LBA9000 **Oral Abstract Session**

Pemetrexed and platinum with or without pembrolizumab for tyrosine kinase inhibitor (TKI)-resistant, *EGFR*-mutant, metastatic nonsquamous NSCLC: Phase 3 KEYNOTE-789 study.

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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, 2023, issue of the *Journal of Clinical Oncology.*

Randomized phase 3 study of first-line AZD3759 (zorifertinib) versus gefitinib or erlotinib in EGFR-mutant (*EGFR*m$^+$) non–small-cell lung cancer (NSCLC) with central nervous system (CNS) metastasis.

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Background: Patients (pts) with *EGFR*m$^+$ NSCLC have high rates of CNS metastasis, few treatment options, and a poor prognosis. So far there are no solid evidence from head to head phase 3 trials in this setting. The potent EGFR TKI AZD3759 has high blood–brain barrier penetration, preliminary data has shown promising intracranial (IC) and systemic antitumor activity, and a tolerable safety profile. **Methods:** This was the first phase 3, open-label, multicenter, randomized controlled trial to compare the efficacy and safety of first-line AZD3759 with first generation EGFR TKIs specifically in pts with *EGFR*m$^+$ (L858R and/or exon 19Del) NSCLC and CNS metastasis. Adult pts were randomized 1:1 to receive AZD3759 (200 mg twice daily) or first generation EGFR TKIs (the control group, gefitinib 250 mg or erlotinib 150 mg once daily). The primary endpoint was progression-free survival (PFS) by blinded independent central review (BICR) per RECIST 1.1. **Results:** Between Feb 1, 2019, and Jan 12, 2021, 439 pts were randomized: 220 to AZD3759 and 219 to the control group. As of July 12, 2022, median follow-up was 20.4 months (mo) for both. Median PFS (95% CI) was significantly superior with AZD3759 *vs* the control group (9.6 [8.2–9.7] *vs* 6.9 [6.3–8.0] mo; HR 0.719, 95% CI 0.580–0.893; p=0.0024). The objective response rate (ORR; BICR/RECIST 1.1) was 68.6% for AZD3759 *vs* 58.4% for the control group (p=0.027), with a trend toward longer median duration of response (DoR) with AZD3759 (8.2 *vs* 6.8 mo; p=0.0997). IC PFS, ORR, and DoR with AZD3759 were all superior *vs* the control group regardless of the assessor or evaluation criteria. The overall survival was immature. The incidence of any-grade treatment-related adverse events (TRAEs) was similar between the two groups (97.7% *vs* 94.0%). Grade ≥3 TRAEs occurred in 65.9% (AZD3759) and 18.3% (the control group) of pts. The main TRAEs were skin and subcutaneous tissue events, gastrointestinal system events and abnormal liver function. No new safety signals arose. **Conclusions:** First-line AZD3759 demonstrated superior systemic and IC antitumor efficacy compared with first generation EGFR TKIs in pts with *EGFR*m$^+$ NSCLC and CNS metastasis. Adverse events were as expected and manageable. IC antitumor activity. Clinical trial information: NCT03653546. Research Sponsor: Alpha Biopharma (Jiangsu) Co., Ltd.

IC variable	Assessor	AZD3759	The control group	HR/OR (95% CI)	*p*
median PFS (mo)	BICR[a]	15.2	8.3	HR 0.467 (0.352–0.619)	<0.0001
	INV[b]	17.9	11.1	HR 0.627 (0.466–0.844)	0.0018
ORR (%)[c]	BICR[a]	75.0	64.2	OR 1.658 (0.993–2.768)	0.0534
	INV[b]	75.6	62.3	OR 1.904 (1.098–3.302)	0.0218
median DoR (mo) [c]	BICR[a]	12.4	7.0	HR 0.521 (0.352–0.773)	0.0009
	INV[b]	13.8	11.1	HR 0.789 (0.501–1.244)	0.3037

[a]IC lesions were evaluated separately per RECIST 1.1. [b]Evaluated per Response Assessment in Neuro-Oncology Brain Metastases (*RANO-BM*). [c]Confirmed responses. INV, investigator; OR, odds ratio.

9002 **Oral Abstract Session**

Sunvozertinib for the treatment of NSCLC with EGFR Exon20 insertion mutations: The first pivotal study results.

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Background: Sunvozertinib(DZD9008) is a rationally designed selective, irreversible EGFR exon20 insertion (exon20ins) inhibitor with wild-type EGFR selectivity. Here we reported the results of WU-KONG6, the first pivotal study of sunvozertinib in previously treated NSCLC patients with EGFR exon20ins. **Methods:** WU-KONG6 (NCT05712902 and CTR20211009) is a phase II, multi-center pivotal study in NSCLC patients with EGFR exon20ins, whose diseases had progressed on or were after platinum-based chemotherapy. Tumor tissue EGFR exon20ins status was tested by local or central laboratory. The primary and key secondary endpoint were objective response rate (ORR) and duration of response (DoR), respectively, assessed by Blinded Independent Central Review (BICR). Patients received 300 mg sunvozertinib once daily until discontinuation criteria were met. **Results:** Between July 19, 2021, and May 6, 2022, a total of 104 Chinese patients were enrolled into WU-KONG6 study. The efficacy analysis set included 97 patients, whose EGFR exon20ins status was retrospectively confirmed by a central laboratory. A total of 30 different exon20ins subtypes were enrolled. The median age was 58 years; 59.8% (58/97) were female; 95.9% (93/97) were adenocarcinoma; 95.9% (93/97) had metastatic diseases at study entry; 32% (31/97) had baseline brain metastasis; the median prior lines of therapy were 2. By the data cutoff date (October 17, 2022), the BICR assessed confirmed ORR (cORR) was 60.8% (59/97). In patients with baseline brain metastasis, the cORR was 48.5% (15/31). Anti-tumor efficacy was observed irrespective of age, gender, smoking status, prior lines of therapies, prior onco-immunotherapies, mutation subtypes, and baseline brain metastasis. By the data cut-off date, median follow-up time for responders was 7.1 months, and 64.4% (38/59) of responders were still responding. The longest DoR was $>$ 11 months, and the median DoR has not been reached. The safety analysis set included all enrolled 104 patients. The most common treatment emergent adverse events (TEAEs) were similar as what have been previously reported for sunvozertinib, and also similar as that of other EGFR inhibitors. Majority of the TEAEs were grade 1 or 2, and clinically manageable. **Conclusions:** The first pivotal study results confirmed sunvozertinib's superior anti-tumor efficacy than the current available therapy for NSCLC with EGFR exon20ins. The safety profile from WU-KONG6 study was consistent with previously reported findings. The updated data will be presented at the meeting. A multinational phase II pivotal study (WU-KONG1, NCT03974022) with the same study design is ongoing in the USA, Australia, and countries/regions in Asia, Europe and South America. Clinical trial information: NCT05712902. Research Sponsor: Dizal Pharmaceutical.

9003 **Oral Abstract Session**

Final overall survival and biomarker analyses of CHOICE-01: A double-blind randomized phase 3 study of toripalimab versus placebo in combination chemotherapy for advanced NSCLC without EGFR/ALK mutations.

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Background: Toripalimab in combination with chemotherapy showed significant improvement over chemotherapy alone in progression-free survival (PFS) and overall survival (OS) as first-line treatment of advanced NSCLC at the final PFS analysis of the CHOICE-01 study (NCT03856411). Here we report the final OS analysis. **Methods:** Patients (n=465) with treatment-naïve, advanced NSCLC without EGFR/ALK mutations were randomized 2:1 to receive toripalimab 240 mg (n=309) or placebo (n=156) in combination with chemotherapy for 4-6 cycles, followed by maintenance toripalimab or placebo plus standard care until disease progression, intolerable toxicity, or completion of 2 years of treatment. Patients from the placebo arm were actively crossed-over to receive toripalimab upon disease progression. The primary endpoint was PFS. The secondary endpoints included OS and safety. **Results:** By the cutoff date of August 31, 2022, when 283 events triggered the final OS analysis, the median survival follow up was 19.4 months. A significant improvement in OS was observed for the toripalimab arm over the placebo arm: HR=0.73 (95% CI: 0.57-0.93), two-sided p=0.0108, median OS 23.8 vs 17.0 months. A consistent effect on OS, favoring the toripalimab arm, was observed all PD-L1 expression subgroups. The OS benefit is greater in non-squamous NSCLC, HR=0.50 (95% CI: 0.36-0.70), median OS 27.8 vs 15.9 months, whereas no significant difference was found in the squamous subgroup (mOS 19.6 vs 18.1 months) despite a significant PFS improvement. The squamous subgroup had a high 70% crossover rate. No new safety signal was identified since the interim report. The incidence of Grade $\geq$3 adverse events (AEs) (78.9% vs 82.1%) was similar between the two arms. AEs leading to discontinuation of toripalimab/placebo (14.3% vs 3.2%), fatal AEs (5.5% vs 2.6%), and immune-related (irAEs) (50.6% vs. 21.2%) were more frequent in the toripalimab arm. Whole exome sequencing results indicated patients with mutations in the FAK-PI3K-Akt pathway achieved significantly better OS from the toripalimab arm. **Conclusions:** The addition of toripalimab to chemotherapy in patients with advanced NSCLC provided significant OS benefit than chemotherapy alone with a manageable safety profile. These results support the use of toripalimab with chemotherapy as 1st line therapy for advanced NSCLC patients without EGFR/ALK mutations. Clinical trial information: NCT03856411. Research Sponsor: Shanghai Junshi Biosciences.

TROPION-Lung02: Datopotamab deruxtecan (Dato-DXd) plus pembrolizumab (pembro) with or without platinum chemotherapy (Pt-CT) in advanced non-small cell lung cancer (aNSCLC).

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Background: Despite advances in first-line (1L) immunotherapy ± CT, most patients (pts) with aNSCLC experience disease progression, necessitating novel strategies. Dato-DXd is an antibody drug conjugate (ADC) composed of a humanized anti-TROP2 IgG1 monoclonal antibody covalently linked to a topoisomerase I inhibitor payload via a plasma-stable tetrapeptide-based cleavable linker. Dato-DXd had encouraging efficacy and manageable safety in heavily pretreated aNSCLC. Dato-DXd + immunotherapy yielded greater preclinical activity than either agent alone. **Methods:** TROPION-Lung02 (NCT04526691) is a phase 1b, global, dose-escalation and -expansion study evaluating Dato-DXd (4 or 6 mg/kg) + pembro 200 mg ± Pt-CT (cisplatin 75 mg/m^2 or carboplatin AUC 5) every 21 days across 6 cohorts. Pts in escalation may have received ≤2 prior lines of therapy for aNSCLC. Pts in expansion were primarily treatment (tx) naive (pts receiving Dato-DXd + pembro may have ≤1 prior Pt-based tx). The primary objective is to assess safety and tolerability, including dose-limiting toxicities (DLTs). Secondary objectives include evaluation of efficacy, pharmacokinetics, and immunogenicity. **Results:** As of the Oct 31, 2022, data cutoff (DCO), 120 pts were treated. All cohorts met DLT criteria to move to escalation. Median age was 65 years. PD-L1 expression was <1%, 1%-49%, and ≥50% in 40%, 33%, and 26% of pts, respectively. Median tx duration was 4.6 mo, with 55% receiving tx at DCO. The most frequent any-grade (gr) tx-emergent adverse events (TEAEs) were nausea (45%) and stomatitis (45%). Gr ≥3 TEAEs occurred in 61% of pts; most frequent were neutrophil count decreased (8%) and amylase increased (8%). TEAEs that were serious, associated with discontinuation, or associated with death occurred in 31%, 24% (16% associated with Dato-DXd), and 6% of pts, respectively. Dose reductions due to TEAEs associated with Dato-DXd occurred in 17%. Drug-related interstitial lung disease occurred in 12 pts (10%; 9 gr 1/2; 3 gr 3). The objective response rate (ORR) with 1L Dato-DXd + pembro doublet and Dato-DXd + pembro + Pt-CT triplet tx was 60% (95% CI, 36%-81%; 12 [2 unconfirmed]/20) and 55% (95% CI, 39%-70%; 23 [5 unconfirmed]/42), respectively. The ORR for any line of therapy was 38% (95% CI, 25%-54%; 18 [2 unconfirmed]/47) with doublet and 47% (95% CI, 34%-60%; 28 [5 unconfirmed]/60) with triplet tx. In both subsets, the disease control rate was 85% and median duration of response was not reached. Responses were observed in all 3 PD-L1 expression level subgroups. Although immature, median progression-free survival (95% CI) was 10.8 (8.3-15.2) and 7.8 mo (5.5-NE) with doublet and triplet tx, respectively. **Conclusions:** Dato-DXd + pembro ± Pt-CT demonstrated tolerable safety with notable 1L activity in this first and largest dataset with an ADC + immunotherapy ± Pt-CT in aNSCLC pts. Clinical trial information: NCT04526691. Research Sponsor: Daiichi Sankyo, Inc.

LBA9005 **Oral Abstract Session**

Tumor treating field (TTFields) therapy with standard of care (SOC) in metastatic non-small cell lung cancer (mNSCLC) following platinum failure: Randomized, phase 3 LUNAR study.

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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, 2023, issue of the *Journal of Clinical Oncology*.

9006 **Oral Abstract Session**

The primary endpoint analysis of SCARLET study: A single-arm, phase II study of sotorasib plus carboplatin-pemetrexed in patients with advanced non-squamous, non-small cell lung cancer with KRAS G12C mutation (WJOG14821L).

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Background: Efficacy and safety of sotorasib in combination with platinum-doublet chemotherapy in KRAS G12C-mutated non-squamous, non-small cell lung cancer (non-Sq, NSCLC) has not been investigated. **Methods:** In this single-arm, phase 2 study, chemotherapy-naïve, advanced non-Sq, NSCLC patients with KRAS G12C mutation were enrolled. Participants were treated with sotorasib 960mg, QD plus carboplatin (AUC 5)/pemetrexed 500mg/m^2 for four cycles, followed by sotorasib plus pemetrexed until disease progression. The primary endpoint was overall response rate (ORR) by independent review. The secondary endpoints were progression-free survival (PFS), overall survival (OS) and safety. Using plasma samples, next-generation sequencing analysis was done at baseline, 3 weeks and disease progression. Regarding statistical consideration, the threshold and the expected ORR were set as 40% and 65%, respectively with one-sided $\alpha = 0.1$, and $\beta = 0.1$, the required sample size was 28 cases (Simon's two-stage design). A total of 30 cases was planned to take into account the possibility of a few dropped or ineligible cases. This study was funded by AMGEN Inc. and Trial identification no. is jRCT2051210086. **Results:** Between Oct 2021 and Jul 2022, 30 patients were enrolled. Twenty-nine and 27 were analyzed for safety and efficacy, respectively. Of those, median age was 70, male/female: 25/5, never-/smoker: 1/29, ECOG performance status: 0/1 11/19 and PD-L1 expression level: ≥50%/1-49%/<1% 15/10/5. The primary endpoint, ORR by independent review was 88.9% (80%CI 78.5-94.8%). Median PFS was not reached mainly due to shorter follow-up period (median 4.2 months) and PFS rate at 6 months was 61.2%. OS rate at 6 months was 87.0%. Subgroup analysis revealed that ORR did not differ by PD-L1 expression level (≥50%/1-49%/<1%: 76.9%/77.8%/80.0%, respectively). Common adverse events were anemia, neutrophil count decreased, nausea and platelet count decreased. Grade≥3 AEs were mostly hematological toxicities, but one treatment-related death (pneumonia) occurred. At baseline, 70% of plasma samples were positive for KRAS G12C and most common co-occurring mutation was TP53 (50%). At 3 weeks, plasma KRAS G12C disappeared among 60% of patients. **Conclusions:** Sotorasib in combination with CBDCA/PEM demonstrated favorable ORR and tolerability in advanced non-Sq, NSCLC patients with KRAS G12C mutation. Clinical trial information: jRCT2051210086. Research Sponsor: AMGEN Inc.

9007 **Oral Abstract Session**

KontRASt-01 update: Safety and efficacy of JDQ443 in *KRAS G12C*-mutated solid tumors including non-small cell lung cancer (NSCLC).

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Background: *KRAS G12C* oncogenic mutations occur in ~13% of NSCLCs and up to 4% of other solid tumors. JDQ443 is a selective, covalent, orally bioavailable $KRAS^{G12C}$ inhibitor that irreversibly traps $KRAS^{G12C}$ in the inactive, GDP-bound state. Clinical activity was seen in initial cohorts of patients (pts) treated with JDQ443 monotherapy, and 200 mg twice daily (BID) was selected as the recommended dose (RD) for expansion (Tan DS, *et al*. AACR 2022; Abstract CT033). **Methods:** KontRASt-01 (NCT04699188) is a Phase Ib/II, open-label, multicenter, dose-escalation (DEs), and dose-expansion (DEx) trial of JDQ443 as a monotherapy or in combination with TNO155 (SHP2 inhibitor) and/or tislelizumab (anti–PD-1 monoclonal antibody). Primary objectives of DEs are to assess safety/tolerability and identify the RD and regimens for future studies. The primary objective of DEx is to assess efficacy. Key inclusion criteria: advanced, *KRAS G12C*-mutated solid tumors; previous standard-of-care treatment; age ≥18 years; and ECOG PS 0–1. Prior $KRAS^{G12C}$ inhibitor treatment is not permitted for the JDQ443 monotherapy arm and is allowed for the JDQ443 + TNO155 and JDQ443 + tislelizumab DEs arms. **Results:** As of Oct 28, 2022, 84 pts were treated with JDQ443 monotherapy, orally, continuously, in DEs, DEx, and food effect (FE) cohorts at 200 mg once daily (QD; n=10), 400 mg QD (n=11), 200 mg BID (n=56), and 300 mg BID (n=7). Median age was 61 years (range 26–83); median prior lines of therapy was 3 (range 1–7); and indications included NSCLC (n=38), colorectal cancer (n=42), and others (n=4). Median duration of exposure was 14.6 weeks (range 0.1–68.4) for all pts and 15.1 weeks (0.1–68.1) for pts treated at 200 mg BID. Among pts treated at 200 mg BID, 40 (71.4%) and 4 (7.1%) experienced treatment-related adverse events (TRAEs) of any grade (Gr) and of Gr 3, respectively. There were no Gr 4–5 TRAEs at any dose level. The most common TRAEs (any Gr, occurring in ≥10% of pts) at 200 mg BID were fatigue (17.9%), edema (14.3%), diarrhea (16.1%), nausea (16.1%), vomiting (10.7%), and peripheral neuropathy (10.7%). Gr 3 TRAEs were neutropenia in 2 pts, ALT and AST increase in 1 pt, and myalgia in 1 pt. One pt receiving 200 mg BID required a dose reduction due to a TRAE of Gr 2 peripheral neuropathy. Among response evaluable pts with NSCLC treated in DEs and FE cohorts, the confirmed overall response rate was 41.7% (10/24 pts) across dose levels and 54.5% (6/11 pts) at the RD of 200 mg BID. Combination JDQ443 + TNO155 and JDQ443 + tislelizumab arms are enrolling. Additional data will be available at the time of presentation. **Conclusions:** JDQ443 demonstrates an acceptable safety and tolerability profile at 200 mg BID, with clinical activity in pts with NSCLC. Enrollment is ongoing to the JDQ443 monotherapy DEx and the JDQ443 + TNO155 and JDQ443 + tislelizumab combination arms. Clinical trial information: NCT04699188. Research Sponsor: Novartis Pharmaceuticals Corporation.

9008 **Oral Abstract Session**

Biomarker subgroup analyses of CodeBreaK 200, a phase 3 trial of sotorasib versus (vs) docetaxel in patients (pts) with pretreated *KRAS* G12C-mutated advanced non-small cell lung cancer (NSCLC).

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Background: Sotorasib is a first-in-class oral, irreversible $KRAS^{G12C}$ inhibitor approved for adults with pretreated *KRAS* G12C-mutated advanced NSCLC. In CodeBreaK 200, the first $KRAS^{G12C}$ inhibitor randomized phase 3 trial, sotorasib demonstrated superior progression-free survival (PFS) and overall response rate (ORR) vs docetaxel and a more favorable safety profile. We report prespecified exploratory biomarker analyses comparing sotorasib vs docetaxel efficacy in molecularly-defined *KRAS* G12C-mutated advanced NSCLC subsets. **Methods:** In CodeBreaK 200, 345 pts with *KRAS* G12C-mutated advanced NSCLC who progressed after platinum-based chemotherapy and a checkpoint inhibitor were randomized 1:1 to oral sotorasib 960 mg daily or IV docetaxel 75 mg/m^2 Q3W. Primary endpoint was PFS by blinded independent central review (RECIST 1.1; key secondary endpoint: ORR). In prespecified exploratory analyses, baseline tissue and plasma samples were analyzed for key genomic alterations (eg, *STK11*, *KEAP1*, *EGFR*, *MET*, *TP53*), by central targeted next-generation sequencing (Skoulidis *N Engl J Med* 2021), and PD-L1 protein level by local standard of care testing in biomarker-evaluable cases; biomarker status was correlated with PFS and ORR. Inferred tumor mutation burden by plasma circulating tumor DNA (sum of mutant molecular variant reads) was assessed. Association of baseline genomic alterations with long-term benefit (PFS $\geq$ 6 m) vs early progression (PFS $<$ 3 m; no complete/partial response) was evaluated. **Results:** Most prevalent *KRAS* G12C co-alterations in biomarker-evaluable cases with available tumor and/or plasma samples (n=317) were *TP53* (181 [57.1%]), *STK11* (119 [37.5%]), and *KEAP1* (82 [25.9%]) in CodeBreaK 200, consistent with CodeBreaK 100; 55 (17.4%) pts had *STK11* and *KEAP1* co-alterations. Sotorasib showed superior clinical benefit vs docetaxel independently of PD-L1 expression and across all prespecified subgroups (eg, *STK11, KEAP1*, *TP53*). No clinical response occurred with either treatment in 26 (8.2%) pts with additional *KRAS* alterations, including amplifications. High baseline plasma tumor burden was associated with greater odds of early progression vs long-term benefit in both arms (odds ratio, 3.54 [95%CI 1.83-6.85] per tertile increase; $p<0.0001$). Correlation of *KRAS* G12C co-alterations with response detected a signal toward shorter median PFS (sotorasib, 2.8 m [95%CI 1.6-3.4]; docetaxel, 7.5 m [95%CI 3.0-NE]) with sotorasib vs docetaxel in pts with *KRAS* G12C and *NOTCH1* co-altered tumors. **Conclusions:** Sotorasib demonstrated consistent clinical benefit vs docetaxel in all prespecified molecularly-defined subgroups (eg, *STK11, KEAP1*, *TP53*) in this exploratory analysis of CodeBreaK 200. No predictive biomarkers were confirmed, but novel hypothesis-generating signals were observed. Clinical trial information: NCT04303780. Research Sponsor: Amgen Inc.

LBA9009 **Clinical Science Symposium**

A phase III study comparing EGFR tyrosine kinase inhibitor (EGFR-TKI) monotherapy and EGFR-TKI with inserted cisplatin (CDDP) plus pemetrexed (PEM) as a first-line treatment in patients (pts) with advanced non-squamous non–small-cell lung cancer (NSqNSCLC) harboring *EGFR* activating mutation (*EGFR*-NSqNSCLC): JCOG1404/WJOG8214L, AGAIN study.

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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, 2023, issue of the *Journal of Clinical Oncology.*

9011 **Rapid Abstract Session**

BLU-945 monotherapy and in combination with osimertinib (OSI) in previously treated patients with advanced *EGFR*-mutant (*EGFRm*) NSCLC in the phase 1/2 SYMPHONY study.

