régional du Cancer de Montpellier (ICM), Head, Early Clinical Trial Unit, Medical Oncology Departement, Inserm U1194, Montpellier University, Montpellier, France; Hospices Civils de Lyon Cancer Institute, Oullins - Pierre-Benite, France; Pharmacie, URCC, Hospices Civils de Lyon, Lyon, France; Pôle Santé Publique, Hospices Civils de Lyon, Lyon, France; Service de biostatistique bioinformatique – Hospices Civils de Lyon, Lyon, France; Centre Hospitalier Universitaire Lyon Sud, Hospices Civils de Lyon, Oullins-Pierre-Bénite, France; Louis Pradel Hospital, Hospices Civils of Lyon, Bron, France

Background: In patients with rare cancers, there is an unmet medical need for investigating innovative therapeutics. Indeed, these diseases are rarely assessed in clinical trials. Thymic epithelial tumors (TET) are rare heterogeneous thoracic malignancies. B3 TET and thymic carcinomas are more aggressive and prone to metastatic spreading. The standard 1st line treatment relies on platinum-based chemotherapy. Consensual 2nd line treatment has not been identified yet. Several studies showed limited efficacy of PD-1 blockade in B3 TET and thymic carcinomas. Concurrent blockage of TIGIT and PD-1 immune checkpoint B3 TET may improve outcomes according to translational studies. **Methods:** IMMUNORARE^{5} (NCT06790706) is a platform of 5 single arm phase II trials testing the safety and efficacy of Domvanalimab (anti-TIGIT) and Zimberelimab (anti PD-1) in 5 independent cohorts of rare cancers. The trial, sponsored by Lyon University Hospital, is conducted in 15 French centers, in partnership with the corresponding French national reference centers. The B3 TET and thymic carcinomas cohort, led in collaboration with the RYTHMIC Network (www.rythmic.org), will enroll 26 patients after failure of at least one line of platinum-based chemotherapy, with evaluable lesions at baseline according to RECIST criteria. Patients previously treated with immunotherapy are not eligible. Patients will receive Domvanalimab and Zimberelimab intravenous, every three weeks, until disease progression or unacceptable toxicity. The primary endpoint is the progression-free survival rate at 6 months. The secondary endpoints are overall response rate and duration of the response, progression-free survival, overall survival and tolerability. The trial is designed with a two-stage Simon design, with early termination for futility (5% one-sided alpha level, 80% power). The treatment would be considered interesting if the percentage of patients free from disease progression at 6-months is statistically higher than 40%; 65% is expected. Translational research projects will be developed aiming at deciphering cellular and molecular mechanisms involved in response to treatment. Moreover, data from the prospective database of the RYTHMIC network will be investigated to build a synthetic historical arm representative of the efficacy of the standard treatments in a similar population of patients. Clinical trial information: NCT06790706. Research Sponsor: GILEAD.