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Background: Despite improved frontline OSI treatment outcomes, patients (pts) with advanced *EGFR*m NSCLC inevitably progress, with worse outcomes in the *EGFR* L858R subgroup (median PFS of 14.4 vs 21.4 mo in pts with exon 19 deletions). BLU-945 is an investigational, next-generation, oral tyrosine kinase inhibitor (TKI) that targets common *EGFR*-activating and T790M and C797X resistance mutations, while being selective against *EGFR* wild type (WT). Preclinically, BLU-945 in combination (combo) with OSI had enhanced potency on L858R and extended antitumor response durability versus OSI alone. SYMPHONY (NCT04862780) is an ongoing first-in-human phase 1/2 study of BLU-945 monotherapy (mono) or combo with OSI. **Methods:** In the phase 1 dose escalation, pts (aged ≥18 y; metastatic *EGFR*m NSCLC; ECOG PS 0–1; treated with ≥1 EGFR TKI) received BLU-945 mono starting at 25 mg QD. Pts progressing on OSI could receive BLU-945 with 80 mg OSI starting at 50% of the highest safe BLU-945 mono dose. Each dose escalation followed a Bayesian Optimal Interval design. Safety, including dose-limiting toxicities (DLT), PK, and circulating tumor DNA (ctDNA) mutational status were assessed. **Results:** As of Jan 6, 2023, 108 pts received BLU-945 mono (25–600 mg QD; 100–300 mg BID). Pts had a median of 3 lines of prior therapy and were genomically complex with ctDNA detectable *EGFR* on-target and/or off-target resistance alterations (46%) at baseline. DLTs included alanine transaminase (ALT) and aspartate transaminase (AST) elevation, hepatic cytolysis, fatigue, nausea, vomiting, and hyponatremia, occurring at doses of ≥400 mg/d. The maximum tolerated dose was 500 mg/d. The most common AEs were nausea (42%), headache (40%), increased ALT (38%), increased AST (37%), and vomiting (32%). Robust on-target *EGFR* activity was observed with ctDNA reduction on day 15 in 90%, 85% and 70% of *EGFR* T790M, C797S, and L858R alleles at ≥400 mg/d doses, respectively. At ≥400 mg/d, 48% had tumor shrinkage, including partial responses (PRs). Twenty-five pts received BLU-945 (200–400 mg QD; 100–200 mg BID) combo with OSI. Pts had a median of 2 lines of prior therapy. The most common combo AEs were fatigue (36%), diarrhea (32%), headache (32%), and nausea (28%). Other *EGFR* WT AEs were dry skin (20%) and rash (8%). One DLT (Grade 4 pneumonitis) was reported in the BLU-945 300 mg QD with OSI group. Tumor reductions, including PRs in 2 pts progressing on OSI, were observed at ≥300 mg/d. Dose escalation is ongoing. **Conclusions:** BLU-945 mono and combo with OSI were generally well tolerated and showed robust on-target *EGFR* ctDNA reduction, with tumor shrinkage in genomically heterogeneous, heavily pretreated pts. Combo showed responses at BLU-945 doses lower than in mono, consistent with additive benefit. The combo safety profile and on-target activity provide rationale for further development in front line. Clinical trial information: NCT04862780. Research Sponsor: Blueprint Medicines.

9012 **Rapid Abstract Session**

First-line immune checkpoint inhibitors alone or in combination with chemotherapy in real-life elderly patients with advanced non-small cell lung cancer (NEJ057).

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Background: Immune checkpoint inhibitor (ICI) plus chemotherapy is now a standard treatment for non-small cell lung cancer (NSCLC) without targetable oncogene alternations. However, the efficacy and safety of ICI plus chemotherapy (ICI-chemo) in 75 years or older patients have not been elucidated. The aim of this study is to reveal the real-world choice of first-line drugs in elderly patients (pts) and evaluate the efficacy and safety of ICI-chemo. **Methods:** We conducted a multicenter (58 centers in Japan), retrospective cohort study of consecutive 75 years or older pts with clinical stage IIIB, IIIC, IV, postoperative or radiotherapy recurrent NSCLC who started first-line systemic therapy between December 2018 and March 2021. Pts with epidermal growth factor receptor mutations, anaplastic lymphoma kinase rearrangements, or whose first-line systemic therapy was molecular targeted therapy were excluded. **Results:** A total of 1245 pts were enrolled: median (range) age 78 (75-95) years; 278 (22%) female; 367 (29%) ECOG PS 0, 680 (55%) PS 1 and 171 (14%) PS 2; 678 (54%) adenocarcinoma; PD-L1 tumor proportion score 268 (22%) $<$1%, 387 (31%) 1-49% and 410 (34%) $\geq$50%; 354 (28%) ICI-chemo, 425 (34%) ICI alone, 311 (25%) platinum-doublet chemotherapy and 155 (12%) single agent chemotherapy. The median overall survival (OS) was 20.0 months (95%CI, 17.1–23.6) in the ICI-chemo group, 19.8 months (95%CI, 16.5–23.8) in the ICI alone group, 12.8 months (95%CI, 10.7–15.6) in the platinum-doublet chemotherapy group and 9.5 months (95% CI, 7.4–13.4) in the single agent chemotherapy group, respectively. After propensity score matching, there was no difference in OS and progression-free survival (PFS) between ICI-chemo group (n=96) and ICI alone group (n=95) in PD-L1 $\geq$1% (OS: HR, 0.98; 95% CI, 0.67-1.42, PFS: HR, 0.92; 95% CI, 0.67-1.25). Regardless of PD-L1 subgroups (1-49% or $\geq$50%), no significant differences in OS and PFS were observed. Concerning safety, Grade 3 or higher immune-related adverse events (irAEs) occurred in 86 pts (24.3%) in the ICI-chemo group and 76 pts (17.9%) in the ICI alone group ($p = 0.03$). The number of pts who required steroids for irAEs was 115 (32.5%) in the ICI-chemo group and 105 (24.7%) in the ICI alone group ($p = 0.02$). Pneumonitis was reported in 83 pts (23.4%) in the ICI-chemo group and 66 pts (15.6%) in the ICI alone group ($p = 0.006$). **Conclusions:** In real-world data for pts aged 75 years or older, ICI-chemo did not improve survival and increased the incidence of grade 3 or higher irAEs compared to ICI alone. Based on our results, ICI alone is recommended for elderly pts with PD-L1 positive NSCLC. Clinical trial information: UMIN000046700. Research Sponsor: None.

9013 **Clinical Science Symposium**

Predictive biomarkers for treatment with amivantamab plus lazertinib among *EGFR*-mutated NSCLC in the post-osimertinib setting: Analysis of tissue IHC and ctDNA NGS.

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Background: Amivantamab (ami) is a bispecific antibody targeting EGFR and MET with immune cell-directing activity, and lazertinib (laz) is a brain-penetrant, third-generation EGFR tyrosine kinase inhibitor. In a previous report, the overall response rate (ORR) of ami+laz in the post-osimertinib (osi) setting was 36%, with median duration of response of 9.6 months (Bauml *JCO* 2021; 39:15_suppl, 9006). Exploratory analyses suggested certain immunohistochemistry (IHC) and ctDNA-based next-generation sequencing (NGS) biomarkers may enrich for response. A prospective study was conducted to further evaluate these potential biomarkers. **Methods:** CHRYSALIS-2 (NCT04077463), an ongoing phase 1/1b study, examines the efficacy (ORR per RECIST v1.1) of ami+laz in patients (pts) with *EGFR*-mutated NSCLC. Cohort D enrolled osi-relapsed, chemotherapy-naïve pts with *EGFR* exon 19 deletion or L858R mutated advanced NSCLC who had tumor tissue for IHC staining and plasma for ctDNA NGS collected after their most recent therapy. Training and validation subsets identified biomarker criteria and predictive validity, respectively. A Bayesian posterior probability (biomarker positive group ORR is ≥35% and negative group ORR is ≤20%) was predefined to be ≥85% for acceptance. **Results:** There were 101 response-evaluable pts enrolled in Cohort D. A total of 87 pts had detectable baseline ctDNA and 77 pts had evaluable MET IHC. The training set (n = 50) identified IHC-based MET expression of 3+ staining on ≥25% of tumor cells (MET+) as a potential predictive biomarker, and the validation set (n = 27) confirmed these results. Of those with MET IHC data, 28/77 (36%) were MET+. The overall ORR for MET+ was 61% (95% CI, 41–78) and 12% (95% CI, 5–25) for MET-, with median PFS for MET+ not reached (95% CI, 4.3–NE) vs 4.1 months (95% CI, 2.8–5.7) for MET-. NGS evaluation of ctDNA did not identify predictive biomarkers meeting predetermined criteria. Of note, only 1 pt was identified by ctDNA as having *MET* amplification (the pt was also MET+ by IHC). Further details will be provided at the time of presentation. **Conclusions:** MET+ by IHC may be a predictive biomarker for response to ami+laz in the post-osi, chemotherapy-naïve setting. In contrast, molecular profiling with ctDNA failed to identify a subgroup of pts more likely to benefit. Ami+laz represents a potential chemotherapy-free option for pts with *EGFR*-mutated advanced NSCLC who have progressed on osi and are also MET+ by IHC. Clinical trial information: NCT04077463. Research Sponsor: Janssen.

Safety and preliminary efficacy of YK-029A, a novel EGFR TKI, in patients with advanced NSCLC harboring ex20ins, T790M or rare mutations.

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Background: This study aimed to evaluate the safety and preliminary efficacy of YK-029A, a novel third-generation epidermal growth factor receptor *(EGFR)* tyrosine kinase inhibitor, in treated or untreated patients with advanced NSCLC. **Methods:** This dose-escalation and dose-expansion phase 1 trial recruited previously untreated or treated patients with *EGFR* ex20ins mutant locally advanced or metastatic NSCLC and previously treated patients with *EGFR* T790M or rare mutations. In dose-escalation phase, patients with *EGFR* T790M mutation were enrolled. YK-029A was given at doses of 50, 100, 150, 200 to 250 mg/day (3+3 design). In dose-expansion phase, patients with *EGFR* T790M, *EGFR* ex20ins, or rare mutations were enrolled. The primary objective was safety. Dose-limiting toxicity (DLT) and maximum tolerated dose (MTD) were explored. In the treatment-naïve cohort of *EGFR* ex20ins mutant NSCLC, patients were administered oral YK-029A 200 mg once daily in a 28-day cycle, and efficacy was assessed by the independent review committee. The study was registered (chinadrugtrials.org.cn,CTR20180350). **Results:** A total of 108 were included in the safety analysis set. DLT did not occur in dose-escalation phase. MTD was not reached. Treatment-emergent adverse events (TEAEs) of any grade and grade≥3 occurred in 106 (98.1%) and 41 (38.0%) patients, respectively. Treatment-related adverse events (TRAEs) of any grade and grade≥3 occurred in 102 (94.4%) and 30 (27.8%) patients, respectively. One patient had liver abscess related to YK-029A and died. Three patients terminated the treatment because of TEAEs. The most common TRAEs were diarrhea (46.3%), anemia (38.0%), and rash (32.4%). For the treatment-naïve *EGFR* ex20ins mutant cohort, 26 patients were included in the efficacy analysis set. Most patients were adenocarcinoma (96.4%) and at stage IV (85.7%). At the cut-off date on October 30, 2022, 19 patients (73.1%) had partial remission, five patients (19.2%) had stable disease, and two patients (7.7%) developed disease progression. The confirmed objective response rate achieved 73.1% (95% confidence interval [CI], 52.21% to 88.43%). The median progression-free survival was 9.3 months (95% CI, 5.85 to not evaluated). **Conclusions:** YK-029A was well tolerated and showed preliminary efficacy in treatment-naïve *EGFR* ex20ins mutant patients with locally advanced or metastatic NSCLC. Research Sponsor: Puhe Biopharma Co., Ltd.

	Treatment-naïve ex20ins cohort (200 mg) (N=26)
Objective response rate	73.1% (95% CI, 52.21% to 88.43%)
Disease control rate	92.3% (95% CI, 74.87% to 99.05%)
Median progression-free survival, months	9.3 (95% CI, 5.85 to NE)
Median duration of response, months	7.5 (95% CI, 3.75 to NE)
12-month overall survival rate	83.1% (95% CI, 47.17% to 95.53%)

9015 **Poster Discussion Session**

FAK inhibition with novel FAK/ALK inhibitor APG-2449 could overcome resistance in NSCLC patients who are resistant to second-generation ALK inhibitors.

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Background: APG-2449 is a novel, orally active FAK inhibitor and an ALK/ROS1 tyrosine kinase inhibitor (TKI) that has shown potent activity in preclinical models. It had been demonstrated that APG-2449 was well tolerated, and preliminary efficacy was observed in pts who were resistant to second-generation ALK/ROS1$^+$ inhibitors (Zhao H et al. *J Clin Oncol* 2022; 40:9071). We provide updated safety and efficacy results and potential mechanisms of action(s) of this therapy. **Methods:** After the RP2D was determined as 1,200 mg daily (QD), NSCLC pts were enrolled into 2 dose expansion cohorts. Cohort 1 included pts who were resistant to second-generation ALK/ROS1$^+$ TKIs. Cohort 2 included those who were ALK or ROS1$^+$ TKI naïve. **Results:** As of December 9, 2022, 130 pts enrolled (median [range] age 53 [21-78] years; 53.8% female) with NSCLC, mesothelioma, or ovarian cancer were treated with APG-2449 at doses ranging from 900 to 1,500 mg. A total of 117 (90%) pts experienced treatment-related adverse events (TRAEs). The most frequent TRAEs included elevated blood creatinine (43.8%), ALT (40.8%), and AST (33.1%) levels, as well as gastrointestinal disorders: nausea (25.4%), vomiting (21.5%), and diarrhea (21.5%). A total of 17 (13.1%) TRAEs were grade $\geq$ 3. In a subgroup of pts with TKI-naïve NSCLC (n = 33; 31 with efficacy evaluable), the overall response rate (ORR) and the disease control rate (DCR = CR + PR + SD) were 70.6% (12/17) and 88.2% (15/17), respectively, in ROS1$^+$ treatment naïve pts; the ORR and DCR were 78.6% (11/14) and 100% (14/14) in ALK$^+$ treatment naïve pts. Of 27 NSCLC pts resistant to second-generation ALK inhibitors, 7 were observed with PR (7/27; 25.9%) during APG-2449 treatment at RP2D. In this subgroup, compared to baseline, pts who experienced PR showed lower phosphorylated FAK (pFAK) levels in peripheral blood mononuclear cells (PBMCs) by Day 28 (24 hours after dosing on D28) than pts who experienced SD. Furthermore, pts with progressive disease showed an increase of PBMC pFAK levels on D28 compared to baseline, indicating that APG-2449 could inhibit FAK phosphorylation. Pts with higher pFAK expression in tumor tissues at baseline tended to achieve better clinical responses than those with lower pFAK expression post APG-2449 treatment. **Conclusions:** APG-2449 showed a favorable preliminary safety profile and antitumor efficacy in pts with NSCLC. Preliminary efficacy was observed in those whose disease was TKI naïve and resistant to second-generation ALK inhibitors. FAK inhibition could be a novel approach to overcome ALK resistance in pts with NSCLC who are resistant to second-generation ALK inhibitors. Internal study identifier: APG2449XC101. Clinical trial information: NCT03917043. Research Sponsor: Ascentage Pharma Group Corp Ltd.

LBA9016 **Poster Discussion Session**

Intracranial efficacy of sotorasib versus docetaxel in pretreated *KRAS* G12C-mutated advanced non-small cell lung cancer (NSCLC): Practice-informing data from a global, phase 3, randomized, controlled trial (RCT).

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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, 2023, issue of the *Journal of Clinical Oncology*.

Intracranial and systemic efficacy of repotrectinib in advanced *ROS1* fusion-positive (*ROS1*+) non-small cell lung cancer (NSCLC) and central nervous system metastases (CNS mets) in the phase 1/2 TRIDENT-1.

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Background: Repotrectinib is a next-generation ROS1 and TRK tyrosine kinase inhibitor (TKI) that has demonstrated durable activity with a manageable safety profile in TKI-naïve and TKI-pretreated patients (pts) with advanced *ROS1*+ NSCLC. We report the first analysis of outcomes on repotrectinib in pts with *ROS1*+ NSCLC by baseline (BL) CNS met status in the global pivotal phase 1/2 TRIDENT-1 trial (NCT03093116). **Methods:** Pts with *ROS1*+ NSCLC were assigned to 4 cohorts by treatment history: ROS1 TKI-naïve, 1 ROS1 TKI and no chemotherapy (chemo), 1 ROS1 TKI and 1 platinum-based chemo, and 2 ROS1 TKIs and no chemo. Treated or untreated asymptomatic CNS mets were permitted. Brain scans were mandated for all pts in phase 2 at screening and at protocol-specified intervals until progression. Endpoints included confirmed objective response rate (cORR) and duration of response (DOR) by blinded independent central review (BICR; RECIST v1.1); intracranial ORR (icORR) in pts with measurable brain mets at BL by BICR per mRECIST v1.1; and safety. **Results:** In pts with BL measurable CNS mets who were TKI-naïve (n = 8) and in those with 1 TKI and no chemo (n = 12), icORR (95% CI) was 88% (47-100) and 42% (15-72), respectively. At data cutoff (June 20, 2022), 0 of 7 responders in the TKI-naïve cohort and 2 of 5 in the cohort with 1 prior TKI and no chemo had intracranial progression or death; intracranial DOR range was 1.9-14.8+ mo (TKI-naïve) and 3.0-11.1+ mo (1 TKI and no chemo), with 86% and 80% of pts with an intracranial response remaining on treatment, respectively. Median follow-up and systemic response by CNS met status are shown in the Table. In pts with *ROS1*+ NSCLC with (n = 118) or without (n = 178) CNS mets, most common any-grade neurologic treatment-emergent adverse events were dizziness (57% / 63%), dysgeusia (42% / 53%), paresthesia (32% / 34%), headache (27% / 12%), ataxia (17% / 22%), and memory impairment (14% / 10%). **Conclusions:** In TRIDENT-1, repotrectinib showed durable clinical activity in ROS1 TKI-naïve and -pretreated pts with or without BL CNS mets, including intracranial responses. Repotrectinib safety profile was similar in pts with *ROS1*+ NSCLC with or without CNS mets. Clinical trial information: NCT03093116. Research Sponsor: Turning Point Therapeutics Inc, a wholly owned subsidiary of Bristol Myers Squibb Company.

Systemic response to repotrectinib in pts with *ROS1*+ NSCLC with/without BL CNS mets per BICR.

	ROS1 TKI naïve n = 71	1 TKI and no chemo n = 56	1 TKI and 1 chemo n = 26	2 TKIs and no chemo n = 18
Median follow-up, mo	18.1	15.5	21.3	14.1
Pts with CNS mets, n (%)	18 (25)	24 (43)	10 (38)	8 (44)
cORR, %	89	33	40	13
95% CI	65-99	16-55	12-74	0.3-53
6-mo DOR 95% CI	100	63	50	100
	100-100	29-96	1-99	100-100
12-mo DOR	93	-	-	-
95% CI[a]	79-100			
Pts without CNS mets, n (%)	53 (75)	32 (57)	16 (62)	10 (56)
cORR, %	76	41	44	40
95% CI	62-86	24-59	20-70	12-74
6-mo DOR	87	92	71	50
95% CI	77-98	76-100	38-100	1-99
12-mo DOR	84	-	-	-
95% CI[a]	72-96			

[a]Not reported for TKI-pretreated cohorts due to small n's at risk.

Efficacy and safety of encorafenib (enco) plus binimetinib (bini) in patients with *BRAF* V600E-mutant (*BRAF*^{V600E}) metastatic non-small cell lung cancer (NSCLC) from the phase 2 PHAROS study.

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Background: The combination of dabrafenib, a BRAF inhibitor, and trametinib, a MEK inhibitor, is a current standard of care for patients (pts) with *BRAF*^{V600E} NSCLC. We report efficacy and safety of enco+bini in pts with *BRAF*^{V600E} metastatic NSCLC. **Methods:** PHAROS is an ongoing, open-label, single-arm, phase 2 study that enrolled pts with *BRAF*^{V600E} metastatic NSCLC who had measurable disease by RECIST 1.1 and Eastern Cooperative Oncology Group performance status of 0 or 1, and who were either treatment-naive or had received 1 prior therapy (chemotherapy, monotherapy, or combination immunotherapy) for metastatic disease. Exclusion criteria included prior treatment with a BRAF or MEK inhibitor. Pts received enco 450 mg QD + bini 45 mg BID administered orally in 28-day cycles. The primary endpoint was confirmed objective response rate (ORR) by independent radiology review (IRR). Secondary endpoints included duration of response (DOR), disease control rate (DCR), progression-free survival (PFS), and time to response (TTR), all by IRR, and safety. Exploratory endpoints included biomarker assessments. **Results:** At the data cutoff (Sep 22, 2022), 98 pts (59 treatment-naive, 39 previously treated) received enco+bini. The median duration of treatment was 9.2 months with enco and 8.4 months with bini. Treatment is ongoing in 34% of the pts; 38% permanently discontinued due to disease progression and 18% due to adverse events (AEs). The ORR (95% CI) by IRR was 75% (62, 85) in treatment-naive and 46% (30, 63) in previously treated pts. Secondary endpoints are shown in the table. The most frequent (≥30%) treatment-related AEs (TRAEs) were nausea (50%), diarrhea (43%), and fatigue (32%). AEs led to permanent discontinuation of enco+bini in 15% of pts and dose reductions in 24% of pts. One grade 5 TRAE of intracranial hemorrhage was reported. Next-generation sequencing analysis was conducted with archival tumor biopsies from 48 treatment-naive and 32 previously treated pts. The most frequent genomic alterations, in addition to *BRAF*^{V600E}, were *SETD2* and *TP53* (43% each), *SMAD4* (21%), *ATM*, *MLL2*, *CSF1R*, and *SMARCA4* (14% each), and *CDKN2A* (11%). **Conclusions:** The combination of enco+bini showed meaningful clinical benefit in treatment-naive and previously treated pts with *BRAF*^{V600E} metastatic NSCLC. The safety profile of enco+bini was generally consistent with that established for pts with *BRAF*$^{V600E/K}$ melanoma. ClinicalTrials.gov: NCT03915951. Clinical trial information: NCT03915951. Research Sponsor: Pfizer.

Secondary endpoints by IRR.

	Treatment-naive	Previously treated
n	**44**	**18**
Median DOR (95% CI), months	NE (23.1-NE)	16.7 (7.4-NE)
DOR ≥12 months, n (%)	26 (59)	6 (33)
Median TTR (range), months	1.9 (1.1-19.1)	1.7 (1.2-7.3)
n	**59**	**39**
DCR after 24 weeks, % (95% CI)	64 (51-76)	41 (26-58)
Median PFS (95% CI), months	NE (15.7-NE)	9.3 (6.2-NE)

NE, not estimable.

9019 **Poster Discussion Session**

LIBELULE: A randomized phase III study to evaluate the clinical relevance of early liquid biopsy (LB) in patients with suspicious metastatic lung cancer.

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Background: Timeliness of molecular testing is essential to minimize the time to appropriate 1st line treatment initiation (TTI) in advanced NSCLC pts. We hypothesized that LB-based molecular testing performed at the patient's 1st visit could reduce this TTI. **Methods:** LIBELULE is a multicenter, randomized, comparative, open-label study, enrolling pts with radiological suspicion of stage IV lung cancer, no prior biopsy or cytology for advanced NSCLC diagnosis. In Arm A, a LB was performed at the 1st visit using the InVisionFirst-Lung assay, an amplicon-based NGS panel covering 37-NSCLC associated genes. When LB results were informative, treatment was initiated on the basis of: InVisionFirst-Lung alone for pts with *EGFR, BRAF V600E* mutation (mut), *ALK* or *ROS1* rearrangement (category 1 alterations); InVisionFirst-Lung and pathological results for pts with *ERBB2*, *MET* exon 14, *KRAS*, *BRAF* non V600 and/or *LKB1* mut, *RET* or *NTRK* rearrangement (category 2 alterations). In control Arm B, histological sampling was planned with genomic analysis when indicated (local LB allowed) and treatment was initiated according to ESMO guidelines. The primary endpoint was the time from randomization to initiation of appropriate treatment based on informative genomic and pathological results. 286 pts were needed to detect a 21% shortening in TTI ($\alpha = 0.05$, $1\text{-}\beta = 90\%$). **Results:** 319 pts were randomized between Arm A (n = 161) and B (n = 158): median age 68 y (39-97), 56.1% male, 28.5% non-smokers, PS0-1 82%, PS≥2 18,1%; adenocarcinoma: 56.7%, squamous cell carcinoma: 11%, SCLC: 10%, other tumor types: 5%. 5.3% of pts had no cancer. In Arm A, 81% of pts had ctDNA findings; category 1 and category 2 alterations were identified on tissue and/or LB in 29.2% (*EGFR* mut: 21.7%) and 24%, respectively, whereas in Arm B, 23.2% of pts had category 1 (*EGFR* mut: 20.3%) and 20% had category 2 alterations detected. Systemic treatment was initiated in 74.5% and 65.8% of pts in Arm A and B, respectively. Main reasons for not initiating treatment were diagnosis other than cancer, local treatment and palliative care. The mean TTI was 29.0 days (d) (95%CI 25.9-32.1) in Arm A vs 33.9 d (95%CI 28.4-39.5) in Arm B in the intention-to-treat population ($p = 0.28$), but significantly shorter in Arm A 29.1 d vs 38.8 d in Arm B for pts receiving systemic treatment ($p = 0.01$). The mean TTI was significantly shorter (21 d vs 37.4 d) in pts with category 1 alterations ($p = 0.004$) as well as the time to contributive genomic analysis (17.9 d vs 25.6 d; $p < 0.001$) in Arm A and B, respectively. In Arm A, 7.4% of pts vs 13.3% in Arm B initiated a treatment without genomic analysis available. **Conclusions:** Early LB significantly reduces the time to contributive molecular analysis and the time to initiation of appropriate 1st line therapy in pts eligible for systemic treatment, especially for pts with actionable alterations indicating targeted 1st line therapy. Clinical trial information: NCT03721120. Research Sponsor: Grant from French Ministry of Health PHRC-K 2017.

9020 **Poster Discussion Session**

Large-scale transcriptomic profiling of the tumor immune microenvironment in *ALK*+ lung cancer.

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Background: Patients (pts) with *ALK*+ Non-Small Cell Lung Cancer (NSCLC) do not derive significant clinical benefit from immune checkpoint inhibitors. To better understand this lack of immunotherapy sensitivity, we aimed to characterize major immune components of the tumor microenvironment (TME) by comprehensive transcriptomic and immunohistochemistry (IHC) analyses. **Methods:** We analyzed NGS data from 5490 NSCLC pts that underwent DNA (592 Gene Panel, NextSeq, or WES, NovaSeq) and RNA (NovaSeq, WTS) sequencing at Caris Life Sciences (Phoenix, AZ). 374 *ALK*-rearranged cases were evaluated, along with 3169 *KRAS*-mut (*STK11*/*KEAP1*-wt) and 1947 *EGFR*-mut cases serving as comparators with known heterogenous and inert immune TMEs, respectively. PD-L1 (22C3) was evaluated by IHC. Immune cell fractions were inferred using quanTIseq. Gene expression profiles were analyzed for a T cell-inflamed signature (TIS) predictive of response to immunotherapy and for other immune modulatory genes such as *IFNG*, *GZMB*, *TGFB1*, and those of the adenosine pathway (*CD73/NT5E, CD39/ENTPD1, ADORA1, ADORA2A/B*). A significant difference between genomic subgroups was defined as fold-change > 1.2. In an independent cohort of 14 *ALK*+ NSCLC pts, density and spatial organization of CD4+ and CD8+ T cells, Tregs, major myeloid lineage cells, PDL1, and CD73 were assessed by quantitative IHC. **Results:** *ALK*+ tumors were associated with high PD-L1 ($\geq$50%) expression (40% vs 47% for *KRAS*-mut vs 18% for *EGFR*-mut, $p < 0.001$) and low TMB (median 3 mut/MB vs 9 for *KRAS*-mut vs 4 for *EGFR*-mut, $p < 0.001$). The abundance of CD8+ T cells (fold-change -1.3, $p < 0.001$), Tregs (fold-change -1.2, $p < 0.001$), M2 macrophages (fold-change 1.2, $p < 0.001$), and CD4+ T cells (fold-change 1.9, $p < 0.001$) differed from *KRAS*-mut; notably, similar to *EGFR*-mut. In *ALK*+ tumors, *IFNG* (fold-change -1.5, $p < 0.001$), *GZMB* (fold-change -1.6, $p < 0.001$), *TGFB* (fold-change -1.3, $p < 0.001$), *LAG-3* (fold-change -1.4 $p < 0.001$), *CD73/NT53* (fold-change -1.7 $p < 0.001$), and *ADORA2A* (fold-change -1.4, $p < 0.001$) were decreased while *ADORA1* (fold-change 1.3, $p < 0.001$) was increased compared to *KRAS*-mut. *EML4-ALK* comprised 94.7% of the ALK+ tumors and distribution of *EML4-ALK* variants was consistent with prior reports (e.g. v1 35.6%, v3 35.1%). Immune cell fractions and immune-related gene expression did not vary significantly between major variant subgroups (v1 vs non-v1, and v3 vs non-v3, $p > 0.05$). **Conclusions:** To our knowledge this is the largest transcriptomic analysis of the *ALK*+ NSCLC TME. Despite high levels of PD-L1, *ALK*+ tumors exhibit multiple features of an inert immune TME, primarily characterized by low TMB and decreased CD8+ T cells and immune activation markers. Our findings suggest that, while immunosuppressive factors such as M2 macrophages and adenosine signaling may also be targeted, strategies to enhance immunogenicity are critical for an effective immune response in *ALK*+ NSCLC. Research Sponsor: Lung Cancer Foundation of America and International Lung Cancer Foundation.

Tepotinib + osimertinib for *EGFR* mutant *(EGFR*m) NSCLC with *MET* amplification (*MET*amp) after first-line (1L) osimertinib.

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Background: *MET*amp is a common resistance mechanism developed in patients (pts) with *EGFR*m NSCLC treated with osimertinib. MET tyrosine kinase inhibitors (TKIs) such as tepotinib may be effective in treating these pts after osimertinib. Here we report interim data from the INSIGHT 2 study evaluating tepotinib + osimertinib in *EGFR*m NSCLC with *MET*amp previously treated with osimertinib. **Methods:** In this open-label Phase II study (INSIGHT 2, NCT03940703), pts with advanced *EGFR*m NSCLC with *MET*amp after progression on 1L osimertinib received tepotinib 500 mg (450 mg active moiety) + osimertinib 80 mg once daily. *MET*amp was centrally detected in tissue biopsy (TBx) by FISH (*MET* gene copy number [GCN] $\geq$5 and/or *MET*/*CEP7* $\geq$2) and/or in liquid biopsy (LBx) by NGS (*MET* plasma GCN $\geq$2.3; Archer). The primary endpoint was objective response by Independent Review Committee in tepotinib + osimertinib treated pts with centrally detected *MET*amp by FISH (FISH+). Efficacy data are reported for pts with $\geq$3 months' follow-up, and safety for all pts who received one dose of tepotinib + osimertinib by Sep 26, 2022 (data cut-off). **Results:** Among 472 pts prescreened, 451 pts had *MET*amp results by either TBx FISH and/or LBx NGS, of which 175 (38.8%) were positive for *MET*amp. 122 pts received tepotinib + osimertinib (median age 61 years [range 20–84], 59.8% female, 59.8% Asian, 68.0% never smoker, 72.1% ECOG PS 1). In 98 pts with FISH *MET*amp (29.6% had $<$ 12 months on 1L osimertinib; median GCN 11 [range 5.0–50.6]; mean $\pm$ SD sum of target lesion diameters [SOLD] 73.2 $\pm$ 47.1 mm), objective response rate (ORR) was 43.9% (95% CI 33.9, 54.3), median (m) DOR was 9.7 months (95% CI 5.6, ne), mPFS was 5.4 months (95% CI 4.2, 7.1), and mOS was not reached (95% CI 11.1, ne). Of the 98 pts, treatment is ongoing in 42 pts. In 31 pts with *MET*amp detected by LBx NGS, of which 24 were also FISH+ (mean $\pm$ SD SOLD 93.9 $\pm$ 51.4 mm), ORR was 51.6% (95% CI 33.1, 69.8), mDOR was 5.6 months (95% CI 2.9, ne), mPFS was 4.6 months (95% CI 2.7, 6.9), and mOS was not reached (95% CI 6.8, ne). Of 122 pts treated with tepotinib + osimertinib, any grade treatment-related AEs were reported by 99 (81.1%) pts including 34 (27.9%) Grade $\geq$3. Most common ($>$ 15% pts) treatment-related AEs included diarrhea 46.7% (0% Grade $\geq$3), peripheral edema 34.4% (4.1% Grade $\geq$3), paronychia 20.5% (0.8% Grade $\geq$3), decreased appetite 18.0% (3.3% Grade $\geq$3), and nausea 16.4% (1.6% Grade $\geq$3). Treatment-related AEs led to a dose reduction in 21 (17.2%) pts, following either or both treatments and led to treatment discontinuation in 7 pts (5.7%). **Conclusions:** In this interim analysis of INSIGHT 2, tepotinib + osimertinib was highly active with durable responses, and was well tolerated in pts with *EGFR*m NSCLC with *MET*amp after progression on 1L osimertinib. Tepotinib + osimertinib provides a potential chemotherapy-sparing oral targeted therapy option in this population with a high unmet need. Clinical trial information: NCT03940703. Research Sponsor: the healthcare business of Merck KGaA, Darmstadt, Germany.

9022 **Poster Discussion Session**

Circulating tumor DNA (ctDNA) dynamics and survival outcomes in patients (pts) with advanced non-small cell lung cancer (aNSCLC) and high (>50%) programmed cell death-ligand 1 (PD-L1) expression, randomized to cemiplimab (cemi) vs chemotherapy (chemo).

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Background: While ctDNA has emerged as a promising tool for monitoring response on therapy, there is a paucity of data from prospective, randomised Phase 3 studies to establish clear criteria for the clinical application of ctDNA. In the EMPOWER-Lung 1 study, first line (1L) cemi monotherapy improved overall survival (OS) vs platinum chemo in pts with aNSCLC, PD-L1 $\geq$50%, and no EGFR, ALK, or ROS1 aberrations and an acceptable risk/benefit profile. We performed personalized tumor-specific analysis of ctDNA from pts treated in the EMPOWER-Lung 1 study to determine the optimal time point and magnitude of ctDNA variation that are associated with OS and progression-free survival (PFS). **Methods:** Tumor tissue next-generation sequencing was performed to identify tumor-specific DNA variants. ctDNA levels were monitored using personalized pt specific probe sets (Natera, Foundation Medicine) in the plasma at baseline, end of week 3 (W3) and W9. Endpoints included overall response rate (ORR) complete or partial response (CR/PR), stable disease (SD) and progressive disease (PD) per RECIST 1.1, OS and PFS. Association between ctDNA decrease and clinical endpoints was tested in 3 groups of pts defined by sensitivity analysis: no-decrease, any decrease (molecular response, MR), and complete clearance (complete MR, cMR) of ctDNA. **Results:** ctDNA analysis was performed on samples from 175 pts (chemo n = 89; cemi n = 86). Baseline characteristics, ORR, OS, and PFS were comparable to those of the intention to treat population. At W9, cMR/MR was associated with clinical response to cemi (CR/PR: 97%, SD:58%, PD:17%), but not with clinical response to chemo, as it was detected in the majority of chemo pts across all RECIST categories (CR/PR: 100%, SD:90%, PD:80%). In the cemi arm, ctDNA cMR was associated with the longest survival, with median OS (mOS) not-reached compared to pts with MR (mOS of 29 months) and pts with no-decrease (mOS of 8 months), as well as statistically significant hazard ratios (cMR vs MR: W9 HR = 8, 95% CI 1.8-35, p = 0.0056; cMR vs no-decrease: W9 HR = 25, 5.7–110, p = 0.000021 and W3 HR = 5.9, 1.4-25, p = 0.017). Delayed MR/cMR (i.e., MR/cMR at W9 but not at W3) was observed in 8/66 pts (12%), and transient MR (i.e., MR at W3 but not W9) in 9/66 pts (14%), with available ctDNA data at both timepoints. **Conclusions:** This is the largest data set to date correlating ctDNA levels with efficacy outcomes from a randomized clinical trial comparing chemo with immunotherapy in 1L aNSCLC. The results indicate that lack of treatment-induced decrease in ctDNA may identify pts with inferior OS benefit from cemi monotherapy as early as 3 weeks following initiation of therapy and can inform future use of early ctDNA response assessment in prospective interventional studies. Clinical trial information: NCT03088540. Research Sponsor: Regeneron Pharmaceuticals, Inc. and Sanofi.

LBA9023 **Poster Discussion Session**

First-line (1L) nivolumab (N) + ipilimumab (I) + chemotherapy (C) vs C alone in patients (pts) with metastatic NSCLC (mNSCLC) from CheckMate 9LA: 4-y clinical update and outcomes by tumor histologic subtype (THS).

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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, 2023, issue of the *Journal of Clinical Oncology*.

9024 **Poster Discussion Session**

Safety and clinical activity of target-preserving anti-CTLA-4 antibody ONC-392 as monotherapy in NSCLC patients who progressed on PD(L)1-targeted immunotherapy.

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Background: PD-1 or PD-L1 inhibitors have transformed clinical care of NSCLC patients. However, many patients may develop primary or secondary resistant to PD-(L)1 inhibitors. The marketed anti-CTLA-4 mAbs are ineffective as monotherapy for NSCLC. ONC-392 is a novel target-preserving anti-CTLA-4 antibodies that confers immunotherapeutic effect by selective depletion of regulatory T cells (Treg) in the tumor microenvironment. Preclinical studies show that ONC-392 is more effective and less toxic for immunotherapy than other clinically used anti-CTLA-4 antibodies. In first-in-human study in patients with advanced solid cancer, the recommended Phase 2 dose (RP2D) for ONC-392 monotherapy was established as 10 mg/kg. In this study, we tested safety and clinical activities of ONC-392 in NSCLC patients who progressed on PD(L)1-targeted therapy. **Methods:** Anti-PD-(L)1 resistant NSCLC patients were enrolled as parts of PRESERVE-001 studies (NCT04140526) expansion cohort Part C Arm I and treated with 2 cycles of 10 mg/kg, followed by 6 mg/kg, q3w, ONC-392 by IV infusion. Safety was evaluated based on treatment emergent and treatment-related adverse events, while efficacy was evaluated by investigators using RECIST1.1 criteria. **Results:** As of December 18, 2022, 33 NSCLC patients have received at least one dose of ONC-392 at 10 mg/kg. The median age is 66 yrs (range 43 - 89 yr), 61% male. 61% were non-squamous cell carcinoma and 39% were squamous cell carcinoma. 27% are ECOG score 0 and 73% were ECOG score 1. The median prior treatment was 2 cycles (range 1 to 4). The average ONC-392 treatment period was 3.5 cycles (range 1 to 13 cycles). Overall, the patients with TRAE in grade 3 or above is 33% (11/33), including diarrhea/colitis (3, 9%), AST/ALT increase or hepatitis (3, 9%), muscular weakness (2, 6%), nephritis (1, 3%), adrenal insufficiency (1, 3%). Due to pace of enrollment, efficacy data are available in 22 patients. 6 of 22 evaluable patients have partial response and 12 patients have stable disease per RECIST 1.1, resulting in a response rate of 27% and disease control rate of 82% among evaluable patients. The median follow-up period for all patients is 5.8 months and 8.6 months for 20 alive patients (range 2.9 to 14.1 months). The estimated 6- and 12-month overall survival (OS) rates were 65% and 55%. Median OS has not reached. **Conclusions:** Overall, ONC-392 monotherapy with 10 mg/kg is safe and tolerable. Onc-392 monotherapy has showed encouraging anti-tumor activity in IO-resistant NSCLC when compared with historical data. Based on these encouraging data, we have initiated a Phase 3 study testing ONC-392 monotherapy among NSCLC who progressed on PD(L)1-targeting immunotherapy (NCT05671510). Clinical trial information: NCT04140526. Research Sponsor: OncoC4, Inc.; U.S. National Institutes of Health.

9025 **Poster Discussion Session**

SI-B001 plus chemotherapy in patients with locally advanced or metastatic EGFR/ALK wild-type non-small cell lung cancer: A phase II, multicenter, open-label study.

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Background: SI-B001 is a first-in-class novel EGFR×HER3 bispecific antibody. The objective of this phase II study was to investigate the efficacy and safety of SI-B001 in combination with chemotherapy in pts with locally advanced or metastatic EGFR/ALK wild-type NSCLC. **Methods:** This phase II study enrolled patients with locally advanced or metastatic EGFR/ALK wild-type NSCLC who had failed first-line anti-PD-1/L1 therapy, with or without platinum-based chemotherapy (PBC). This study consisted of three cohorts: In Cohort A pts received SI-B001 plus PBC as second-line treatment after failure to first-line anti-PD-1/L1 antibody monotherapy; Cohort B pts received SI-B001 plus docetaxel as second-line treatment after failure to first-line anti-PD-1/L1 therapy plus PBC; Cohort C pts received SI-B001 plus docetaxel as third-line or higher treatment after failure to first-line anti-PD-1/L1 therapy and PBC. This study evaluated SI-B001 in three distinct dosing schedules: Schedule 1 (16+9mg/kg once weekly), Schedule 2 (14mg/kg on Days 1 and 8 every 3 weeks), and Schedule 3 (21+12mg/kg once weekly). The primary endpoints of the study were to determine the objective response rate (ORR) in evaluable patients and to identify the optimal dose. The secondary endpoints included assessment of progression-free survival (PFS), disease control rate (DCR), duration of response (DOR), and safety. **Results:** As of November 11, 2022, 55 pts have been enrolled in the study, including 1 pt in Cohort A, 45 pts in Cohort B, 8 pts in Cohort C, and one pt enrolled based on the investigator's discretion. Of the 55 pts, 48 were evaluable for efficacy; ORR (n/N, [95%CI]) of 31.3% (15/48, [18.7, 46.3]), DCR of 77.1% (37/48, [62.7, 88.0]). In Cohort B, 23 pts were enrolled in schedule 1, 21 pts were enrolled in schedule 2, and 1 pt was enrolled in schedule 3. Of the 45 pts enrolled in Cohort B, 38 were evaluable for efficacy. Among 22 evaluable pts in schedule 1 the ORR was 45.5% (10/22, [24.5, 67.8]) and the DCR was 68.2% (15/22, [45.1, 86.1]). 18 out of the 22 had no actionable genomic alterations (AGA), the ORR was 50.0% (9/18, [26.0, 74.0]), the DCR was 72.2% (13/18, [46.5, 90.3]), and the mPFS has not been reached. The most common grade ≥3 treatment-related adverse events (TRAEs) were myelosuppression (17%), decreased neutrophil count (15%), and decreased white blood cell count (12%). There was no drug-related death. **Conclusions:** SI-B001 plus docetaxel demonstrated antitumor activity in locally advanced or metastatic NSCLC EGFR/ALK wild-type pts who failed on prior first-line anti-PD-1/L1 antibody plus PBC, especially without AGA. The toxicity of SI-B001 + docetaxel was manageable. These findings support the continued investigation of SI-B001 and docetaxel as a treatment option in NSCLC. Clinical trial information: NCT05020457. Research Sponsor: Sichuan Baili Pharmaceutical Co., Ltd.

9026 **Poster Session**

Large-scale comparative analysis of clinico-genomic characteristics, treatment outcomes and resistant mechanisms of *ALK/ROS1/RET*-rearranged non-small cell lung cancer (NSCLC) in a nationwide genomic screening project (LC-SCRUM-Asia/TRY).

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Background: There is limited understanding of the clinico-genomic differences among *ALK/ROS1/RET*-rearranged NSCLC due to their low frequency. We aimed to characterize these fusions using a large-scale LC-SCRUM-Asia/TRY database. **Methods:** We conducted a prospective screening of treatment-naïve and refractory lung cancer to identify genomic alterations using RT-PCR and/or targeted next-generation sequencing (NGS) assays in LC-SCRUM-Asia/TRY. We compared clinico-genomic characteristics, treatment outcomes and resistant mechanisms among *ALK/ROS1/RET*-rearranged NSCLC. **Results:** Between February 2013 and December 2022, 18,616 lung cancer patients (pts) were enrolled in LC-SCRUM-Asia/TRY and 16,583 were NSCLC pts. *ALK/ROS1/RET* fusions were identified in 430 (2.6%)/240 (1.4%)/202 (1.2%) pts in NSCLC. The patient characteristics were as follows (*ALK/ROS1/RET*): median age, 58/60/63 years; females, 53/54/54%; never-smokers, 57/55/59%; adenocarcinoma, 93/95/96%. The frequencies of brain metastasis at diagnosis were 26/20/19% ($p = 0.15$). Among pts tested by NGS, the frequencies of *TP53*, *TET2* and *NOTCH1* mutations were lower in *ALK* than in *ROS1* and *RET* (*TP53*; 23/34/27%, *NOTCH1*; 17/34/35%, *TET2*; 17/30/32%). Overall survival (OS) was significantly longer in *ALK* than in *ROS1* (mOS [*ALK/ROS1/RET*] 108.8 vs. 43.6 vs. not reached [NR] months, *ALK* vs. *ROS1*; $p < 0.01$, *ALK* vs. *RET*; $p = 0.04$) among stage IV pts underwent TKI therapy. *TP53* mutation was associated with shorter OS in all three fusions (mOS [*TP53* mt+/mt-] *ALK*; 35.7 vs. 108.8, $p < 0.01$, *ROS1*; 26.4 vs. 47.4, $p = 0.06$, *RET*; 28.9 vs. 76.1 months, $p = 0.05$), shorter PFS with first line alectinib in *ALK* (mPFS [*TP53* mt+/mt-] 11.0 vs. 38.4 months, hazard ratio [HR] 2.5 [95% CI, 1.5-4.2], $p < 0.01$) and shorter PFS with initial crizotinib in *ROS1* (mPFS [*TP53* mt+/mt-] 5.8 vs. 25.2 months, HR 2.6 [95% CI, 1.3-4.8], $p < 0.01$). There was no significant difference in PFS with first-line platinum plus pemetrexed among fusions (mPFS 12.6 vs. 10.7 vs. 9.2 months) and PFS with initial immune checkpoint inhibitors among fusions (mPFS 3.9 vs. 5.1 vs. 3.0 months). Among 60/13/10 re-biopsy samples refractory to TKI, on-target resistant mutations were identified in 14 (23%) /3 (23%) /1 (10%) samples. **Conclusions:** Pts with *ALK/ROS1/RET*-rearranged NSCLC shared similar characteristics, but the occurrence of concomitant mutations was lower in *ALK* than in *ROS1* and *RET*. *TP53* mutation was associated with worse prognosis in pts with *ALK/ROS1/RET*-rearranged NSCLC. Among those received TKI, pts with *ALK*-rearranged NSCLC had better prognosis than those with *ROS1* and *RET*-rearranged NSCLC. The development of highly effective molecular targeted therapies for *ROS1*- and *RET*-rearranged NSCLC is warranted. Research Sponsor: None.

9027 **Poster Session**

The genomic, transcriptomic, and immunological landscape of SGLT2 in lung cancer.

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Background: Retrospective data suggest that SGLT2 inhibitors, commonly used in diabetes, are associated with a lower incidence of cancer development and *in vivo* data indicate SGLT2 plays a role in the development of NSCLC. We investigated the genomic and immunological landscape of NSCLC [adenocarcinoma (AC) or squamous cell carcinoma (SCC) histology] with high and low expression of the SGLT2-coding gene *SLC5A2* and the relationship with clinical outcomes. **Methods:** NSCLC tumors of AC (N = 11,725) or SCC (N = 4,158) histology were tested at Caris Life Sciences (Phoenix, AZ) with NextGen Sequencing on DNA (592 genes or whole exome) and RNA (whole transcriptome). PD-L1 expression (22C3; Positive (+): TPS $\geq$1%) was assessed by IHC. High tumor mutational burden (TMB-H) was defined as $\geq$10 mutations/MB. Mutations were defined as pathogenic SNVs/indels. *SLC5A2*-H and -L expression (transcripts per million) was defined as top and bottom quartile, respectively. A transcriptomic signature predictive of response to immunotherapy was applied (T cell-inflamed). The Mann-Whitney U test was applied as appropriate, with P-values adjusted for multiple comparisons ($p < .05$). Real-world overall survival (OS) data was obtained from insurance claims and Kaplan-Meier estimates were calculated for molecularly defined subpopulations of patients (N = 13,505). **Results:** In AC tumors, *SLC5A2*-H was associated with higher rates of *EGFR* (20.8 vs 13.5%, $p < .05$) and *STK11* mutations (20.1 vs 12.9%, $p < .05$), but lower rates of *TP53* (50.8 vs 69.5%, $p < .05$) and *ARID1A* (8.7 vs 4.6%, $p < .05$) mutations. There was no significant difference in the *KRAS* mutation rate (35.6 vs 37.1%, $p = 1$). AC and SCC *SLC5A2*-H tumors had a lower prevalence of PD-L1+ (AC: 47 vs 68%, SCC: 50 vs 67%, $p < .05$). AC *SLC5A2*-H tumors had a lower prevalence of TMB-H (30 vs 39%, $p < .05$), but not in SCC (40 vs 41%, $p = .6$). *SLC5A2*-H tumors were associated with a higher prevalence of T cell-inflamed tumors (AC: 40 vs 19%, SCC: 33 vs 11%, $p < .05$). *SLC5A2*-H AC had longer OS as compared to *SLC5A2*-L AC tumors (HR = 0.787 [.73-.85], $p < .001$) but no significant difference in time on treatment (TOT) with pembrolizumab was observed (HR .90 [.78-1.03], $p = .13$). *SLC5A2*-H SCC tumors had significantly longer OS (HR .88, [.78-1.00], $p = .045$) and they had significantly longer TOT with pembrolizumab (HR .72 [.56-.94], $p = .01$). Finally, *SLC5A2*-H, *KRAS* mutant AC tumors had significantly longer OS (HR .64 [.57-.73], $p < .001$) whereas *SLC5A2*-H KRAS mutant SCC tumors (HR 1.46 [.83-2.57], $p = .19$) trended towards shorter OS. **Conclusions:** *SLC5A2* expression was associated with a highly altered genomic landscape in AC. In specific mutational and histological subgroups, differences in *SLC5A2* expression were associated with OS and responsiveness to immunotherapy. These mutational and histological subtypes should be further investigated as research on SGLT2 inhibitors progresses. Research Sponsor: None.

9028 **Poster Session**

Peripheral myeloid cells as prognostic markers in patients (pts) with non-small cell lung cancer (NSCLC) treated with cemiplimab: Pooled analysis of EMPOWER-Lung 1 and EMPOWER-Lung 3 phase 3 trials.

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Background: Circulating innate and adaptive immune cells can modulate clinical responses to immune checkpoint inhibition in pts with cancer; however, there are no clear validated baseline clinical tests to guide clinicians, outside of programmed cell death-ligand 1 (PD-L1) IHC tests on limited biopsy specimens. High neutrophil/lymphocyte ratio (NLR) is associated with poor prognosis in NSCLC, but data are limited on the potential contribution of other immune cells such as monocytes and eosinophils in modulating systemic immune response. Further, previous correlative studies have not established clinically actionable immune cell cut-off values. **Methods:** We used multiple quantitative analytic methods including multivariable Cox regression and conditional decision trees to assess the prognostic importance of NLR and peripheral myeloid cells, including monocytes and eosinophils, in pts with NSCLC treated with cemiplimab in Phase 3 trials EMPOWER-Lung 1 (NCT03088540) and EMPOWER-Lung 3 (NCT03409614). In EMPOWER-Lung 1, pts with PD-L1 $\geq$50% were randomized 1:1 to cemiplimab 350 mg every 3 weeks (Q3W) or platinum-based chemotherapy (chemo). EMPOWER-Lung 3 was a 2-part study. In Part 1, pts with PD-L1 $<$ 50% were randomized 1:1:1 to chemo, cemiplimab 350 mg Q3W + chemo, or cemiplimab 350 mg Q3W + ipilimumab 50 mg Q6W + chemo. In Part 2, pts were randomized 2:1 to receive cemiplimab 350 mg or placebo Q3W + chemo. **Results:** Overall, 691 pts in EMPOWER-Lung 1 and 769 pts in EMPOWER-Lung 3 were included in this analysis. The results showed significant association between multiple factors including NLR and overall survival (OS) and progression-free survival (PFS). For pts with NLR $>$ 3.98 vs $\leq$3.98, median OS (95% CI) was 10 (9–13) vs 20 (17–24) months (HR: 2.04; 95% CI: 1.60–2.61; $P<$ 0.001) and median PFS (95% CI) was 4 (4–6) vs 6 (6–7) months (HR: 1.80; 95% CI: 1.50–2.18; $P<$ 0.001), respectively, accounting for known prognostic factors. In multivariable analyses, monocytes (OS HR: 1.72; 95% CI: 1.29–2.30; $P<$ 0.001; PFS HR: 1.37; 95% CI: 1.08–1.75; $P=$ 0.010) and log eosinophils (OS HR: 0.90; 95% CI: 0.85–0.97; $P=$ 0.003; PFS HR: 0.93; 95% CI: 0.88–0.98; $P=$ 0.004) were significantly associated with OS and PFS in both studies. (Neutrophil + monocyte)/lymphocyte ratio was the top predictor of both OS and PFS in decision tree analysis. Peripheral blood cell count correlations were not affected by tumor PD-L1 levels ($\rho < 0.15$ for all markers). **Conclusions:** This is a large and comprehensive prognostic analysis of data from two prospective Phase 3 clinical trials in advanced NSCLC. Clinically actionable peripheral blood cell count parameters, incorporating putative immunosuppressive myeloid cells (neutrophils and monocytes) and protective lymphocytes and eosinophils, may help predict response to anti–PD-1 therapy in advanced NSCLC. Clinical trial information: NCT03088540, NCT03409614. Research Sponsor: Regeneron Pharmaceuticals, Inc., and Sanofi.

9029 **Poster Session**

Impact of *EML4-ALK* fusion variant and co-occurring *TP53* mutation on treatment duration of first-line next-generation ALK TKIs in *ALK* fusion+ NSCLC.

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Background: Molecular biomarkers such as *EML4-ALK* fusion variant 3 (V3) and *TP53* mutation are associated with poor prognosis in patients (pts) with anaplastic lymphoma kinase fusion positive (*ALK*+) non–small cell lung cancer (NSCLC). We evaluated the effect of *EML4-ALK* fusion variants and *TP53* mutation status on time to treatment discontinuation (TTD) of first-line (1L) treatment with a next-generation ALK tyrosine kinase inhibitor (TKI) in pts with *ALK+* NSCLC in the real-world setting. **Methods:** Pts with advanced/metastatic NSCLC who were *ALK*+ in circulating tumor DNA by Guardant360 (G360) liquid biopsy test from Jan 1, 2018, to Dec 31, 2021, and received 1L monotherapy with a next-generation ALK TKI (alectinib, brigatinib, ceritinib, lorlatinib) were identified in the Guardant INFORM clinical-genomics database. Median TTD of 1L ALK TKI treatment was determined by Kaplan-Meier (KM) methods. The impact of *EML4-ALK* fusion variant and *TP53* mutation status on TTD was evaluated. **Results:** Database search identified 495 pts with advanced/metastatic NSCLC who had *ALK* fusion by G360; of these, 214 pts received 1L treatment with a next-generation ALK TKI; 164 had G360 testing before treatment (alectinib, n=147; brigatinib, n=7; ceritinib, n=2; lorlatinib, n=8). Among these 164 pts, median age was 58.6 y, 53% were female, and 29% had baseline brain metastases. Median follow-up from start of 1L treatment was 14.8 mo. Median TTD was 19.6 mo (95% CI: 13.6–not reached [NR]). *TP53* mutations were detected in 66 pts (40%). Median (95% CI) TTD in pts with *TP53* mutation vs WT was 17.1 (9.5–28.5) vs 21.9 mo (14.3–NR; log-rank *P*=0.1712). Of 130 pts with *EML4-ALK* fusion variant type detected, 63 (48%) had V1, 54 (42%) V3, 8 (6%) V2, 4 (3%) V5, and 1 (1%) V8. In pts with *EML4-ALK* fusion V1 vs V3, median (95% CI) TTD was 19.0 (13.6–NR) vs 21.8 mo (8.7–NR; HR: 0.73; log-rank *P*=0.3039), with the KM plot showing numerically longer TTD in pts with V1 vs V3 during the first 18 mo and lines crossing at the tail end. Of 117 pts with both an *EML4-ALK* fusion variant (V1/V3) and *TP53* data, 21 (18%) had both V3 and a *TP53* mutation. Pts with co-occurring *EML4-ALK* V3 and *TP53* mutation had the shortest TTD (median TTD 8.7 [3.9–NR; HR: 2.59; *P*=0.0219]; Table). **Conclusions:** Among pts with NSCLC and *ALK* fusion, co-occurrence of *EML4-ALK* V3 and *TP53* mutation is common and associated with poor prognosis and high risk of early discontinuation of 1L treatment with a next-generation ALK TKI, most likely due to disease progression. Additional novel or combination therapies are warranted for this subpopulation. Research Sponsor: Takeda Development Center Americas, Inc., Lexington, MA, USA.

	n[a]	Median TTD (95% CI), mo	HR (95% CI)	*P* value
***EML4-ALK* V1 and *TP53* WT**	38	19.5 (11.4–NR)	Reference	
***EML4-ALK* V1 and *TP53*+**	25	19.0 (9.5–NR)	1.01 (0.42–2.44)	0.9849
***EML4-ALK* V3 and *TP53* WT**	33	NE (9.4–NR)	0.89 (0.38–2.09)	0.7873
***EML4-ALK* V3 and *TP53*+**	21	8.7 (3.9–NR)	2.59 (1.15–5.84)	0.0219

[a] 117 pts had data for both *TP53* and *EML4-ALK* V1 or V3.

9030 **Poster Session**

Real-world testing and treatment patterns among patients with stage IV non-small cell lung cancer: A retrospective observational study.

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Background: Guidelines (NCCN, CAP/IASLC/AMP) recommend clinical molecular testing of patients with advanced NSCLC to inform therapy decisions. We investigated the testing and treatment patterns of patients with stage 4 NSCLC treated in the real-world setting. **Methods:** This retrospective observational study included de-identified stage 4 NSCLC patients from the Integra Connect PrecisionQ database (ICD) enriched with information obtained by curation. Patients with a positive mutation for EGFR, ALK, ROS1, BRAF, MET, RET, HER2, or NTRK and who initiated treatment for stage 4 NSCLC between 01/01/2018 and 12/31/2021 were included with follow-up through 05/31/2022. Also included were demographics, ECOG score, time of ordering test, and date of death. Genomic test data were classified by method and type of test. Overall survival (OS) was calculated using Kaplan-Meier curves and data are presented using descriptive statistics. **Results:** Of 5195 patients in the ICD with stage 4 NSCLC, 3532 patients initiated first line of therapy (LOT1), and 2899 had somatic molecular testing ordered, specifically via tissue-based next-generation sequencing (NGS, 30%), plasma-based NGS (26%), or non-NGS methods (44%). A total of 934 patients tested positive for a driver mutation at any time during the study observation period, and 671 patients (72%) had test results available before initiating treatment. Of those treated after receiving biomarker results, 407 (61%) initiated treatment with a tyrosine kinase inhibitor (TKI), 43 (6%) with chemotherapy (chemo), 156 (23%) with chemo + immuno-oncology (IO), and 65 (10%) with IO. The median OS (95% confidence interval [CI]) was 24.46 (21.90-29.18) months for patients treated with TKI and 14.2 (11.6-16.5) months for patients treated without TKI (unadjusted hazard ratio [95% CI], 1.56 [1.26, 1.92]; $P < 0.001$). **Conclusions:** Among patients with stage 4 NSCLC treated in the real-world setting, patients treated with TKI after receiving test results had better overall survival than patients treated without TKI. While subject to the limitations of a retrospective observational real-world data study, this study suggests that, with regard to utilizing genomic testing and appropriate selection of targeted treatment, adherence to treatment guidelines may improve patient outcomes. As new targeted agents continue to emerge in NSCLC, these data encourage utilization of genomic testing data to guide treatment selection. We acknowledge the significant contributions of our dear friend, Dr. Robert E. Smith, whose cheerful enthusiasm and deep expertise were a driving force of this work. Research Sponsor: Thermo Fisher.

9031 **Poster Session**

MSH3 and MSH6 gene polymorphisms: Association with lung cancer susceptibility and prognostic value in patients with NSCLC undergoing platinum-based chemotherapy.

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Background: DNA mismatch repair (MMR) pathway is responsible for recognizing and repairing errors (insertion, deletion and misincorporation of bases) occurring during DNA replication and recombination. Single nucleotide polymorphisms (SNPs) in *MSH3* and *MSH6* genes are related to development of various cancers. SNPs of particular interest include rs26279 G > A polymorphism for *MSH3* and rs3136228 557G > T polymorphism for *MSH6*. In this cohort study, we evaluated the association of *MSH3* (rs26279) and *MSH6* (rs3136228) SNPs with occurrence of lung cancer (LC), baseline demographic and clinical characteristics and with overall survival (OS) amongst LC patients undergoing platinum-based doublet chemotherapy. **Methods:** 500 LC patients and 500 healthy controls were enrolled. Genomic DNA was isolated from 4ml of peripheral blood using a phenol-chloroform extraction procedure and genotyping of patients and controls was performed using PCR-RFLP. All enrolled patients had pathologically confirmed LC. Written informed consent was obtained from all enrolled subjects and the study was approved by institutional ethics committee. Odds ratio (OR) and 95% confidence intervals (CIs) were calculated using logistic regression analysis. Kaplan-Meier method was used for OS analysis and (multivariate) Cox regression models to obtain (adjusted) hazards ratios (HRs). **Results:** Mean age (61 years) was similar for cases and controls. Compared to controls, LC cohort had higher prevalence of non-smokers (20% vs. 10%), female sex (20% vs. 9%) and smoking pack-years (mean 20.8 vs. 13.8). Majority of LC patients had metastatic disease (54%) and ECOG performance status of 0-1 (45%) or 2 (40%). Adenocarcinoma and squamous were equi-prevalent (41% each). Mutant genotype (TT) for *MSH6* polymorphism was more frequent in LC patients (OR = 1.43; 95% CI = 1.01 – 2.03; p = 0.03) with the association more marked in adenocarcinoma histology (OR = 1.74; 95% CI = 1.05 – 2.93; p = 0.03). For non-smokers, mutant genotype (TT) for MSH6 polymorphism was associated with a 3-fold increased risk of LC (OR = 3.22; 95% CI = 1.26 – 8.18; p = 0.01). Amongst females, heterozygous genotype (GA) for *MSH3* polymorphism was more frequent amongst LC cases (24%) than controls (16%) (OR = 2.35, 95% CI = 0.85 – 6.52, p = 0.04). Patients treated with docetaxel-platinum chemotherapy and carrying heterozygous (GT) genotype for MSH6 polymorphism had worse OS (median 4.9 vs 9.1 months; adjusted HR = 2.3; p = 0.03). No association was observed between *MSH3* (rs26279) and *MSH6* (rs3136228) polymorphisms and other baseline clinical/demographic characteristics. **Conclusions:** The results of this cohort study suggest that *MSH3* and *MSH6* polymorphisms are involved in modulating the risk towards LC occurence. *MSH6* polymorphism is also associated with higher mortality amongst patients treated with docetaxel-platinum chemotherapy. Research Sponsor: None.

9032 **Poster Session**

Impact of genomic alterations measured in circulating tumor DNA (ctDNA) on clinical response to telisotuzumab vedotin treatment in patients with non-small cell lung cancer (NSCLC).

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Background: The antibody-drug conjugate telisotuzumab vedotin (Teliso-V) is composed of the c-Met–targeting antibody telisotuzumab (ABT-700) linked to the microtubule inhibitor monomethyl auristatin E. In the LUMINOSITY study (NCT03539536), efficacy of Teliso-V was seen in patients (pts) with *EGFR* wildtype nonsquamous NSCLC and c-Met overexpression (≥25% tumor cells at 3+ intensity by IHC); overall response rate: 36.5%. Data are limited on whether specific driver oncogene states affect responses. We investigated genomic alterations in relation to response to Teliso-V in this population. **Methods:** Pts received 1.9 mg/kg Teliso-V monotherapy once every 2 weeks in LUMINOSITY. ctDNA was isolated from plasma collected at different timepoints. The PGDx elio plasma complete assay was used to identify genomic alterations in ctDNA samples. This assay included 521 genes for single nucleotide variants and insertion-deletion mutations, 38 for amplifications (amp), and 21 for translocations. **Results:** In total, 52 pts were included in the study; ctDNA from 48 pts was analyzed. The overall response rate among pts with ctDNA results was 37.5% (18 pts with partial response) compared with 36.5% for the ITT population of 52 pts. Genomic alterations are listed in the Table.Three out of 4 pts with *MET* amp at baseline responded, accounting for 17% of total responses. The observed *MET* amp frequency in this *MET* IHC preselected cohort was 8%, which is similar to the prevalence observed in tissue analysis by FISH. Of note, 1 nonresponder harbored a *MET* ex14del mutation at baseline, and a responder had a low-frequency mutation detected at the final visit. Mutations in *KRAS* were the most common genomic alteration and were detected in 13 (27%) pts at baseline. Three pts with a *KRAS* mutation were responders; among these, 2 out of 3 had a *KRAS* G12C mutation (seen in 3 pts total). Response rates were higher in pts with *MET* amp (75%; 95% CI: 0.30, 0.95) vs those without *MET* amp (34%; 0.22, 0.49), and higher in pts without *KRAS* mutations (43%; 0.28, 0.59) vs those with *KRAS* mutations (23%; 0.08, 0.50); however, confidence intervals were wide and larger sample sizes are needed. **Conclusions:** *MET* amp occurred more frequently in responders; however, Teliso-V activity was not restricted to these pts, as most responders were not *MET* amplified. Specific genomic alterations beyond *MET* may influence clinical response. The current analysis demonstrated numeric differences between pts with identified drivers who did or did not respond to Teliso-V. Additional research on this topic is needed in larger pt cohorts and/or with tissue-based NGS analyses. Research Sponsor: AbbVie Inc.

Genomic alterations at baseline.

n (%)	Responders n = 18	Nonresponders n = 30
Amplification		
MET	3 (17)	1 (3)
Translocations		
RET	2 (11)	0
ALK	0	1 (3)
FGFR1	0	1 (3)
ROS1	0	1 (3)
Mutations		
KRAS	3 (17)	10 (33)
***MET* ex14del**	0	1 (3)
BRAF	0	1 (3)

9033 **Poster Session**

Analytical and clinical validation of oncomine Dx target (ODxT) test and local testing for identifying patients with HER2 (*ERBB2*)-mutant (HER2m) non–small-cell lung cancer (NSCLC) for treatment with trastuzumab deruxtecan (T-DXd) in DESTINY-Lung01/02 (DL-01/02).

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Background: Based on the international DL-01 trial, the US Food and Drug Administration (FDA) approved the ODxT Test as a companion diagnostic (CDx) to identify patients (pts) with NSCLC harboring activating HER2 mutations who may benefit from T-DXd. The ODxT Test uses next-generation sequencing (NGS) to detect genomic alterations in formalin-fixed, paraffin-embedded tumor tissue. The accuracy of the ODxT Test by central testing and its agreement with clinical trial assays (CTAs; NGS, polymerase chain reaction, etc.) by local testing was evaluated using analytical and clinical validation data from DL-01 cohort 2 and DL-02 arm 1. **Methods:** ODxT Test and Illumina TruSight Tumor170 NGS assay results were compared for analytical accuracy in NSCLC samples from DL-01 and commercial vendors. Diagnostic agreement was assessed for DL-01/02 by concordance between the ODxT Test and CTAs. Clinical accuracy per objective response rate (ORR) and duration of response (DoR) to T-DXd were evaluated in all pts with HER2m NSCLC identified by ODxT Test vs CTA. Activating HER2 mutations included single nucleotide variants and exon 20 insertions. Pts received T-DXd 6.4 mg/kg in DL-01 or 5.4 mg/kg (FDA-approved dose) in DL-02 every 3 weeks. **Results:** NSCLC samples from DL-01 (n = 91), DL-02 (n = 102), and commercial vendors (n = 129) were individually assessed. The ODxT Test met requirements for analytical accuracy (≥90% agreement when excluding unknown results), with a positive percent agreement (PPA) of 100% and negative percent agreement (NPA) of 99.1% for detecting HER2 mutations. Clinical accuracy of the ODxT Test also met FDA requirements (excluding unknowns) for NPA (≥98%) and PPA (95% CI lower bound ≥85%). DL-01 PPA (95% CI) was 98.0% (89.2%-100%) and NPA was 100.0% (96.6%-100%); for DL-02, PPA was 96.7% (88.7%-99.6%) and NPA was 100% (96.6%-100%). In DL-01, confirmed ORR (95% CI) for pts with HER2m NSCLC identified by central ODxT Test was 58.3% (43.2%-72.4%) vs 54.9% (44.2%-65.4%) of pts identified by local CTA; median DoR (95% CI) was 12.0 mo (5.5 mo-18.2 mo) per the ODxT Test vs 9.3 mo (5.7 mo-14.7 mo) per CTA. In DL-02 (prespecified interim analysis early cohort), ORR (95% CI) was 53.6% (33.9%-72.5%) per ODxT Test vs 53.8% (39.5%-67.8%) per CTA; median DoR (95% CI) was not estimable (NE [NE-NE]) per the ODxT Test and NE (4.2 mo-NE) per CTA. **Conclusions:** This study demonstrates the analytical and clinical accuracy of the ODxT Test as a CDx for detecting activating HER2 mutations in NSCLC to identify pts who may benefit from T-DXd. A high level of agreement was also shown between the ODxT Test and CTAs. Clinical trials for HER2m NSCLC may successfully use a central testing assay as a CDx while allowing adequately validated local testing assays to expedite patient enrollment. Clinical trial information: NCT03505710, NCT04644237. Research Sponsor: Daiichi Sankyo, Inc and AstraZeneca.

9034 **Poster Session**

Molecular characterization of resistance to immune checkpoint inhibitor and chemotherapy treatment in advanced non-small cell lung cancer.

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Background: Non-small cell lung cancer (NSCLC) is the most common type of lung cancer and a leading cause of cancer death. Standard of care (SOC) treatment for advanced NSCLC patients include immune checkpoint inhibitors (ICI) and/or chemotherapy (CT). However, the majority of patients do not respond to SOC therapy. Mechanisms of resistance and how they differ across treatments are not fully understood. We characterized molecular markers of resistance for advanced NSCLC patients with ICI monotherapy, CT, or combination ICI-CT. **Methods:** Advanced stage III or IV NSCLC patients with adenocarcinoma histology who received at least 21 days of ICI monotherapy, CT, or combination ICI-CT were identified from a de-identified, multimodal real-world database from Tempus Labs, Inc. All patients had a tissue biopsy taken within 100 days prior to the specified therapy start and all samples underwent next generation sequencing with the Tempus xT assays (DNA-seq of 596-648 genes at 500x coverage and whole transcriptome RNA-seq). Resistance to therapy was defined as having time to next treatment $<$ 90 days, or disease progression or death within 120 days of therapy initiation. We characterized the clinical and molecular characteristics of patients and compared differential expression of genes by resistance status for each cohort. **Results:** A total of 365 patients were included in the study (ICI = 121, CT = 122, ICI-CT = 122). Across cohorts, 30% of patients were identified as having resistance to treatment (ICI = 35%, CT = 23%, ICI-CT = 32%). 53% of patients were $>$ 65 years (median [range] = 67 [25- 88]), and 53% were males. Most patients were white (63%) and had a history of tobacco use (85% current or former smoker). At the time of biopsy, most patients were diagnosed with metastatic NSCLC (Stage IV = 73%) and had received no previous lines of therapy (92%). The alteration frequencies of known NSCLC oncogenic driver mutations including TP53 (65%), KRAS (42%), STK11 (14%), KEAP1 (11%), and EGFR (9%) were broadly consistent with previous characterizations of NSCLC. Validated biomarkers of response to ICI treatment such as Tumor Mutation Burden, IFN-γ signaling, PD-1, and PD-L1 expression were negatively associated with resistance to ICI treatment. Across the ICI, ICI-CT, and CT cohorts, 253, 153, and 178 genes, respectively, were significantly upregulated (FDR $<$ 0.05, LogFC $>$ 1) in patients with resistance to treatment. Of the 550 distinct genes correlated to resistance across treatments, 95% were unique to each cohort, and only 32 genes (5%) were shared across more than one treatment cohort. **Conclusions:** Distinct molecular characteristics were associated with resistance to ICI and/or CT treatment. This suggests that mechanisms of resistance to ICI monotherapy, ICI-CT, or CT could be separate and unique. Further research can provide valuable insights for novel therapies or combinations. Research Sponsor: Gilead Sciences.

9035 **Poster Session**

The effect of ctDNA tumor fraction (TF) on overall survival and concordance between tissue genomics and ctDNA in Lung-MAP.

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Background: Discordance in genomic profiling between tumor tissue and ctDNA can occur due to *inter-patient* variability in shed tumor DNA, and *intra-patient* variability in sources of cell-free DNA (tumor heterogeneity, metastatic variants, CHIP). TF is an aneuploidy-based estimation of tumor-specific DNA in circulation. We evaluated the impact of TF levels on overall survival (OS), mutation concordance and tumor mutation burden in tissue (tTMB) and ctDNA (bTMB) in the LUNGMAP screening study. **Methods:** Eligible advanced NSCLC pts had blood drawn ≤30 days of fresh tissue biopsy with no intervening therapies. Genomic profiling was done by FoundationOne CDx and FoundationOne Liquid CDx. ctDNA TF was quantified via aneuploidy using deviations in genome-wide SNP coverage or somatic allele frequencies if under aneuploidy LoD. High TF was defined as ≥10%. Concordance among driver genes, cancer genes of interest (CGoI: T*P53, PIK3CA, STK11, KEAP1, RB1, PTEN, ATM, BRCA1/2*), and variant subtype were assessed by the percentage positive agreement (PPA) and positive predictive value (PPV) with 95% confidence intervals (CI). OS by TF used a Cox model and log-rank test. PPA and TF among CGoIs was compared with a Wilcoxon test. Correlation between tTMB and bTMB used Lin's coefficient (LC). **Results:** 167 pts met inclusion criteria; 161 had TF data with 51 (32%) ≥10% (high TF). High TF was associated with worse OS (HR: 2.06 [1.43-2.95], p<0.001). The PPA and PPV ranged from 50%-100% and 60%-100%, respectively for driver genes. The PPA was numerically larger for high versus low TF for most drivers (p=0.18) and significantly larger for all mutations and SNVs combined (Table). For CGoI, the distribution of PPA differed between high and low TF (p=0.03). The median PPA for CGoI (25^{th}%ile,75^{th}%ile) was 56% (50,87) for low TF and 100% (100,100) for high TF. PPV for CGoI did not differ by TF (p=0.20). High TF was associated with higher levels of TMB and bTMB (p<0.01 for both). TMB LC (CI) for low and high TF were 0.46 (0.27,0.61) and 0.69 (0.53,0.81). **Conclusions:** High TF was associated with worse OS, better PPA among CGoI, and better LC for t/bTMB. TF may improve the clinical utility of mutations detected by liquid biopsies and should be reported and considered in interpreting these results. Research Sponsor: U.S. National Institutes of Health; National Institutes of Health; Friends of Cancer Research.

	All Samples: PPA (CI)	High TF: PPA (CI)	Low TF: PPA (CI)	All Samples: PPV (CI)	High TF: PPV (CI)	Low TF: PPV CI)
KRAS	83 (70,92)	100 (75,100)	76 (60,89)	100 (92,100)	100 (75,100)	100 (88,100)
EGFR	80 (44,97)	100 (40,100)	67 (22,96)	89 (52,100)	100 (40,100)	100 (40,100)
MET	50 (12,88)	67 (9,99)	33 (1,91)	60 (15,95)	67 (9,99)	50 (1,99)
ERBB2	100 (16,100)	100 (2,100)	100 (16,100)	67 (9,99)	50 (1,99)	100 (16,100)
RET	100 (16,100)	NA	100 (2,100)	100 (16,100)	NA	100 (2,100)
All mutations	57 (52,62)	69 (61,78)	49 (43,56)	72 (68,77)	78 (70,86)	67 (62,73)
Short-variants	80 (75,86)	96 (93,100)	71 (63,79)	72 (68,77)	78 (72,85)	68 (62,73)

9036 **Poster Session**

Efficacy and safety of polymeric micelle paclitaxel (pm-Pac) plus tislelizumab and carboplatin for first-line treatment of patients with advanced squamous non-small-cell lung cancer.

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Background: The pm-paclitaxel formulation for injection (pm-Pac), a novel drug delivery system composed of nanoparticle-encapsulated paclitaxel micelles, combined with cisplatin has been proven to improve clinical outcomes in patients with advanced non-small-cell lung cancer (NSCLC). But the efficacy and safety of pm-Pac in addition to PD-1/PD-L1 inhibitors had never been reported before. **Methods:** Treatment-naive, stage IIIB/IV Sq-NSCLC patients with ECOG PS 0-2(≤1, 91.1%) were eligible. Participants were given intravenous Tislelizumab (200mg, d1) plus pm-Pac (230 mg/m^2, d1) and carboplatin (AUC 5, d1), every 3 weeks until progression or unacceptable toxicity, with local radiotherapy or surgery allowed if treatment needed. The primary endpoints were ORR and safety. The secondary endpoints include DCR, PFS, and OS. AEs were graded according to CTCAE v5.0. **Results:** From Nov 2021 to Dec 2022, 45 patients were enrolled. The median age was 68 years (range 41-84), and most were male (93%) and former/current smokers (87%). 3 patients had baseline brain metastases and 31 patients had baseline PD-L1 evaluated. Twenty-two patients (48.9%) received subsequent local treatment because of the stable efficacy, including 18 radiotherapy and 4 surgery. Among all, 2 achieved confirmed CR, 36 achieved PR, 7 achieved SD, ORR was 84.4% and DCR was 100%. PFS and OS were immature. Kaplan-Meier survival analysis indicated that the 6m-PFS rate was 94.8% (95%CI:89.8% , 97.6%), and a total of 41 (91.1%) patients are still alive on 1L treatment at the last follow-up on Feb 2023.The most common TRAE were alopecia (91.1%), leukopenia (80%), peripheral neurosensory numbness (55.6%) and extremity pain (24.4%). The most common grade 3 or higher AE was neutropenia (33.3%), which is commonly associated with chemotherapy. **Conclusions:** This is the first report about the new chemo-drug pm-Pac plus PD-1 inhibitor regimen that significantly improved ORR for advanced Sq-NSCLC with a tolerable safety profile, supporting further development of this new combination in the first-line treatment. Response rates. Research Sponsor: None.

Characteristic	Total (n)	CR(n)	PR(n)	SD (n)	PD (n)	ORR (%)	DCR (%)
Male	42	1	34	7	0	83.3	100
Female	3	1	2	0	0	100	100
Stage III	17	2	13	2	0	88.2	100
Stage IV	28	0	23	5	0	82.1	100
PD-L1 expression							
< 1%	15	2	10	3	0	80	100
1%-49%	10	0	9	1	0	90	100
≥50%	6	0	5	1	0	83.3	100
Unknown	14	0	12	2	0	85.7	100

Keywords: Pm-paclitaxel, PD-1 inhibitor, Advanced Sq-NSCLC.

9037 **Poster Session**

Exploring the potential of combination immune checkpoint strategies in non-small cell lung cancer (NSCLC).

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Background: The clinical outcomes for patients with NSCLC remain suboptimal despite recent advancements in anti-PD-1/PD-L1 immunotherapies. Thus, identification of rational combinations of novel immune checkpoint (IC) strategies is imperative. This study aimed to comprehensively characterize the expression of IC targets to inform drug development and design effective combinatorial strategies, to advance the search for optimized therapies for NSCLC. **Methods:** We analyzed the differential gene expression of IC targets in 537 primary lung adenocarcinoma (LUAD) samples and 59 normal lung tissue samples pre-immunotherapy receipt using RNA-sequencing data from The Cancer Genome Atlas. Gene expression of IC-targets including *PDCD1* (PD-1), *CD274* (PD-L1), *CTLA4*, *TIGIT*, *LAG3*, *HAVCR2* (TIM-3), *VSIR* (VISTA), *ICOS*, *CD276* (B7-H3), *BTLA*, *IDO1*, *KLRD1* (CD94/NKG2A), *NT5E* (CD73), *TNFRSF4* (OX-40), *TNFRSF18* (GITR), and *TNFRSF9* (4-1BB) were obtained. Differential gene expression was determined intra-tumorally by comparison of transcripts per million and inter-tumorally using the DESeq2 algorithm. Log2 fold change >0.5 and false discovery rate adjusted $P<0.05$ were used as criteria for significant differential expression. Hierarchical clustering was used to identify subsets of tumors with similar profiles of IC-targetable gene expression. **Results:** Tumors showed significantly increased expression of *TNFRSF18* (GITR), *NT5E* (CD73), *TNFRSF9* (4-1BB), *LAG3*, *TIGIT*, *CTLA4*, *PD-1*, *BTLA*, *B7-H3*, and *OX-40* (Table 1). On the other hand, tumors exhibited significant downregulation of *CD274* (PD-L1), *HAVCR2* (TIM-3), *ICOS*, *KLRD1* (CD94/NKG2A), and *VSIR* (VISTA). Hierarchical clustering revealed recurrent patterns of IC gene overexpression which were characterized by: 1) *IDO1*-hi, 2) *CD276*-mid + *TNFRSF18*-mid, 3) *VSIR*-hi, 4) *CD276*-hi, 5) *NT5E*-hi, and 6) *CD276*-mid + *NT5E*-mid. Interestingly, patterns of IC gene expression distinguish tumors from controls. Of note, high *VSIR* expression was specific to normal tissue rather than tumors. **Conclusions:** Our study identified many IC targetable genes that were significantly overexpressed in tumors. However, subsets of tumors showed distinct and segregable combinations of overexpressed IC genes. These results suggest heterogeneous mechanisms of immune evasion in NSCLC, which may explain suboptimal outcomes with anti-PD-1/PD-L1 based strategies in this patient population. Our findings emphasize the importance of biomarker-guided approaches for the optimal selection of ICs and the development of rational combinatorial immunotherapies in NSCLC. Research Sponsor: None.

9038 **Poster Session**

Co-mutational status and PD-L1 expression in *KRAS* mutant non-small cell lung cancer (NSCLC): Role in treatment selection and association with clinical outcomes.

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Background: In NSCLC, different *KRAS* mutations (mt) define unique subgroups and certain co-mutations (co-mt) could have prognostic and therapeutic implications. Retrospective studies associate poor prognosis with co-mts in *STK11* and *KEAP1* with *KRAS*. It is unclear if PD-L1 expression and co-mt in *KRAS* mt NSCLC impacts outcomes. **Methods:** Molecular profiles of 27748 NSCLC tumors were tested with next-generation sequencing (Caris Life Sciences, Phoenix, AZ) and classified by *KRAS* mt. PD-L1 IHC (22C3) was reported as TPS. Real-world post-immunotherapy (IO) overall survival (OS) was obtained from insurance claims and calculated from start of an immune check-point inhibitor (with or without chemotherapy) to the last day of follow-up. **Results:** In all, 7634 (28%) samples had a *KRAS* mt; most common being G12C (11%), G12V (5.3%), G12D (3.9%) and G13X (2.0%). The most frequent co-mt was *KRAS-TP53* (KP) (46%), similar in all *KRAS* subtypes. *KRAS-STK11*(KL) was in 23% of *KRAS* mt, enriched in G13X (33%) and lowest in G12D (16%). *KRAS-KEAP1*(KK) was co-mt in 10% of *KRAS* mt, highest in G13X (16%) and lowest in G12D (8%). *KRAS*mt/*STK11*wt/*KEAP1*wt/*TP53*wt (K only) was 27% of *KRAS* mt, highest in G12D (36%) and lowest in G13X (16%). A small subgroup, 5.6% was *KRAS-STK11-KEAP1* co-mt (KKL). The majority of pts in the KL (61%), KK (52%) and KKL (62%) cohorts had TPS $<$1%. In 1723 *KRAS* mt NSCLC pts treated with IO, KL, KK and KKL had significantly worse post-IO OS than KP and K only (table); KKL had the lowest OS. In the TPS$\geq$1% KRAS mt group, KL, KK and KKL had worse post-IO OS than KP and K-only. In TPS$<$1% group, KL and KK had poor post-IO OS and K-only had favorable outcomes. However, KP had worse post-IO OS compared to K-only in TPS$<$1%. In G12C and G12V, similar trend with worse post-IO OS in KL, KK and KKL, compared to KP and K only was noted. **Conclusions:** We report a large real-world dataset evaluating outcomes with check-point inhibitors in NSCLCs with *KRAS* and specific co-mts. KL, KK and KKL subgroups demonstrate universally poor outcomes in all *KRAS* subtypes irrespective of PD-L1. Pts with KP co-mts have adverse post-IO outcomes in TPS$<$1% but favorable in TPS$\geq$1%. TPS score remains a predictive marker of IO outcomes in KP, but not in KL, KK and KKL. These observations emphasize that both PD-L1 and co-mts have a clear association with clinical outcomes in *KRAS*-mt NSCLC, and must be used in predictive models for individualized therapy. Research Sponsor: None.

	Post-IO OS (months) (95% CI)			
	N	All	TPS<1%	TPS≥1%
All *KRAS*	1723	16.8 (15-18.6)	13.3 (11.6-15.6)	15.4 (13.1-18.3)
KP	826	17.9 (15.3-20.7)	10.4 (8.8-13.5)*	17.5 (13.2-21)
KL	350	10.7 (9.4-12.3)*&	11.8 (10-14.4)*	9.1 (6.1-12.3)*&
KK	163	8.9 (6.7-10.7)*&	8.9 (6.1-11)*	7.5 (2.3-11.6)*&
KKL	83	8 (5.3-9.9)*&	8.9 (6.1-11)*	3.7 (1.3-9.8)*&
K-only	465	21 (17.6-25.7)	23.2 (14.9-31.1)&	18.4 (13.5-24.5)

Some with overlaps: *: significantly different from K-only &: significantly different from KP.

9039 **Poster Session**

Effects of mutations in SWI/SNF subunits on context-specific prognosis in driver positive and driver negative NSCLC.

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Background: Mutations(mt) in the Switch/Sucrose-Nonfermentable chromatin remodeling complex (SWI/SNF) are commonly found in NSCLC and have been associated with worse prognosis. However, the overall prognostic role of the individual SWI/SNF subunits in all NSCLCs and in oncogenic driver-positive (D+) and driver-negative (D-) groups remains unclear. Our study attempts to clarify the prognostic role of SWI/SNF subunit alterations in these populations. **Methods:** 42,379 NSCLC tumor specimens were tested at Caris Life Sciences (Phoenix, AZ) with NextGen Sequencing (NGS) of DNA (592-gene panel or whole-exome sequencing). Based on the observed frequency of likely pathogenic/pathogenic (LP/P) mts, the four most commonly-altered SWI/SNF subunits – ARID1A (8.29%), SMARCA4 (6.29%), ARID2 (3.05%) and PBRM1 (1.98%) – were further analyzed. We divided the cohort by driver mts. D+ tumors possessed at least one of the following alterations: LP/P mts in KRAS, EGFR, BRAF, ERBB2 or MET; METex14 skipping; ERBB2 amplification, LP/P fusions in ALK (including IHC overexpression), RET, ROS1, NTRK (1-3) & NRG1. D- tumors were devoid of mts/amplifications/fusions in all genes mentioned above. Kaplan-Meier analysis was performed on real world survival data (n = 24685) obtained from insurance claims. Statistical significance was determined using chi-square and Mann-Whitney U test adjusted for multiple comparisons ($q < 0.05$). **Results:** Of the SWI/SNF genes, only SMARCA4mts were associated with worse survival in the overall (HR = 1.46), D+ (HR = 1.984) and D- (HR = 1.224) cohorts (all $p < 0.01$). While SMARCA4mt was associated in the D- cohort with KEAP1 and STK11 mts, the worse prognosis persisted even in their absence (HR = 1.41, $p < 0.001$). To understand the role of SWI/SNF mts in the context of driver co-mts, we compared the survival of D+ vs D- tumors for each SWI/SNF subunit. As expected, D+ tumors were associated with better survival in SWI/SNF wild-type (wt) tumors (HRs 0.76-0.78, $p < 0.00001$). There was no survival effect of ARID1A, ARID2 or PBRM1 mts (HRs = 0.9-1, p = ns). In contrast, in SMARCA4mts, D+ tumors had much worse survival than D- (HR = 1.295, p = 0.003). This effect is driven by the KRASmt cohort, as KRASmt/SMARCA4mt tumors had significantly worse survival compared with D- tumors (HR = 1.882, $p < 0.001$). Of note, KRASmts are enriched in the D+/SMARCA4mt subgroup (78% of all oncogenic drivers). When KRASmts were removed from the D+ group, no survival difference was observed between D+ and D- SMARCA4mt tumors (HR = 0.938, p = ns). **Conclusions:** In this largest-ever retrospective cohort of NSCLC patients with SWI/SNF mutations, SMARCA4mt is the only SWI/SNF alteration broadly associated with worse survival. SMARCA4mt is associated with particularly short survival in KRASmt tumors. These data suggest underlying biology which may inform further investigation and therapeutic development. Research Sponsor: None.

9040 **Poster Session**

TROP2 expression and response to immune checkpoint inhibition in patients with advanced non-small cell lung cancer.

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Background: Despite anti-monoclonal antibodies targeting programmed cell death-1 (PD-1) or its ligand PD-L1 revolution, most patients (pts) with advanced NSCLC displayed primary resistance to PD1/PD-L1 blockade. Identifying targetable alterations involved in resistance represent a promising approach to improve immunotherapy efficacy. TROP2 expression is associated with a poor prognosis in NSCLC, and offers a promising target for treatment with the development of new antibody drug conjugate. TROP2 has been suggested to play a role in innate immunity response, but, it's unclear whether TROP2 expression by tumor cells is detrimental specifically in the context of PD1/PD-L1 blockade. The aim of our study was to investigate the the role of TROP2 expression in outcome of NSCLC pts treated with ICI. **Methods:** We analyzed the largest NSCLC gene expression data set worldwide including the whole-transcriptome profile of 891 pre-treatment tumors from POPLAR and OAK trials, two randomized studies assessing the efficacy of atezolizumab versus docetaxel in NSCLC. We complemented this transcriptional approach with multiplex IF and digital pathology analysis to confirm our findings at the protein level We investigated whether a non-invasive approach focusing on the level of plasma levels of circulating TROP2 may be relevant to predict efficacy of ICI. **Results:** The PFS of pts with high expression of TROP2 was significantly lower than in pts with low expression 2.5 vs 4.1 months, $p < 0.001$. Strikingly, high TROP2 expression was also associated with lower clinical benefit rate 15% vs 28%, $p = 0.009$ and worse overall survival (OS) 12.6 vs 16.3 months, $p = 0.007$ When adjusting for covariates such as histological subtype, TLS signature, PD-L1 expression, TROP2 remained independently associated with PFS and OS. None of these correlations were observed in the docetaxel arm, suggesting a predictive value of TROP2 gene expression specifically for response to ICI. By using a deconvolution approach, we also observed that TROP2-high tumors were characterized by a significant lowest expression of genes specific to immune populations (T effector memory cells,Th17 cells). Multiplex IF on an independent cohort 53 NSCLC tumors confirmed the correlation between high TROP2, microenvironment features and poor response to PD1 inhibition. Analysis of circulating plasma levels of TROP2 in 97 NSCLC patients revealed a strong correlation with expression in tumor tissue. High plasma levels of circulating TROP2 was also significantly associated with worse ORR, PFS and OS on treatment with PD1/PDL1 antagonist. **Conclusions:** Our study revealed that TROP2 expression by tumor cells in NSCLC is associated with worse outcome in patients with NSCLC independently of PDL1 expression. Targeting TROP2 in combination with ICI may represent a promising strategy to improve ICI efficacy in pts with TROP2-high NSCLC. Research Sponsor: None.

9041 **Poster Session**

Pre-treatment plasma-informed circulating tumor DNA detection as an early identification of therapeutic benefit for patients with untreated advanced lung squamous cell carcinoma.

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Background: Circulating tumor DNA (ctDNA) detection as a promising prognostic factor to assess treatment response has been widely studied with customized tumor-informed strategies, the application of which was limited by the inaccessibility for tumor biopsies in a substantial proportion of patients. To overcome this challenge, we presented a proof-of-concept study for the development of a novel personalized pre-treatment plasma-informed next generation sequencing (NGS) panel and investigated its prognostic value for first line treatment in patients with advanced lung squamous cell carcinoma (LUSC). **Methods:** Paired plasma and white blood cell (WBC) samples were collected from 227 of stage IIIB-IV LUSC patients who were treated with first line either chemotherapy or chemotherapy plus PD-1 blockade at pre- and post-treatment. Somatic mutations in pre-treatment plasma were identified with a 769-gene based NGS panel (Genecast, Wuxi, China) followed with germline or clonal hematopoietic variants filtering by referring to the WBC samples. Positive variants detected in the pre-treatment plasma served as a basis for personalized variants tracking in post-treatment plasma. ctDNA kinetics was measured by plasmaDelta (Δgenevaf=((post-treatment genevaf – pre-treatment genevaf) / pre-treatment genevaf; genevaf was defined by variant allele frequency for each individual gene). Progression-free survival (PFS) as the primary endpoint and overall survival (OS) as the secondary endpoint were assessed. **Results:** ctDNA positivity was observed in 80% (182/227) of pre-treatment samples and subsequently 54% (99/182) of post-treatment samples. ctDNA positivity at post-treatment was shown to be a significant predictor for both PFS and OS in the whole group as well in the sub-treatment groups (Table). After adjusting for clinicopathologic variables, ctDNA positivity remained significantly associated with both worse PFS and OS (PFS: HR = 2.3, $P<0.001$ and OS: HR= 2.56, $P<0.001$). ctDNA kinetics further identified a worse treatment response group. Patients with high plasmaDelta had remarkably worse outcomes than patients with low plasmaDelta (PFS: HR =4.8; 95%CI=2.8-8.3; $P< 0.001$ and OS: HR=2.8; 95%CI=1.7-4.6; $P<0.001$). **Conclusions:** These results demonstrated the feasibility of pre-treatment plasma-informed ctDNA detection and kinetics for monitoring treatment response in LUSC patients whose tumor biopsies were unavailable. Research Sponsor: None.

Prognostic value of ctDNA positivity.

Groups	No. of ctDNA positive patients	No. Of ctDNA negative patients	PFS		OS	
			HR (95%CI)	*P* value	HR (95% CI)	*P* value
All	99	83	3.2 (2.3-4.4)	<0.001	3.4 (2.3-5.0)	<0.001
Chemotherapy plus PD-1 blockade	39	49	2.7 (1.7-4.4)	<0.001	3.8 (2.1-6.8)	<0.001
Chemotherapy only	60	34	3.5 (2.1-5.7)	<0.001	2.9 (1.6-5.0)	<0.001

9042 **Poster Session**

Treatment at twilight: Is less more in the management of octogenarians with non-small cell lung cancer (NSCLC)?

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Background: Treatment of advanced/metastatic NSCLC in older patients is hindered by performance status, comorbidities, and treatment toxicities. Moreover, whether multiagent chemotherapy in combination with immune checkpoint inhibitor (ICI) therapy outweighs a conservative approach is controversial. This study aims to assess treatment patterns and outcomes in patients ≥80 years with NSCLC through data provided by the national cancer database (NCDB). **Methods:** Adults ≥80 years with stage III/IV NSCLC, available treatment data, and diagnosis between 2015-2018 were included. Patients were stratified by therapy including none, ICI alone, chemotherapy alone, and chemotherapy+ICI; radiation and surgical management was also assessed. Median overall survival (OS) was evaluated by Kaplan-Meier survival methods, and differences were assessed by hazard ratios (HR) and 95% confidence intervals (CI). The mean difference in OS was compared between systemic therapy arms. Pearson Chi-Squared tests assessed the significance of treatment differences, with a p-value of $<$ 0.05 considered statistically significant. **Results:** There were 42,356 patients included; 29,698 (70.1%) had stage IV disease and 26,314 (62.1%) had adenocarcinoma. A total of 3,248 (7.7%) received ICI, 11,505 (27.2%) received chemotherapy, 2,393 (5.6%) received chemotherapy+ICI, and 25,210 (59.5%) received no therapy. Median OS for no therapy, ICI, chemotherapy, and chemotherapy+ICI was 2.63 (95% CI: 2.57, 2.69), 10.68 (95% CI: 9.96, 11.39), 12.35 (95% CI: 11.98, 12.72), and 14.03 (95% CI: 13.87, 14.88) months, respectively. Compared to no therapy, ICI alone (HR: 0.377 [95% CI: 0.361, 0.393], p = 0.000), chemotherapy alone (HR: 0.439 [95% CI: 0.426, 0.452], p = 0.000), and chemotherapy+ICI (HR: 0.345 [95% CI 0.328, 0.363], p = 0.000) improved OS. Compared to ICI, chemotherapy and chemotherapy+ICI had a longer mean OS difference of 2.48 (95% CI 1.82, 3.13) ($p < 0.001$) and 1.9 (95% CI 1.01, 2.78 ($p < 0.001$) months, respectively. In chemotherapy alone, the median OS was 1.12 months (95% CI: 0.55, 1.70) ($p < 0.001$) longer with multiagent vs single agent. There was no difference between chemotherapy vs chemotherapy+ICI (0.57 months [95% CI: 0.16, 1.31], p = 0.234), or for ICI+single agent vs ICI+multiagent (0.67 months [95% CI -1.18, 2.54], p = 1.00). Treatment with radiation (HR: 0.664 [95% CI: 0.649, 0.679], $p < 0.001$), primary-sit(HR: 0.495 [95% CI: 0.465, 0.527], $p < 0.001$) and non-primary surgery (HR: 0.867 [95% CI: 0.811, 0.927], $p < 0.001$), and receipt of ICI vs no ICI (HR: 0.912 [95% CI 0.873, 0.954], $p < 0.001$) improved OS. **Conclusions:** Patients ≥80 years with NSCLC derived most benefit from multiagent chemotherapy or chemotherapy+ICI, with no OS difference between ICI+single or ICI+multiagent therapy. ICI alone and no therapy had inferior OS. Future trials to corroborate this finding would benefit the elderly population. Research Sponsor: None.

9043 **Poster Session**

Factors impacting outcomes in individuals ≥80 years with non-small cell lung cancer (NSCLC): A national cancer database (NCDB) analysis.

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Background: Older individuals with advanced/metastatic NSCLC have inferior outcomes compared to younger patients. Aside from baseline comorbidities and treatment-limiting toxicities, identifying factors that impact overall survival (OS) in this population is needed. The aim of this study is to assess characteristics impacting outcomes in patients ≥80 years with NSCLC using the NCDB. **Methods:** Adults ≥80 years with NSCLC, stage III/IV disease, diagnosed between 2015-2018, and available demographic data were included. Age, sex, race, insurance status, hospital subtype, Charelson-Deyvo comorbidity (CDCC) index, cancer stage (III/IV), geographic region in the United States (US), and histologic NSCLC subtypes were compared. Kaplan-Meier methodology assessed differences in median OS, and differences were compared using hazard ratios (HR) with 95% confidence intervals (CI). Pearson Chi-Squared test assessed the significance of covariates, and a p value < 0.05 was considered statistically significant. **Results:** There were 42,356 patients included. Median age was 83 (80-90) years, 20,422 were (48.2%) female, 35,653 (84.2%) were white, 37,738 (89.1%) had medicare coverage, 11,055 (26.1%) received treatment at an academic hospital, and 14,383 (33.9%) received care in the southern United States. Treatment at an academic hospital (HR: 0.91 [95% CI: 0.87, 0.95], $p < 0.001$), females (HR: 0.82 [95% CI 0.81, 0.84], $p < 0.001$), Medicaid (HR: 0.77 [95% CI: 0.65, 0.93], $p = 0.005$) vs no insurance, and adenocarcinoma (HR: 0.79 [95% CI: 0.74, 0.84], $p < 0.001$) or squamous cell carcinoma (HR: 0.84 [95% CI: 0.80, 0.90, $p < 0.001$] had better outcomes. Patients in the Northeastern (HR: 0.90 [95% CI: 0.87, 0.93], $p < 0.001$), Southern (HR: 0.92 [95% CI: 0.89, 0.94], $p < 0.001$), and Western (HR: 0.89 [95% CI: 0.88, 0.93], $p < 0.001$) US had better OS compared to the Midwest. Compared to whites, patients who were black (HR: 0.92 [95% CI: 0.88, 0.85], $p < 0.001$), Asian (HR: 0.77 [95% CI: 0.72, 0.82], $p < 0.001$), Hispanic (HR: 0.83 [95% CI: 0.78, 0.88], $p < 0.001$), or other (HR: 0.88 [95% CI: 0.79, 0.97) had better outcomes. Per year increase in age (HR 1.009 [95% CI: 1.006, 1.013], $p < 0.001$), patients with CDCC score of 1 (HR: 1.16 [95% CI: 1.14, 1.19], $p < 0.001$), 2 (HR: 1.22 [95% CI: 1.18, 1.27], $p < 0.001$), and ≥3 (HR: 1.33 [95% CI: 1.284, 1.380], $p < 0.001$) vs 0, and stage IV NSCLC (HR: 1.83 [95% CI: 1.79, 1.88], $p = 0.000$) had poorer survival. **Conclusions:** White race, males, uninsured status, receipt of treatment in the Midwest, community hospital treatment, large cell histology, advancing age, stage IV disease, and increasing CDCC score all had poorer outcomes in adults ≥80 years with advanced NSCLC. These factors should be taken into consideration when discussing the diagnosis, management, and expectations of the disease course with patients in the geriatric age group. Research Sponsor: None.

9044 **Poster Session**

A phase II study of afatinib in combination with pemetrexed and carboplatin in patients with EGFR mutation positive non-squamous, advanced non–small-cell lung cancer (NSCLC) refractory to first-line osimertinib treatment: NEJ025B.

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Background: To date, osimertinib has been commonly used as a first-line treatment for EGFR mutated advanced NSCLC. However, the issue of what constitutes effective treatment after osimertinib failure remains . We evaluated treatment with afatinib plus chemotherapy for EGFR mutated NSCLC resistant to osimertinib. **Methods:** Patients (pts) with EGFRm (Del19 or L858R) after failure of osimertinib treatment were assigned to a regimen of afatinib 20mg daily combined with carboplatin AUC5 mg/ml/min and pemetrexed 500mg/m2 every 3 weeks followed by maintenance treatment with afatinib plus pemetrexed until disease progression or unacceptable toxicity was noted. The primary endpoint was rate of PFS at 6 months after initiation of treatment (6M-PFSR). The threshold was set at 35% and the expected value at 60% (two-sided P-value of 5% and power of 80%). Thirty-one patients were required, and the target number of patients was set at 35 after accounting for ineligible cases. Secondary endpoints were PFS, OS, ORR, DOR, and Safety. In this study, blood samples were collected before and after study treatment and at the time of PD to examine biomarkers using CAPP-SEQ. This biomarker study is ongoing. **Results:** Between June 7, 2020 and January 19, 2022, 36 pts were enrolled. One patient was found to meet the exclusion criteria, and the efficacy was analyzed in the other 35 patients. The mean age was 70 years, 60% were women, and 54.3% were nonsmokers. The 6M-PFSR, the primary endpoint, was 57.1%. The confidence interval of 39.3%-71.5% exceeded the threshold of 35%, and the study met its primary endpoint. Notably, 24.1% of pts had a long-term PFS of 1 year or longer. ORR was 48.6%, DCR was 88.6%, median PFS was 8.2M, median DOR was 5.6 M, and median OS was not reached. By mutation type, ORR were similar for Del19 and L858R (46.7% and 50.0%, respectively), but median PFS tended to be longer for Del19 compared to L858R (9.6M and 5.2M, respectively). Pts who responded to previous osimertinib therapy (CR and PR: n = 29) tended to have longer mPFS compared to non-responders (SD, PD, and NE: n = 6) (8.5M and 5.8M, respectively). Adverse events due to TKI and chemotherapy were observed. Diarrhea (52.8%), anorexia (44.4%), fatigue (33.3%), and paronychia (36.1%) were the most frequent adverse events, and these adverse events were predictable and manageable. Interstitial pneumonia developed in three patients (8%), one of whom was the only death in the study. **Conclusions:** The combination of afatinib and the platinum doublet showed satisfactory efficacy with manageable adverse events in tumors refractory to osimertinib, and met its primary endpoint. OS follow-up and biomarker analyses are still ongoing. This regimen is expected to be a candidate for second-line therapy after osimertinib. Clinical trial information: jRCTs021200005. Research Sponsor: supported by Boehringer.

9045 **Poster Session**

Uncommon *EGFR* mutations conducted with osimertinib in patients with NSCLC (UNICORN): A phase 2 study.

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Background: Non-small cell lung cancer (NSCLC) harboring uncommon *EGFR* mutation (uC-*EGFR*m), excluding exon 20 insertion, is a heterogenous rare fraction consisting of 10% of all *EGFR* mutations. Key drugs for metastatic NSCLC (mNSCLC) uC-*EGFR*m are limited, with only afatinib being FDA approved. Data on the efficacy of osimertinib for previously untreated metastatic patients (pts) harboring uC-*EGFR*m NSCLC is limited. **Methods:** UNICORN study for previously untreated mNSCLC pts harboring uC-*EGFR*m, excluding exon 20 insertion mutation, evaluating osimertinib with a dose of 80 mg QD orally is a multicenter, open-label, single-arm phase 2 study. The primary endpoint was the overall response rate (ORR) evaluated by central review according to the Response Evaluation Criteria in Solid Tumors (version 1.1), and key secondary endpoints were disease control rate (DCR), progression-free survival (PFS), overall survival (OS), duration of response (DoR), and safety. **Results:** Between March 2020 to May 2022, a total of 42 pts were registered. Among the eligible 40 pts, 45.0% were female; the median age was 72 years (range 39-88); 42.5% were never smokers or light smokers; 92.5% were adenocarcinomas, solitary uC-*EGFR*m/compound mutation ratio was 57.5%/42.5%. The most common mutations were G719X (50.0%), followed by S768I (25.0%), L861Q (20.0%), and others, including compound mutation data. The ORR was 55.0 % (90% confidence interval [CI]; 40.9-68.5), the DCR was 90.0 % (95% CI; 76.3-97.2), the mPFS was 9.4 months (95% CI; 3.7-15.2) after a median follow-up of 27.0 months, the mOS was not reached (NR) (95% CI, 19.23- NR), and the mDoR 22.7 months (95% CI; 9.43-NR). In solitary and compound mutations with uC-*EGFR* m NSCLC, ORR was 52.2%/58.8%, mPFS was 5.4 months/11.4 months, mOS 23.0 months/NR, and mDoR was 22.7 months/NR, respectively. Safety was similar to previous reports and Grade 3/4 AEs were reported in 8 of 36 pts (27.5%) and 12.5% of pts developed pneumonitis. All of the AEs were manageable and there were no treatment-related deaths. **Conclusions:** Osimertinib in mNSCLC pts harboring uC-*EGFR*m other than exon 20 insertions showed clinical activity with manageable toxicities. These results suggest that osimertinib can be considered as a treatment option for this specific population. Clinical trial registration: jRCTs071200002. The study was funded by AstraZeneca. Clinical trial information: jRCTs071200002. Research Sponsor: AstraZeneca.

9046 **Poster Session**

Role of immunotherapy in stage IV non-small cell lung cancer with liver metastasis: A NCDB analysis.

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Background: Despite approvals of immune checkpoint inhibitors in stage IV non-small cell lung cancer (NSCLC), survival benefit of immunotherapy (IO) in those with liver metastasis is controversial. Randomized controlled trials demonstrated conflicting results. **Methods:** Using National Cancer Database (NCDB), Stage IV NSCLC cases diagnosed in 2016-2017 with at least 30-day follow up were analyzed. Clinical demographics included age (20-69 vs. 70+), sex (male vs. female), race (whites vs. others), institution (academic vs. others), Charlson-Deyo score (0-1 vs. 2-3), year of diagnosis (2016 vs. 2017), Histology (adenocarcinoma NOS vs. other), brain metastasis (Yes vs. No), bone metastasis (Yes vs. No), liver metastasis (Yes vs. No). They were divided into liver-metastasis positive (LM+) vs. negative (LM-). Information regarding cancer treatment was limited to the first course of therapy, including surgery for primary lesion (Yes vs. No), radiation (Yes vs. No), multi-agent chemotherapy (Yes vs. No), and IO (Yes vs. No). Overall Survival (OS) analysis was performed using Kaplan-Meier curves and Log-rank tests. Cox proportional hazard model was used for multivariate analyses. A two-sided p-value < 0.05 was considered as significant. **Results:** A total of 13,594 LM+ and 69,885 LM- cases met eligibility and further analyzed. 2,944 and 15,553 patients were treated with IO, respectively. No significant association between use of IO and status of liver metastasis was observed ($p = 0.124$). The median OS in LM+ cases was significantly shorter than that in LM- cases (5.0 vs 8.8 months, respectively, $p < 0.0001$). Use of IO was associated with improved OS in both LM+ and LM- cohorts with similar HRs/p-values (0.62/ < 0.0001 and 0.64/ < 0.0001, respectively). Multivariate analysis demonstrated that use of IO had a significantly improved OS in both LM+ (HR = 0.69, $p < 0.0001$) and LM- (HR = 0.64, $p < 0.0001$) cohorts. The OS benefit of IO in LM+ cohort remained with propensity score matching analysis (mOS 9.0 vs. 4.4 months, HR = 0.62, $p < 0.0001$). Further exploratory analysis focusing on those treated with multiagent chemotherapy showed that the addition of IO improved OS in both LM+ (HR = 0.77, $p < 0.0001$) and LM- (HR = 0.79, $p < 0.0001$) cohorts. **Conclusions:** This retrospective study using one of the largest cancer databases suggests that use of IO improves OS of NSCLC patients with LM regardless of chemotherapy status, and its magnitude of OS benefit is similar to that in LM- patients. Research Sponsor: None.

	LM+ with IO	LM+ without IO	LM- with IO	LM- without IO
Median OS (month)	9.0	4.1	15.6	7.2
12-month OS (%)	41.7	24.1	57.8	37.9
24-month OS (%)	24.8	13.1	37.6	23.7

9047 **Poster Session**

Updated efficacy and safety of entrectinib in patients (pts) with locally advanced/metastatic *NTRK* fusion-positive (fp) non-small cell lung cancer (NSCLC).

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Background: *NTRK* fusions, encoding for constitutively active oncogenic tropomyosin receptor kinase proteins, are present in many solid tumors, including NSCLC. As central nervous system (CNS) metastases are common in pts with advanced NSCLC, treatments with intracranial efficacy are needed. Entrectinib, a potent CNS-active tyrosine kinase inhibitor, has previously demonstrated efficacy in pts with *NTRK*-fp NSCLC in an integrated analysis of three phase I/II trials (ALKA-372-001 [EudraCT, 2012-000148–88], STARTRK-1 [NCT02097810], STARTRK-2 [NCT02568267]); objective response rate (ORR) was 63.6% (14/22; data cutoff: August 31 2020). We present updated data for this cohort. **Methods:** Pts ≥18 years old with locally advanced/metastatic *NTRK*-fp tumors were enrolled and received 600 mg oral entrectinib until disease progression, toxicity, or death. At Week 4 and then every 8 weeks, tumour response was assessed by blinded independent central review (BICR) per RECIST v1.1. Co-primary endpoints were ORR and duration of response (DoR). Secondary endpoints included progression-free survival (PFS), overall survival (OS), intracranial efficacy, and safety. Enrolment cutoff: July 2 2020; data cutoff: August 2 2021. **Results:** The efficacy-evaluable population included 31 pts with *NTRK*-fp NSCLC. Median age was 60.0 years (range 22–88); 26 pts (83.9%) had adenocarcinoma; 11 pts (35.5%) had ≥2 prior lines of systemic therapy; 18 pts (58.1%) were current or former smokers; 15 pts (48.4%) had investigator-assessed baseline CNS metastases. Median survival follow up was 21.8 months (95% CI 19.5–30.2). Entrectinib treatment showed efficacy in pts with *NTRK*-fp NSCLC, including those with baseline CNS metastases by investigator (Table). In pts with BICR-assessed CNS metastases, intracranial ORR was 60.0% (6/10; 95% CI 26.2–87.8), median intracranial DoR was not estimable (NE), and median intracranial PFS was 8.9 months (95% CI 5.6–NE). In the safety-evaluable population (N=35), most treatment-related adverse events (TRAEs) were Grade 1–2 and non-serious. TRAEs led to dose reduction, interruption and discontinuation in 31.4%, 28.6%, and 5.7% of pts, respectively, and no treatment-related deaths occurred. **Conclusions:** In line with previously reported data, treatment with entrectinib was associated with deep and durable systemic and intracranial responses in pts with advanced *NTRK*-fp NSCLC. Clinical trial information: EUCTR 2012-000148-88, NCT02097810, NCT02568267. Research Sponsor: This study is sponsored by F. Hoffmann-La Roche Ltd. Third-party medical writing assistance, under the direction of authors, was provided by Vanessa Poon, BSc, of Ashfield MedComms, an Inizio company, and was funded by F. Hoffmann-La Roche Ltd.

	All pts (N=31)	Baseline CNS metastases* (n=15)	No baseline CNS metastases* (n=16)
ORR, n (%)	20 (64.5)	9 (60.0)	11 (68.8)
95% CI	45.4–80.8	32.3–83.7	41.3–89.0
Complete response	5 (16.1)	1 (6.7)	4 (25.0)
Partial response	15 (48.4)	8 (53.3)	7 (43.8)
Median time to event, months (95% CI)			
DoR	27.1 (14.8–29.4)	29.4 (13.0–NE)	19.9 (10.4–NE)
PFS	20.8 (13.8–30.4)	30.3 (4.7–30.4)	20.8 (14.9–NE)
OS	NE	NE (8.9–NE)	NE

*Per investigator
CI, confidence interval

9048 **Poster Session**

Initial chemotherapy for locally advanced and metastatic NUT carcinoma: A report from the NUT carcinoma registry.

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Background: NUT carcinoma (NC) is an uncommon squamous cell cancer. This disease is driven by a *NUTM1* gene fusion, most commonly encoding a BRD4-NUT fusion oncoprotein, that enhances transcription of numerous genes including *MYC*. BET bromodomain inhibitors (BBDi), which block oncoprotein binding, are being studied in clinical trials. A subset of NC is sensitive to chemotherapy, but the optimal regimen is unknown; experts have recommended platinum- (PLAT) and ifosfamide-based (IFOS) therapy based on case reports. **Methods:** Patients with NC with known chemotherapy treatment and survival outcomes who consented to participate in a worldwide registry were included. Cohorts of patients with non-metastatic and metastatic disease were of interest. Medical records were manually reviewed. Results were summarized using 95% confidence intervals (95CI) and Kaplan Meier survival estimates, when appropriate. **Results:** A total of 60 patients with NC were included and received either PLAT (83%) or IFOS (17%); 38% were female and the median age was 37 (range 10-82); 55% of tumors were thoracic primaries, 48% had squamous differentiation, and 70% were driven by BRD4-NUTM1 (n = 43 with known fusion status). Of 31 patients with non-metastatic disease, 32% had a thoracic primary; 23% received peri-operative chemotherapy and 77% received concurrent chemo-radiation (cRT). The most common chemotherapies used for cRT were cisplatin (n = 12), platinum-taxane (n = 6), and platinum-etoposide (n = 5). Of 4 non-metastatic patients who received IFOS, 4 (100%) had a disease-free survival (DFS) $>$ 3 months and 1 (25%) had a DFS $>$ 1 year. By comparison, of the 27 patients who received PLAT, the estimated 3-month and 1-year DFS was 70% (95CI 48-84%) and 53% (95CI 30-71%) respectively. Of the 29 patients with metastatic disease, 79% had a thoracic primary; 6 received IFOS and 23 received PLAT. The most common chemotherapies were platinum-taxane (52%), platinum-etoposide (17%), and ifosfamide-etoposide (14%). ORR of IFOS vs PLAT was 50% (95CI 12-88%) vs 23% (95CI 7-44%). Compared to IFOS, PLAT had similar 3-month and 6-month PFS (3;6mo: PLAT est: 36% [95CI 18-56%]; 9% [95CI 2-25%] vs IFOS 50%; 17%). The estimated 1-year OS and 1-year OS were 18% (95CI 6-35%) vs 33% for PLAT vs IFOS respectively. Of the 5 patients (8%) with a known OS $>$ 3 years, all had a non-thoracic primary, non-metastatic disease, and had received PLAT. **Conclusions:** NUT carcinoma is a highly aggressive disease. There may be a numerically higher ORR for ifosfamide-based therapy as compared to platinum-based therapy, with limited durability. Development of effective combination targeted therapies, eg. combinations with BBDis, is an urgent unmet need for this patient population. Research Sponsor: U.S. National Institutes of Health; Lowe Center for Thoracic Oncology, Friends of Jay Dion, Ryan Richards Foundation, McDevitt Strong, Max Vincze Foundation; U.S. National Institutes of Health; R01CA124633-16.

9049 **Poster Session**

Thoracic SMARCA4-deficient cancer descriptors and clinicopathologic determinants of survival: Analysis of a pooled database.

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Background: Inactivation of SMARCA4, a catalytic subunit of the SWI/SNF complex, has been linked to high-grade aggressive cancers with poor prognoses. SMARCA4-deficient thoracic tumors (SDTT) can involve any part of the chest cavity, including the lungs, mediastinum, pleura, and chest wall. SDTT's detailed clinical features and optimal treatment still need to be clarified. Therefore, we conducted this pooled database analysis to delineate key clinicopathological characteristics, prognostic indicators, and treatment modalities that affect survival in this unique group of thoracic cancers. **Methods:** To study the demographic characteristics, molecular and immunohistochemical signatures, therapeutic interventions, survival, and prognostic factors, we compiled a pooled database of 120 cases of SDTT. Kaplan-Meier survival curves were constructed. Cox proportional hazards model and Log-rank tests were used to assess the influence of demographic and clinicopathologic factors on overall survival (OS). **Results:** A total of 120 patients with confirmed SDTT were identified. The median age was 54, with a peak incidence between 56 and 68. There was a male preponderance with M:F of 3. The median duration of symptoms before diagnosis was 3.5 months. Patients presented with local disease in 11%, locally advanced in 21%, and metastases in 61%. The primary sites were the lungs (45%), mediastinum (42%), and pleura (13%). Common metastatic sites were bone (32%), adrenals (30%), liver (20%), Brain (20%), and lungs (18%). The median OS of the whole group was 6 months. Ninety percent of patients had a smoking history with a median of 26 pack-years. Histology comprised epithelioid/rhabdoid (79%) and carcinoma (adenocarcinoma, mucinous, and undifferentiated, 21%). Carcinomas had a better median OS than sarcomatous histology (11 vs. 6 months, p=0.03). Furthermore, early stages (N0/N1) had a superior median OS compared to advanced stages ($N \geq 2$, M+) (16 vs. 5 months, p=0.02). Compared to no treatment, local therapies (surgery (S) or radiation (RT)), combination chemotherapy (CT), and combined modalities ($CT \pm S/RT$) were statistically superior with a median OS of 1, 4, 6, and 11 months, respectively ($p < 0.0001$). Further analysis revealed CT+S had superior median OS to CT+RT (16 vs. 9.5 months). Moreover, those with immune checkpoint inhibitors incorporated into their therapies had the best median OS outcomes ($p < 0.0001$). Age, sex, primary site, and size did not impact OS. **Conclusions:** This study presents updated clinicopathologic data from a pooled cohort of patients with SDTT cancers. It identifies the histologic type, stage, and treatment approach as critical determinants of OS. Research Sponsor: None.

9050 **Poster Session**

Safety, pharmacokinetics (PK), pharmacodynamics (PD) and preliminary efficacy of AZD2936, a bispecific antibody targeting PD-1 and TIGIT, in checkpoint inhibitor (CPI)-experienced advanced/metastatic non-small-cell lung cancer (NSCLC): First report of ARTEMIDE-01.

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Background: PD-1 and TIGIT are implicated in cancer-related T cell immunosuppression. AZD2936 is a bispecific, humanized IgG1 (triple-mutated to minimize Fc effector function) targeting PD-1 and TIGIT. It has demonstrated encouraging activity compared to both anti-PD-1 and anti-PD-1/-TIGIT combinations in murine models. We report data from dose escalation (Part A) and an expansion cohort (Part B) of the first-in-human study ARTEMIDE-01 (NCT04995523). **Methods:** This open-label, multicenter study enrolled pts with advanced NSCLC who had prior CPI treatment and a PD-L1 tumor proportion score ≥1%. Part A evaluated doses of 70–1500 mg IV Q3W; Part B evaluated the recommended phase 2 dose (RP2D). Primary endpoints included safety, tolerability, dose-limiting toxicities (DLTs) and preliminary efficacy. Secondary endpoints included PK and PD, defined as percentage PD-1 and TIGIT receptor occupancy (RO). **Results:** As of Dec 5, 2022, 80 pts were enrolled (Part A, n=48; Part B, n=32). Pts were 62.5% male, median age 63.5 years; 72.5% had adenocarcinoma, 23.8% had squamous cell carcinoma; 96.3% had metastatic disease; and 22.5% had brain metastases. They had a median of 2 prior regimens. Median duration of therapy was 11 wks. AZD2936 was well tolerated with no DLTs. In total, 46.3% of pts had treatment-related adverse events (TRAEs), all grade 1–3; the most common were pruritus, rash and lipase increased (6.3% each). Serious TRAEs occurred in 3 pts (3.8%): immune system disorder, acute hepatitis and fatigue (n=1 each). AZD2936 systemic exposure increased in a near dose-proportional manner. Doses of ≥210 mg achieved ~90% PD-1 and TIGIT RO in peripheral T cells. The RP2D was determined to be 750 mg Q3W based on safety, preliminary efficacy, PK/PD and modeling analysis predicting intratumoral RO. Among 76 evaluable pts, 3 had a partial response and 30 had stable disease (Table). Time to response was 1.9–4.0 mos and duration of response was 2.1–6.4 mos. **Conclusions:** In this interim analysis, AZD2936 showed an acceptable safety profile and preliminary antitumor activity in pts with advanced/metastatic NSCLC previously treated with standard therapy including CPIs. Further exploration of AZD2936 in CPI-naïve NSCLC pts, including a randomized dose optimization cohort is ongoing. Clinical trial information: NCT04995523. Research Sponsor: AstraZeneca.

Safety and preliminary antitumor efficacy of AZD2936.

Safety, n (%)	**N=80**
Treatment-emergent AEs, any grade / grade ≥3	70 (87.5) / 22 (27.5)
AEs related to AZD2936, any grade / grade ≥3	37 (46.3) / 4 (5.0)
AEs leading to discontinuation	3 (3.8)
Response and disease control	**Evaluable pts (n=76)**
Overall response rate, % (95% CI)	3.9 (0.8, 11.1)
Partial response, n (%)	3 (3.9)
Stable disease, n (%)	30 (39.5)
Disease control at 9 weeks, n (%)	33 (43.4)
Disease control at 27 weeks, n (%)	11 (14.5)

9051 **Poster Session**

Clinical outcomes among patients with advanced non-small cell lung cancer who received targeted therapy in a real-world setting.

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Background: In the past decade, therapies targeting *EGFR, KRAS, ALK, ROS1, BRAF, NTRK, MET, RET, HER2* and PD-L1 were approved and recommended by National Comprehensive Cancer Network (NCCN) for use in advanced non-small cell lung cancer (aNSCLC). This study compared real-world clinical outcomes in biomarker positive patients with aNSCLC who received treatments based on the NCCN NSCLC Guidelines (v5.2021) versus other therapies in the US. **Methods:** This is a retrospective cohort study of patients with aNSCLC using the TEMPUS oncology dataset. Patients were included if they were diagnosed with stage IIIB-IV NSCLC (index date) between 1/1/2012 and 12/31/2020, ≥18 years of age at index, were biomarker (i.e., *EGFR, KRAS, ALK, ROS1, BRAF, NTRK, MET, RET,* or PD-L1) positive, and received at least one line of treatment. Patients were stratified by NCCN recommended treatment (v5.2021) receipt anytime following aNSCLC diagnosis. Median overall survival (mOS), progression free survival (mPFS), and time to next treatment (mTTNT) were evaluated by treatment group using Kaplan Meier analysis. Patient demographic and clinical characteristics were evaluated as potential predictors of receipt of NCCN recommended therapy. **Results:** Of the 2,158 biomarker positive patients who met study criteria, 55.7% (N=1,201) received NCCN recommended treatment. PDL1 (38.0%), *EGFR* (32.2%), and/or *KRAS* (30.3%) were the most common over-expressions/mutations. Biomarker positive patients with aNSCLC treated with NCCN recommended treatment (N=1,201) in any line had significantly longer mOS (24.7mo, 95% CI: 22.5–27.6) than those treated with non-recommended treatment (N=957, 19.8mo, 95% CI: 17.5–22.6) ($p<0.001$). Biomarker positive patients with aNSCLC treated with NCCN recommended treatment also had significantly longer mPFS (8.5mo, 95% CI: 7.9–9.0) and mTTNT (20.6mo, 95% CI:19.3–23.7) than those treated with non-recommended treatment (4.9mo, 95% CI: 4.5–5.4) and (11.0mo, 95% CI: 10.0–12.7), respectively (both $p<0.001$). Never smokers (vs current smokers), patients of unknown or other race (vs whites), and patients who received 2 or more lines of treatment (vs 1) were more likely to receive NCCN recommended treatment and those with squamous or other/unknown histology (vs non-squamous) or missing ECOG scores (vs ECOG 0) were less likely to receive NCCN recommended treatment. **Conclusions:** In this study, biomarker positive patients with aNSCLC who received NCCN recommended treatment had significantly longer mOS, mPFS, and mTTNT than those who were treated with non-recommended regimens. Following the recommendations of the NCCN NSCLC Panel improves real-world clinical outcomes among biomarker positive patients with aNSCLC. Meanwhile, some biomarker positive patients—including current smokers and those with squamous cell histology—were less likely to receive targeted treatments. Research Sponsor: The healthcare business of Merck KGaA, Darmstadt, Germany.

9052 **Poster Session**

Prognostic and predictive implications of plasma ctDNA in guiding first-line targeted therapy for metastatic *HER2*-mutant non-small cell lung cancer (NSCLC).

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Background: Trastuzumab deruxtecan (T-DXd) is the first HER2-targeted drug approved for NSCLC with human epidermal growth factor receptor 2 (*HER2*, *ERBB2*) mutation in the second or later line settings. However, the optimal first-line treatment for these patients remains unclear. Access to rapid tissue sequencing is not always available, thus presenting challenges to first-line drug development. Circulating tumor DNA (ctDNA) analysis has the potential to overcome these obstacles to guide optimal first-line targeted therapy for patients with *HER2*-mutant NSCLC. **Methods:** We retrospectively analyzed patients with metastatic *HER2*-mutant NSCLC who underwent prospective clinical ctDNA sequencing at Memorial Sloan Kettering Cancer Center (MSK) from January 2016 to September 2022. *HER2* mutations were identified by next-generation sequencing through MSK-IMPACT, MSK-ACCESS or Resolution ctDx Lung. **Results:** We identified 64 patients with metastatic *HER2*-mutant NSCLC who had received at least one line of systematic therapy. The median age was 63 years (range: 23–90), and there were more women (n = 38, 60%), and never-smokers (n = 38, 60%). The activating *HER2* mutations included exon 20 insertions (73%), exon 8 (11%), 19 (11%), and 20 SNVs (5%). Plasma ctDNA was tested before initial therapy in 40 patients with a median overall survival (OS) of 28 months (95% CI 21-34), in whom 31 patients (78%) had at least one detectable ctDNA alteration by MSK-ACCESS and ctDx Lung. 55% (17/31) received chemoimmunotherapy with pembrolizumab as the first-line treatment. The median time to treatment discontinuation (TTD) was 6 months (95%CI 5.5-6.9). Additionally, 19% of patients (6/31) received a HER2-targeted antibody-drug conjugates (ADC) as first-line treatment with a median TTD of 6 months (95% CI 2-10), including 5 with T-DM1 and one who received first-line T-DXd treatment with a TTD of 9 months. Patients with baseline ctDNA alterations had significantly shorter OS (hazard ratio (HR), 5.25; 95% CI, 1–24; p = 0.019). **Conclusions:** Baseline plasma ctDNA has the potential to guide first-line targeted therapy for patients with *HER2*-mutant NSCLC. As an independent negative prognostic biomarker, detectable ctDNA at baseline would need to be taken into account for patient selection in future studies to avoid underestimating the effects of therapy. Research Sponsor: TBD.

9053 **Poster Session**

Safety and efficacy of immune checkpoint inhibitors in patients with cancer and pre-existing autoimmune disease: A systematic review and meta-analysis in non-small cell lung cancer.

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Background: Cancer patients with pre-existing autoimmune diseases (AID) have been traditionally excluded from clinical trials of immune checkpoint inhibitors (ICI) due to concerns for immune activation leading to toxicity. As indications for ICI expand, there is a need for robust data on safety and efficacy of ICI in cancer patients with AID. Existing studies examined a heterogenous group of cancers and do not include a comparison to cancer patients without pre-existing AID. Therefore, data are lacking concerning how safety and efficacy of ICI in this group of patients may differ from the general population and whether the results are generalizable to non-small cell lung cancer (NSCLC). **Methods:** We searched for studies consisting of NSCLC, AID, ICI, treatment response, and adverse events using database-controlled vocabulary terms. We systematically searched Medline (PubMed), EMBASE, Scopus, CINAHL, and Web of Science. We selected studies that included NSCLC and excluded abstracts, case reports, review articles, and articles lacking outcomes or populations of interest. Three authors (WA, CL, NS) independently reviewed all abstracts to determine study eligibility and quality. Study quality was assessed using the Newcastle-Ottawa Scale. Study data were pooled using random-effects meta-analysis. **Results:** Data were extracted from 24 cohort studies, consisting of 10,924 cancer patients, of which 4353 were NSCLC patients. Studies examined a broad spectrum of AID consisting of 1157 patients, of which 291 were NSCLC patients. Pooled analysis revealed an AID flare incidence of 36% (95%CI 27%-46%) in all cancers and 23% (95%CI 9%-40%) in NSCLC. Tests of subgroup difference revealed no significant difference in AID flares by organ system in all cancers and NSCLC ($p = 0.602$ and $p = 0.19$, respectively). Pre-existing AID was associated with a higher risk of de novo iRAE in all cancer patients (RR 1.38, 95%CI 1.16-1.65) and in NSCLC patients (RR 1.51, 95%CI 1.12-2.03). There was no difference in de novo grade 3-4 iRAE and tumor response between cancer patients with and without AID. However, in NSCLC patients, pre-existing AID was associated with a 2-fold increased risk of de novo grade 3-4 iRAE (RR 1.95, 95%CI 1.01-3.75) but also better tumor response in achieving a complete or partial response (RR 1.56, 95%CI 1.19-2.04). **Conclusions:** Pre-existing AID confers an increased risk of toxicity during ICI therapy. NSCLC patients with AID are at a higher risk of de novo grade 3-4 iRAE but are also more likely to achieve treatment response than those without AID. Multidisciplinary collaboration is paramount when considering ICI therapy in this patient population with careful calculation of risk and benefit as well as close monitoring for toxicity. Research Sponsor: None.

Phase II trial of lazertinib in patients with epidermal growth factor receptor (EGFR) mutation-positive (M+), metastatic non-small cell lung cancer (NSCLC) with asymptomatic or mild symptomatic brain metastases after failure of EGFR tyrosine kinase inhibitor (TKI) (KCSG LU20-15).

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Background: Central nervous system (CNS) metastases occur not infrequently, ultimately devastating consequences in advanced EGFR M+ NSCLC. Lazertinib, a 3rd-generation (G) EGFR-TKI, has shown potent antitumor activity in *EGFR*-mutant NSCLC. We conducted a phase II single-arm study of lazertinib in EGFR M+ NSCLC patients (pts) having CNS metastases to evaluate its CNS activity. **Methods:** The patients exhibiting CNS progression upon 1st or 2nd-G EGFR-TKIs with least one measurable CNS lesion were enrolled. The primary endpoint was intracranial objective response rate (iORR) in evaluable for response set (ERS). Secondary endpoints included iORR without T790M mutation, overall ORR (oORR), disease control rate (DCR), intracranial progression-free survival (iPFS) in ERS. Overall survival (OS) and safety analyses were performed in pts who received at least one dose of lazertinib. Cerebrospinal fluid (CSF) penetration was measured as exploratory biomarker study. **Results:** Of 40 pts enrolled, 38 were evaluable for tumor response. Nineteen pts harbored exon 19 deletion and 21 pts for exon 21 L858R and 30% of pts had radiologic evidence of leptomeningeal carcinomatosis (LM) with 2 cytological confirmed cases. Forty-five percent of pts received afatinib as first line treatment, followed by 42.5% of gefitinib and 12.5% of erlotinib. Baseline plasma samples of all the 40 patients obtained for liquid-based next-generation sequencing (Guardant360) and T790M was found in 5 pts prior to lazertinib treatment. iORR was 57.9% (22/38). iORR with T790M-negative, oORR, and DCR were 54.5%, 39.5%, and 97.4%, respectively. With median follow-up of 13.6 months, median iPFS and OS were not reached. Treatment-related adverse events (TRAEs) emerged in 85.0% of pts with most common TRAEs being skin rash (50.0%) and paresthesia (42.5%). Grade 3 or 4 TRAEs were reported in 10.0%. The CSF penetration rates of lazertinib and its metabolite (YH26334) were 46.2% and 33.1%, respectively in paired CSF and plasma samples, suggesting high CNS penetration efficacy. **Conclusions:** Lazertinib has substantial CNS activity regardless of T790M status against the progression of intracranial metastases ± LM during the treatment of 1st or 2nd-G EGFR-TKIs in metastatic EGFR M+ NSCLC pts. These results suggest that using lazertinib instead of brain local treatment would be a potential strategy in EGFR M+ NSCLC, who progressed on CNS metastases after prior EGFR-TKI. Clinical trial information: NCT05326425. Research Sponsor: Yuhan.

Efficacy outcome.	
Intracranial response, % (95% CI)	
iORR	57.9 (40.8 – 73.7)
iORR in T790M-negative patients	54.5 (36.4 – 71.9)
Best intracranial response, No. (%)	
Complete response	2 (5)
Partial response	20 (52.6)
Stable disease	15 (37.5)
Progressive disease	1 (2.5)
Not evaluable	2 (5)

9055 **Poster Session**

Assessment of sociodemographic disparities in outcomes among pts with metastatic NSCLC (mNSCLC) receiving select immuno-oncology (IO) regimens: CORRELATE.

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Background: IO treatment (tx) has transformed the care of pts with mNSCLC, persistently demonstrating significant survival benefits over chemotherapy. Prior analyses have shown OS and PFS are shorter in the real-world (rw) setting compared with randomized clinical trials (RCTs). A contributing factor may be the more diverse sociodemographic characteristics of pts in the rw. Race and socio-economic status (SES), in particular, have been associated with disparities in cancer outcomes, which may be related to inequalities in healthcare access. One aim of CORRELATE was to assess whether outcomes differ based on sociodemographic characteristics in pts receiving IO in the rw setting. **Methods:** Eligible pts from the US Flatiron Enhanced Datamart database had mNSCLC (progressed or *de novo*), started 1L IO tx between Nov 1 2016 and May 31 2021, and met eligibility criteria based on 6 RCTs (KEYNOTE [KN]-024, KN-189, KN-407, IMpower150, CheckMate [CM] 9LA and CM 227) for IO regimens approved in the US for mNSCLC. Flatiron's area-level measure of SES, available for pts treated at community oncology centers, was based on a validated composite index and has 5 levels (highest [5] to lowest [1]). Multivariate Cox regression models were used to determine the association of sociodemographic variables (age, sex, race, US region and SES) with OS and rwPFS separately; smoking history, ECOG performance status (PS) and PD-L1 expression were also included in the models, as were any pairwise interactions that were statistically significant ($P < 0.05$). **Results:** 2070 pts with non-missing data on the variables of interest were included in the dataset: 60% were aged ≥65 y, 86% white, 55% male and 53% were from the US Southern region. SES was relatively evenly distributed (SES 1–5: 18%, 22%, 21%, 24% and 15%, respectively); 41% of pts had PD-L1 ≥50% (17% unknown PD-L1 expression), 61% had ECOG PS 1 and 92% were former/current smokers. Median OS was 13.3 mos (95% CI 12.3–14.7); median rwPFS was 5.9 mos (5.6–6.2). In the multivariate analyses, race, region and SES did not have a statistically significant association with either OS or rwPFS. Older age (≥65 y; $P = 0.0091$) and male sex ($P < 0.0001$) were associated with a higher risk of death (HR [95% CI] 1.16 [1.04–1.29] and 1.28 [1.15–1.43], respectively). For rwPFS, the interaction between sex and smoking status was statistically significant ($P = 0.0312$); specifically, female non-smokers had a higher risk of progression or death vs female smokers (HR 1.45 [95% CI 1.15–1.82]). **Conclusions:** Our results from a nationally representative dataset of pts with mNSCLC treated at non-academic facilities show that, in pts who had equivalent access to IO tx, the OS and rwPFS benefits derived from IO were similar, irrespective of race, region or SES. More efforts are required to identify and address barriers of access to care to ensure that all pts receive appropriate cancer tx. Research Sponsor: AstraZeneca.

9056 **Poster Session**

Long-term efficacy and safety of larotrectinib in patients with tropomyosin receptor kinase (TRK) fusion lung cancer.

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Background: Neurotrophic tyrosine receptor kinase (*NTRK*) gene fusions are oncogenic drivers in a variety of tumor types, including lung cancer. Larotrectinib is a highly selective, central nervous system (CNS)-active TRK inhibitor that demonstrated rapid, deep, and durable responses in patients (pts) with TRK fusion lung cancer (Drilon et al. ASCO 2022) and is considered a preferred first-line therapy option for these pts (Owen et al. J Clin Oncol 2022). We report updated data from a larger cohort with longer follow-up. **Methods:** Pts with TRK fusion lung cancer enrolled in 2 larotrectinib clinical trials (NCT02576431 and NCT02122913) were included in this analysis. Larotrectinib was administered at 100 mg twice daily, and response was assessed by independent review committee (IRC) per RECIST v1.1. **Results:** As of July 20, 2022, 30 pts with a median age of 55.5 years (range 25–81) with TRK fusion lung cancer enrolled, including 12 pts with CNS metastases at baseline. The gene fusions involved *NTRK1* (n = 24; 80%) or *NTRK3* (n = 6; 20%). Pts received a median of 2 prior lines of systemic therapies, with 20 pts (67%) receiving ≥2. Among 27 pts eligible for IRC assessment, the objective response rate (ORR) was 74% (95% CI 54–89): 3 complete responses, 17 partial responses (PR), 4 stable disease (SD), 2 progressive disease (PD), and 1 not evaluable. Among the 12 pts with baseline CNS metastases, the ORR was 67% (95% CI 35–90): 8 PR, 2 SD, and 2 PD. The median time to response for all responders was 1.8 months. Median duration of response (DoR) was 33.9 months (95% CI 9.5–not estimable [NE]); median follow-up was 22.9 months. Median progression-free survival (PFS) was 33.0 months (95% CI 11.3–NE); median follow-up was 24.7 months. Median overall survival (OS) was 39.3 months (95% CI 17.2–NE); median follow-up was 23.1 months. For the 12 pts with CNS metastases, the medians for DoR, PFS, and OS were 9.5, 9.9, and 19.4 months, with median follow-ups of 17.4, 19.3, and 22.2 months, respectively. Duration of treatment for all pts evaluable per IRC ranged from 0.3+ to 75.2+ months. At data cut-off, 10 pts had progressed, with 6 continuing treatment post-progression for ≥4 weeks due to continued clinical benefit. Treatment-related adverse events (TRAEs) were predominantly Grade 1–2. Grade 3–4 TRAEs were reported in 5 pts (2 each increased aspartate aminotransferase, increased weight; 1 each increased alanine aminotransferase, myalgia, hypersensitivity). There were no treatment discontinuations due to TRAEs. **Conclusions:** In this larger dataset with longer follow-up, larotrectinib continued to demonstrate rapid and durable responses, extended survival, and favorable long-term safety in pts with advanced TRK fusion lung cancer, including those with CNS metastases. These results support the wider adoption of next-generation sequencing testing for *NTRK1–3* gene fusions in pts with lung cancer. Clinical trial information: NCT02576431, NCT02122913. Research Sponsor: These studies were funded by Bayer HealthCare Pharmaceuticals, Inc. and Loxo Oncology, Inc., a wholly owned subsidiary of Eli Lilly and Company.

9057 **Poster Session**

The safety and efficacy of SNK01 (autologous natural killer cells) in combination with cytotoxic chemotherapy after failure of prior tyrosine kinase inhibitor in non-small cell lung cancer: Preclinical mouse model and phase I/IIa clinical study.

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Background: It is challenging to choose subsequent treatment option in patients with Osimertinib resistance in epidermal growth factor receptor (EGFR)-mutated non-small cell lung cancer (NSCLC). Meanwhile, antitumor effect of the antibody-dependent cellular cytotoxicity of natural killer (NK) cells mediated by cetuximab –anti-EGFR monoclonal antibody– has been reported. Therefore, we aimed to evaluate the safety and efficacy of SNK01 (non-genetically modified autologous NK cell) in combination with cytotoxic chemotherapy including cetuximab in NSCLC after failure to prior tyrosine kinase inhibitor (TKI) in a preclinical humanized cell line-derived xenograft (CDX) mouse model and phase I/IIa clinical study. **Methods:** We established a humanized CDX mouse model using Osimertinib-resistant lung cancer cell line. Reconstruction of the humanized mouse, CDX-related skills, and analytic data were made according to C&SR Inc. manufacturing technique & SOP protocol. The mice were divided into 4 groups based on treatment (no treatment [n = 2]; Cetuximab only [n = 3]; SNK01 only [n = 4]; SNK01 plus Cetuximab [n = 4]) and treated weekly for 5 weeks (SNK01, $1x10^7$ cells/dose; Cetuximab, 20 ug/dose). In the clinical study, 12 patients with EGFR-mutated NSCLC who failed prior TKI treatment were finally enrolled. They received weekly SNK01 in combination with Gemcitabine/Carboplatin (n = 6) or Gemcitabine/Carboplatin/Cetuximab (n = 6), and dose escalation of SNK01 following "3+3" design (4×10^9 cells/dose or 6×10^9 cells/dose). The primary endpoint was safety, and secondary endpoint was efficacy. **Results:** In the preclinical study, flow cytometry analysis showed that NK cells (CD45+/CD56+/CD3-) were significantly increased in the groups administrated SNK01. The volume of tumor extracted after completion of treatment was the smallest in SNK01 plus cetuximab group. In the clinical study, the median age of patients was 61 years, 33.3% were male, and all patients had adenocarcinoma. The enrolled patients received weekly infusions of SNK01 for 7 to 8 weeks (4×10^9 cells/dose [n = 6]; 6×10^9 cells/dose [n = 6]). Since dose limiting toxicity was not observed, maximum tolerated dose of SNK01 was determined to be 6×10^9 cells/dose. SNK01-related adverse event ≥grade 3 was also not observed. In the efficacy analysis, objective response rate was 25%, disease control rate was 100% (partial response, n = 3/12; stable disease, n = 9/12), and median progression free survival (PFS) was 143 days. PFS will be updated as some patients are still being followed. **Conclusions:** SNK01 in combination with cytotoxic chemotherapy, including cetuximab in EGFR-mutated NSCLC with resistance to TKI was safe and showed a potential antitumor effect in this preclinical study and early phase I/IIa clinical trial. Clinical trial information: NCT04872634. Research Sponsor: NKMAX.

9058 **Poster Session**

Impact of first-line immunotherapy on survival and intracranial outcomes from a real-world cohort of patients with non-small cell lung cancer with brain metastases at diagnosis.

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Background: Although brain metastases (BM) at diagnosis are common in non-squamous NSCLC patients (ns-NSCLC), they have been mostly excluded from randomized trials. The aim of this retrospective study was to evaluate real-word outcomes of frontline immune checkpoint inhibitor (ICI) in these patients. **Methods:** We conducted a retrospective study to assess the intracranial and overall efficacy of first-line ICI-based therapy compared to chemotherapy (CT) in ns-NSCLC patients diagnosed with BM, showing no targetable alterations. Patients were divided according to systemic therapy: CT, ICI, or CT-ICI respectively. Primary endpoint was overall survival (OS), compared using Kaplan-Meier and Cox methodology. Secondary endpoint was intracranial progression free survival (icPFS). **Results:** Between 01-2018 and 05-2021, 118 newly diagnosed ns-NSCLC patients with BM were included (52 CT, 38 ICI and 28 CT-ICI). Median follow-up was 30.0 months [95% CI: 25.9-36.0]. Intracranial radiotherapy was delivered for 75.0%, 68.4% and 67.9% of patients for CT, ICI and CT-ICI groups (p = 0.805) respectively. OS rates at 24 months were respectively 25.3% (95% CI: 15.7-40.9), 44.6% (95% CI: 30.8-64.7) and 50.5% (95% CI: 34.3-74.4) in CT, ICI and CT-ICI groups (p = 0.048). Twelve-month icPFS was respectively 17.0% (95% CI: 9-32), 47% (95% CI: 33-66) and 45% (95% CI: 30-69) in CT, ICI and CT-ICI groups . After adjustment, ICI and CT-ICI were associated with a better OS compared to CT (HR = 0.46, 95%CI: 0.23-0.89, p = 0.021 and HR = 0.52, 95%CI: 0.27-1.01, p = 0.054 respectively). ICI and CT-ICI were associated with a significant reduction in the risk of intracranial progression by 54% (HR = 0.46, 95%CI: 0.25–0.84, p = 0.0123) and 59% (HR = 0.41, 95%CI: 0.23–0.77, p = 0.0050) compared to CT. Stereotactic radiosurgery was associated with an increased icPFS compared to systemic therapy alone (HR = 0.51, 95% CI: 0.29 – 0.92, p = 0.0247), whereas whole-brain was not (p = 0.096). **Conclusions:** Real-life ns-NSCLC patients with BM at diagnosis treated frontline with ICI presented OS and icPFS benefit compared to CT alone. A prospective assessment of the ideal type and sequence of systemic and local therapy should be conducted. Research Sponsor: None.

9059 **Poster Session**

Phase 2 clinical trial of the proautophagic drug ABTL0812 combined with paclitaxel and carboplatin in first-line patients with advanced squamous non-small cell lung carcinoma.

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Background: ABTL0812 induces the inhibition of Akt/mTOR pathway by upregulation of TRIB3 protein, an endogenous Akt inhibitor, and promotes endoplasmic reticulum (ER) stress. As a result, ABTL0812 induces cytotoxic autophagy that leads to specific death of cancer cells, without affecting non-tumor cell viability. A Phase II clinical trial was designed where ABTL0812 was evaluated in combination with paclitaxel and carboplatin in first-line patients with advanced squamous non-small cell lung cancer (NSCLC). **Methods:** ABTL0812 was administered 1300 mg TID orally with 175 mg/m^2 paclitaxel and AUC5 carboplatin every 3 weeks, for up to 8 cycles, followed by ABTL0812 as a maintenance until disease progression or unacceptable toxicity. The study enrolled patients with non-irradiable IIIb stage or stage IV squamous NSCLC. Primary endpoint was overall response rate (ORR) by RECIST criteria v.1.1. Secondary endpoints were progression free survival (PFS), overall survival (OS), duration of response (DOR), safety and tolerability according to CTCAE v4.03, pharmacokinetics (PK) of ABTL0812 enantiomers ((-)-ABTL and (+)-ABTL) and pharmacodynamics assessed by two surrogate blood biomarkers: TRIB3 and CHOP. **Results:** Forty patients were included; median age was 66.1 years old; 90% men/10% women; 100% ECOG 0-1; 30% current smokers/67.5% former smokers and 37.5% had received prior chemotherapy $>$ 12 months before inclusion. 39 patients had at least 1 adverse event (AE), anemia appeared in 32.5% of the patients (5.0% grade 3), neutropenia in 27.5% (25% grades 3-4) and thrombocytopenia in 17.5% of the patients (2.5% grade 3). For non-hematological AEs, asthenia was reported in 62.5% of the patients (2.5% grade 3); diarrhea in 45% (no grade 3-4) and nausea in 37.5% (5% grades 3-4). Twenty-five patients reach the primary endpoint for efficacy evaluation. ORR was 52.0% (95% CI 34.2-65.9) and 32.0% of the patients had stable disease. Median OS was 22.5 months (10.4-NC), median progression free survival 6.2 months (4.4-8.8), and DOR 5.1 months (3.9-7.4). Area under the curve (μg·h/ml) for (-)-ABTL and (+)-ABTL were 39.0$\pm$12.3 and 17.1$\pm$6.3 respectively, maximal concentrations (μg/ml) were 6.4$\pm$2.6 and 5.1$\pm$2.2 and minimum concentrations (μg/ml) 2.2$\pm$1.5 and 0.8$\pm$1.3. TRIB3 and CHOP PD biomarkers were induced by the treatment. **Conclusions:** The combination of ABTL0812 with paclitaxel and carboplatin shows survival outcomes that compare favorably with historical controls in squamous-NSCLC with an acceptable safety profile. PK analysis is compatible with drug activity, and pharmacodynamic analysis shows drug engagement. Clinical trial information: NCT03366480. Research Sponsor: Ability Pharmaceuticals SA; Government of Spain.

9060 **Poster Session**

Long-term outcomes of tepotinib in patients with *MET* exon 14 skipping NSCLC from the VISION study.

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Background: Tepotinib is a highly selective MET inhibitor with clinical activity in patients (pts) with *MET* exon 14 (*MET*ex14) skipping NSCLC. We previously reported robust and durable activity of tepotinib from the Phase II VISION study (NCT02864992; data cut: Feb 20, 2022; median follow-up: 26.1 months [mos]; Thomas, et al. WCLC 2022). Here, we report long-term outcomes from VISION, fulfilling an FDA post-market requirement (data cut: Nov 20, 2022; follow-up: Cohort A [primary cohort] ≥35 mos, Cohort C [confirmatory cohort] ≥18 mos). **Methods:** Pts with advanced *MET*ex14 skipping NSCLC detected by liquid and/or tissue (T+) biopsy received tepotinib 500 mg (450 mg active moiety) once daily. The primary endpoint was objective response by independent review using RECIST v1.1. Secondary endpoints included duration of response (DOR), progression-free survival (PFS), overall survival (OS), and safety. **Results:** Of 313 pts enrolled, median age was 72 years (range 41–94) and pts received tepotinib for a mean (standard deviation [SD]) of 11.5 mos (11.6); median follow-up was 32.6 mos (range 0.3–71.9). First line (1L) pts (n=164; median age: 74 years [range 47–94]; male: 50.6%; ECOG PS 1: 72.0%; smoking history: 53.7%) received tepotinib for a mean (SD) of 12.4 mos (12.2), with 27 pts still receiving treatment. ORR was 57.3% (95% CI: 49.4, 65.0), mDOR was 46.4 mos (13.8, not estimable [ne]), mPFS was 12.6 mos (9.7, 17.7), and mOS was 21.3 mos (14.2, 25.9). Among 111 1L T+ pts, ORR was 58.6% (48.8, 67.8), mDOR was 46.4 mos (15.2, ne), mPFS was 15.9 mos (11.0, 49.7), and mOS was 29.7 mos (18.8, ne) (Table). Second-or-later line (2L+) pts (n=149; median age: 71 years [range 41–89]; male: 47.7%; ECOG PS 1: 75.8%; smoking history: 40.9%) received tepotinib for a mean (SD) of 10.5 mos (11.0), with 10 pts still receiving treatment. ORR was 45.0% (36.8, 53.3) and mDOR was 12.6 mos (9.5, 18.5). Across all 313 pts, ORR was 51.4% (45.8, 57.1), mDOR was 18.0 mos (12.4, 46.4), mPFS was 11.2 mos (9.5, 13.8), and mOS was 19.6 mos (16.2, 22.9). No new safety concerns were observed. Grade ≥3 treatment-related adverse events (TRAEs) occurred in 34.8% of pts; 14.7% of pts discontinued treatment due to TRAEs. Any grade related peripheral edema occurred in 67.1% of pts (Grade ≥3: 11.2%). **Conclusions:** The long-term outcomes of VISION demonstrate the robust and durable clinical activity of tepotinib, particularly in 1L T+ pts, and manageable safety profile, further defining its use in clinical practice. Clinical trial information: NCT02864992. Research Sponsor: The healthcare business of Merck KGaA, Darmstadt, Germany.

Efficacy	Overall N=313	1L n=164	2L+ n=149	1L T+ n=111	2L+ T+ n=97
ORR, %	51.4	57.3	45.0	58.6	49.5
(95% CI)	(45.8, 57.1)	(49.4, 65.0)	(36.8, 53.3)	(48.8, 67.8)	(39.2, 59.8)
mDOR, mos	18.0	46.4	12.6	46.4	12.4
(95% CI)	(12.4, 46.4)	(13.8, ne)	(9.5, 18.5)	(15.2, ne)	(8.3, 18.0)
mPFS, mos	11.2	12.6	11.0	15.9	11.5
(95% CI)	(9.5, 13.8)	(9.7, 17.7)	(8.2, 13.7)	(11.0, 49.7)	(8.2, 14.7)
mOS, mos	19.6	21.3	19.3	29.7	20.4
(95% CI)	(16.2, 22.9)	(14.2, 25.9)	(15.6, 22.3)	(18.8, ne)	(17.0, 25.5)

9061 **Poster Session**

Long-term follow-up of "adjuvant" pembrolizumab following locally ablative therapy for oligometastatic non-small cell lung cancer.

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Background: Patients with oligometastatic (OM) non-small cell lung cancer (NSCLC) benefit from local ablative therapies (LAT); however, the role of adjuvant systemic therapies post LAT remains less clear. In a single-arm Phase II clinical trial (NCT02316002), we demonstrated that patients with OM NSCLC treated with adjuvant pembrolizumab following LAT had superior progression free survival (PFS) compared to historical controls. Here, we present long term follow-up on PFS and overall survival (OS). **Methods:** Patients with OM ($\leq$ 4 metastatic sites) NSCLC treated with LAT to all sites received pembrolizumab every 21 days for up to 16 cycles from February 1, 2015 through September 30, 2017. Other key inclusion criteria included ECOG PS 0-1 and the absence of autoimmune diseases. Patients were eligible regardless of the number of prior therapies or PD-L1 status. Our study design was an intention to treat analysis with a null hypothesis that PFS would be equivalent to historical controls (6.6 months) compared with the alternative that PFS would be greater than 10 months. Assuming 42 patients enrolled over 2 years, we calculated 80% power to detect improvement in PFS with a 1-sided 5% significance level. Primary efficacy endpoint was PFS from the start of pembrolizumab and was defined as evidence of progressive disease (PD) via RESCIST v1.1 criteria, death, or last contact. Secondary endpoints included OS, determined by date of death or last contact, and safety. Cox proportional hazard models were performed to assess associations between clinicopathologic features and PFS or OS. **Results:** 51 patients enrolled in the study; 45 patients (median age, 64 years [range, 46-82]; 21 [47%] women; 31 [69%] with solitary OM site) received pembrolizumab following LAT. Patients received a median of 11 cycles of pembrolizumab; 18 (40%) patients completed 16 cycles. At the data cutoff (December 1, 2022; median f/u, 65.8 months), 32 patients had PD, 19 patients died, and 13 patients had no evidence of relapse. Median PFS was 19.7 months (95% CI, 7.6-31.7 months); median OS was not reached (95% CI, NR-NR). OS rate at 5 years was 60.0% (SE, 7.4%). Upon PD, 94% of patients received salvage therapies. Median OS from the time of PD was 39.7 months (95% CI, 13.8-65.6 months). Metachronous OM disease was significantly associated with improved OS (HR, 3.2 [95% CI, 1.5-6.7] and PFS (HR, 2.9 [95% CI, 1.2-7.5]) via multivariate Cox proportional-hazard models. The number of OM sites, CNS disease, nodal stage at diagnosis, or tumor PD-L1 status was not significantly associated with PFS or OS. We did not observe new safety signals for pembrolizumab following LAT aside from those previously reported. **Conclusions:** Pembrolizumab following LAT for OM NSCLC results in promising PFS and OS compared to historical experience with a tolerable safety profile. Further investigation of this approach with a randomized trial is warranted. Clinical trial information: NCT02316002. Research Sponsor: Merck & Co.; U.S. National Institutes of Health.

9062 **Poster Session**

Mechanisms of resistance to tyrosine kinase inhibitor treatments in patients with ROS1 fusion-positive non-small cell lung cancer.

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Background: ROS1 rearrangement was found in about 1% non-small cell lung cancer (NSCLC), and the fusion proteins created during this process will result in the successive activation of the ROS1 kinase domain. NSCLC patients with ROS1 gene fusions were considered a unique subtype highly sensitive to related tyrosine kinase inhibitor (TKI) treatments. However, the acquired TKI resistance was the major hurdle preventing patients from getting prolonged treatment benefits. **Methods:** 107 patients diagnosed with advanced or metastatic NSCLC harboring ROS1 fusion were retrospectively recruited. All patients were treated with crizotinib as first-line treatment, and 21 patients received lorlatinib after crizotinib progression. Samples were collected at baseline, after crizotinib progression, and after lorlatinib progression, which all underwent targeted DNA sequencing. TKIs binding to mutated ROS1 fusion proteins was simulated using molecular dynamics simulations. **Results:** The most witnessed fusion partner of ROS1 was CD74 (58%), followed by SDC4 (14%), EZR (11%), and SLC34A2 (9%). The median progression-free survival was 12.9 months for crizotinib and 6.4 months for lorlatinib. Patients with CD74-ROS1 and SLC34A2-ROS1 had significantly longer PFS than those with other ROS1 fusion types when treated with crizotinib. Patients with baseline TP53 mutations showed worse PFS compared to TP53 wild-type (WT) patients ($P < 0.001$, HR: 0.19, 95%CI: 0.09-0.39) under crizotinib treatment. An accumulation of both on-target (baseline vs. post-crizotinib vs. post-lorlatinib: 0% vs. 43% vs. 62%) and off-target resistant mutations (baseline vs. post-crizotinib vs. post-lorlatinib: 22% vs. 26% vs. 43%) after multiple TKI treatments was observed. A total of ten on-target resistance mutations were detected after TKI therapies, with 4 first-reported mutations (ROS1 L2010M, G1957A, D1988N, L1982V). According to the molecular dynamics simulation results, ROS1 L2010M mutations (happening in the ROS1 kinase ATP binding cassette) maybe resistant to lorlatinib, entrectinib, cabozantinib, and crizotinib. ROS1 G1957A may lead to resistance to cabozantinib. Moreover, all four novel on-target mutations may lead to resistance to crizotinib. **Conclusions:** In summary, CD74- and SLC34A2-ROS1 patients showed better crizotinib efficacy with different resistance mutation patterns. Patients of these subtypes are potential beneficiaries of molecular testing after crizotinib progression, directing future treatment strategies. Multiple TKI treatments may lead to the accumulation of both on-target and off-target resistance mutations. In addition, 4 novel ROS1 on-target mutations identified underwent molecular dynamics simulations, unveiling potential resistance to different TKIs, which can provide vital information for future ROS1 fusion-positive NSCLC patient treatment selections. Research Sponsor: None.

9063 **Poster Session**

Management of patients with *ALK*-positive advanced non-small cell lung cancer who received brain radiotherapy on study in the phase 3 CROWN trial.

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Background: Approximately 30% of patients with *ALK*-positive non-small cell lung cancer (NSCLC) present with brain metastases at diagnosis. Lorlatinib is a potent brain-penetrant ALK tyrosine kinase inhibitor (TKI) that showed improved time to intracranial (IC) progression compared with crizotinib in patients with and without brain metastases at baseline. This post hoc analysis from the phase 3 CROWN study summarizes the management of patients who received brain radiotherapy (RT) during the study. **Methods:** In the CROWN study, 296 patients with previously untreated *ALK*-positive advanced NSCLC were randomized 1:1 to receive oral lorlatinib 100 mg once daily (n = 149) or crizotinib 250 mg twice daily (n = 147). Patients who received brain RT while on study treatment or after the initiation of subsequent systemic anticancer therapy were included in this post hoc analysis. **Results:** As of September 20, 2021, at approximately 3 years of follow-up, median time to IC progression was not reached (NR; 95% CI, NR-NR) in the lorlatinib arm and was 16.6 (95% CI, 11.1-NR) months in the crizotinib arm. At the time of this analysis, 4 of 149 patients (2.7%) in the lorlatinib arm and 20 of 147 patients (13.6%) in the crizotinib arm received brain RT; study treatment was ongoing in 2 of 4 patients (50.0%) in the lorlatinib arm and discontinued in all 20 patients in the crizotinib arm. Median time from randomization to first brain RT was 18.2 (range, 6.4-31.3) months in the lorlatinib arm and 11.1 (range, 2.5-37.5) months in the crizotinib arm. In patients who had brain RT, median duration of treatment was 20.0 (IQR, 6.3-37.1) months with lorlatinib and 7.8 (IQR, 4.0-11.1) months with crizotinib. In the lorlatinib arm, 2 of 4 patients (50.0%) received concomitant brain RT and continued lorlatinib beyond progression. In the crizotinib arm, patients received brain RT while on study treatment or on subsequent systemic anticancer therapies with ALK TKIs or chemotherapy. Follow-up analysis is ongoing. **Conclusions:** At approximately 3 years of follow-up in the CROWN study, fewer patients in the lorlatinib arm received brain RT than those in the crizotinib arm. At the time of this analysis, study treatment was ongoing in 2 of 4 patients (50.0%) in the lorlatinib arm but was discontinued in all patients in the crizotinib arm. Patients were mostly managed with other ALK TKIs and/or chemotherapy following brain RT in the crizotinib arm. ClinicalTrials.gov: NCT03052608. Clinical trial information: NCT03052608. Research Sponsor: Pfizer.

9064 **Poster Session**

Emerging phase 1 data of BLU-451 in advanced NSCLC with EGFR exon 20 insertions.

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Background: In patients (pts) with NSCLC harboring *EGFR* exon 20 insertions (ex20ins), treatment options are limited, with platinum-based chemotherapy with/without programmed death-ligand 1 inhibitors being the standard of care in first line, and recent accelerated approvals of mobocertinib and amivantamab in the USA for second-line treatment. These second-line therapies have overall response rates of 28% and 40%, respectively, limited CNS activity, and are associated with AEs such as severe gastrointestinal AEs and edema. BLU-451 is an investigational, CNS-penetrant, potent, selective, and wild-type sparing EGFR tyrosine kinase inhibitor that is under investigation in the ongoing phase 1/2 CONCERTO trial (NCT05241873), including in pts with ex20ins. **Methods:** In phase 1 dose escalation using a 3+3 design, BLU-451 monotherapy was administered orally QD or BID and given in continuous 21-day cycles. The primary objectives include maximum tolerated dose (MTD) and/or recommended phase 2 dose (RP2D) determinations and safety. Key secondary objectives include antitumor activity, PK, and pharmacodynamics. Pts with *EGFR* ex20ins–positive NSCLC after prior platinum-based chemotherapy were enrolled. Prior ex20ins–targeted therapy and asymptomatic CNS disease were permitted. Tumor response was assessed per RECIST v1.1. Serial blood samples for analysis of BLU-451 PK and circulating tumor DNA (ctDNA) were collected. **Results:** As of Jan 20, 2023, 28 pts have been enrolled and dosed in 5 cohorts (100 mg–400 mg QD and 200 mg BID), including 19 (68%) pts with exon 20 insertions. The median number of prior systemic lines of therapy was 2.5 (range, 1–10), and 19/28 (68%) pts had prior ex20ins-targeted agents. The most common AEs were diarrhea (21%), cough (18%), fatigue (14%), pruritis (14%) and rash (14%); all were Grade 1 or 2. There were no dose-limiting toxicities. Partial responses, including a disappearance of a CNS target lesion, were seen, and early evidence of on-target activity with ctDNA reductions was observed. **Conclusions:** As of the data cutoff, BLU-451 monotherapy was generally well tolerated, with early evidence of clinical activity in heavily pretreated pts with *EGFR* ex20ins–positive NSCLC. Early data at initial dose levels consisted of tumor reduction including responses, CNS activity, and ctDNA responses. The dose escalation is ongoing to determine the MTD and/or RP2D. Clinical trial information: NCT05241873. Research Sponsor: Blueprint Medicines.

9065 **Poster Session**

First results from the RETgistry: A global consortium for the study of resistance to RET inhibition in *RET*-altered solid tumors.

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Background: Rearranged during transfection (*RET*) gene alterations are the oncogenic driver in diverse tumor types, including *RET* fusions identified in 1-2% of non-small cell lung cancers (NSCLC). While RET-selective tyrosine kinase inhibitors (TKIs) selpercatinib and pralsetinib are effective, acquired drug resistance remains a challenge. Here, we report the initial results from the RETgistry, an international consortium aimed at elucidating mechanisms of resistance to RET TKIs across *RET*-altered solid tumors. **Methods:** This was a retrospective analysis performed across 16 institutions. Patients (pts) were eligible if they had advanced solid tumor harboring an oncogenic *RET* alteration, received ≥1 RET TKI with disease progression, and underwent resistant tumor or liquid biopsy for next-generation sequencing (NGS). **Results:** A total of 103 time-distinct biopsies (62 tissue, 30 plasma, 11 paired tissue/plasma) were included in analysis, obtained from 88 pts with progression on a RET-selective TKI [selpercatinib (n = 70), pralsetinib (n = 14), selpercatinib and pralsetinib sequentially (n = 4)]. Pts had the following tumor types: 72 NSCLC (69% *KIF5B-RET*, 21% *CCDC6-RET*, 10% other *RET* fusion), 13 medullary thyroid cancer (TC) (54% *RET* M918T, 46% other *RET* mutation), and 2 papillary and 1 anaplastic TC (all, *RET* fusion). Median age was 58 (range, 21-86); 48% were male with 89% never/light smokers. Median duration of RET TKI preceding biopsies [first-line, n = 32 (31%); second-line, n = 42 (41%); third-/greater-line, n = 29 (28%)] was 16.5 months (mos) (95% CI, 14.0-19.6); median PFS was 14.1 mos (95% CI, 9.3-17.0). Resistant biopsies were obtained at median 15.0 mos from TKI initiation (range, 1.8-58.8). Acquired *RET* mutations were detected in 14 (14%), most common being G810 substitutions in 12 (12%). Potential off-target resistance gene alterations identified in 43 cases (42%) included *MET* amplification (14%), *BRAF* V600E or fusion (2%), *KRAS* gain or mutation (5%), *ERBB2* amplification (2%), *EGFR* amplification (3%), *ROS1* fusion (1%), and activating *PIK3CA* mutation or *PTEN* loss (4%). No resistant lung cancer biopsy demonstrated small cell transformation. The duration of TKI therapy (HR 0.64, p = 0.11) or PFS (HR 0.75, p = 0.33) did not differ according to the presence of on-target vs off-target resistance. NGS analyses of pre-RET-selective TKI tumors (n = 92) revealed frequent co-occurring alterations in *TP53* (29%) and CDKN2A/B (12%). **Conclusions:** On-target resistance to RET inhibition due to acquired *RET* mutations was less common than off-target resistance, identified in 14%. The majority of RET TKI resistance is mediated by off-target mechanisms such as bypass receptor tyrosine kinase activation. Further studies are warranted to enable the development of therapeutic strategies to address resistance in pts with *RET*-altered tumors. The RETgistry accrual and data analyses continue. Research Sponsor: Happy Lungs.

9066 **Poster Session**

Efficacy and safety of PD-1/PD-L1 inhibitor plus platinum-based chemotherapy vs. platinum-based chemotherapy alone in patients with previously untreated advanced large-cell neuroendocrine cancer of the lung.

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Background: Large-cell neuroendocrine carcinoma (LCNEC) is a rare tumor with a poor prognosis and limited treatment options. The efficacy of first-line therapies for LCNEC has not yet been established. This study evaluated the efficacy and safety of the combination of PD-1/PD-L1 inhibitor and platinum-based chemotherapy in treatment-naïve patients with advanced LCNEC. **Methods:** We retrospectively analyzed patients with advanced LCNEC who were treated with a PD-1/PD-L1 inhibitor plus platinum-based chemotherapy (PD-1/PD-L1 inhibitor group) or with platinum-based chemotherapy alone (chemotherapy group) based on data obtained from electronic databases of three participating cancer centers from January 2015 to August 2022. Progression-free survival (PFS), overall survival (OS), objective response rate (ORR), and disease control rate (DCR) were evaluated for each group. Safety was assessed in all patients who received at least one dose of their assigned treatment. **Results:** Among the 75 enrolled patients, 25 were allocated to receive PD-1/PD-L1 inhibitor plus platinum-based chemotherapy and 50 were allocated to receive platinum-based chemotherapy alone (patients were matched 1:2 on baseline characteristics). The median PFS was 15.1 months (95% confidence interval [CI], 7.1–23.2) in the PD-1/PD-L1 inhibitor group and 5.3 months (95% CI, 4.4–6.2) in the chemotherapy group (hazard ratio [HR], 0.26; 95% CI, 0.113–0.428; $p < 0.0001$). The 12-month OS was 88.0% (95% CI, 67.7–96.9) in the PD-1/PD-L1 inhibitor group and 56.0% (95% CI, 41.4–69.7) in the chemotherapy group ($p = 0.0056$). The ORRs in the two groups were 40% and 16%, respectively ($p = 0.022$), and the DCRs were 96% and 70%, respectively ($p = 0.010$). Regarding safety, the most common incidences of grade ≥ 3 adverse events involved neutropenia, leukopenia, anemia, and fatigue. There were no significant differences between the two groups. Immune-related adverse events (irAEs) in the PD-1/PD-L1 inhibitor group included cutaneous hemangiomas, hypothyroidism, anaphylaxis, and pneumonitis. Grade 3 or 4 irAEs were not observed. No new safety signals were noted. **Conclusions:** First-line PD-1/PD-L1 inhibitor plus platinum-based chemotherapy significantly improved PFS in patients with advanced LCNEC compared with platinum-based chemotherapy alone. Research Sponsor: None.

9067 **Poster Session**

Sex differences in prognostic utility of peripheral eosinophil count in first-line immune checkpoint therapy against metastatic NSCLC.

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Background: To date, few studies have associated elevated Absolute Eosinophil Count (AEC) with improved outcome to a single agent immune checkpoint inhibitor (ICI) as first or subsequent line of therapy in patients with NSCLC. Here, we investigated prognostic utility of AEC and the sex difference in patients undergoing standard-of-care first-line ICI with or without chemotherapy for metastatic NSCLC. **Methods:** This was a retrospective cohort study of 310 patients with Stage IV NSCLC treated with first-line ICI-based therapies (alone or in combination with chemotherapy) under IRB approved protocol 2021C0069. Demographic data are summarized in the table. Peripheral AEC measured by cells/microL was collected within 1 week before the start of therapy. Eosinophil count was evaluated in males and females by both descriptive statistics and Chi-squared test as a continuous and categorical variable, respectively. High level of baseline AEC was defined as 75th percentile (270 cells/microL). Overall Survival (OS) was plotted using the Kaplan-Meier method and *p*-values from log-rank test were reported. PD-L1 was assessed by tumor proportion score (TPS) and classified into $< 1\%$, 1 to 49% and $\geq 50\%$. **Results:** 14% male vs 6% female patients were found to have peripheral eosinophilia (AEC ≥ 500) at the start of immunotherapy, $p = 0.02$. Patients with lower AEC had a median OS of 18.6 months vs 29.3 months in those with higher AEC ($p = 0.02$, HR: 1.465, 95% CI: 1.073-2.001). Patients with higher baseline AEC showed a sex difference, with median OS of 23.9 months in males vs NR median OS in females with over 60% survival at the time of last follow up ($p = 0.04$, HR: 1.934, 95% CI: 1.040-3.597). This difference was seen with ICI monotherapy ($p = 0.02$, HR: 2.630, 95% CI: 1.192-5.805), but not ICI with chemotherapy ($p = 0.83$, HR: 1.116, 95% CI: 0.4054-3.070). Higher AEC was associated with TPS $\geq 50\%$ in both males and females ($p = 0.004$ and 0.001, respectively), though no significant sex difference was observed. **Conclusions:** Our data highlight critical sex differences in interpretation of baseline AEC in patients on ICI therapy for metastatic NSCLC. While males have a higher frequency of peripheral eosinophilia, higher AEC correlates to improved OS predominantly in females. Further, this female-biased outcome is seen only with ICI monotherapy, even though higher AEC is associated with high PD-L1 expression in both sexes. Future studies are indicated to assess the longitudinal trend in eosinophil count as well as their active versus passive role in anti-tumor immunity and toxicity in the presence or absence of chemotherapy. Research Sponsor: REDCap project (National Center for Advancing Translational Sciences, Grant UL1TR001070); Corresponding author Dr. Owen is supported by a LUNGevity Career Development Award.

Demographic summary.

	Male	Female
Sex	55%	45%
Age		
Median (range), in years	66 (39-89)	64 (31-95)
ECOG		
0	20%	22%
1	53%	50%
≥ 2	27%	28%
Histology		
Squamous	25%	12%
Non-squamous	75%	88%
PD-L1 TPS		
< 1%	29%	41%
1–49%	26%	21%
≥ 50%	45%	38%
Treatment		
ICI monotherapy	47%	37%
ICI with chemotherapy	53%	63%

9068 **Poster Session**

Nivolumab (Nivo) plus ipilimumab (Ipi) 6-month treatment versus continuation in patients with advanced non-small-cell-lung cancer (aNSCLC): 3-year results of the IFCT-1701 DICIPLE phase 3 trial.

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Background: 1st-line immunotherapy (io) is a standard treatment for patients (pts) with advanced NSCLC devoid of targetable mutation. Classical 2-year io duration does not rely on indubitable evidence. We aimed to assess whether 6-month nivo/ipi was equivalent to continuation until progression or unacceptable toxicity in pts with disease control (DC). **Methods:** In this multicenter non-inferiority randomized phase 3 trial, eligible treatment-naive pts, age>18, PS 0-1, had stage IV NSCLC and measurable disease. They received Nivo 3 mg/kg q2w plus Ipi 1 mg/kg q6w, until progression or unacceptable toxicity for a maximum of 6-month induction treatment. At 6 months, pts with DC and no severe TRAEs were randomized (1:1) into io continuation (arm A), and observation (arm B). At progression, arm A pts received an investigator's choice 2nd line platinum-based chemo, while arm B pts resumed double io. Primary endpoint was progression-free survival (PFS). 450 pts x 2 were to be randomized, to achieve 80% power, with 0.025 one-sided a error. Observing that European filing for the io combo was not submitted, the trial's steering committee recommended to stop the accrual on Jan. 2021. **Results:** From May. 2018 to Jan. 2021, 265 pts (70.6% male, 62.7yr median age, 59% stage IVB, 22.3% SCC, 9.9% PDL1≥50%, 12.2% PDL1<1%) were accrued. 138 (72.6%) pts had disease progression before 6 months, 11 died (5.8%), 30 (15.8%) experienced TRAEs contra-indicating continuation, 11 (5.8%) were deemed ineligible for randomization. 71 pts with DC were randomized. With a median follow-up from randomization of 29.9 months, median PFS was 20.5 (7.4-36.7) months in arm A, 35.2 (21.4-NR) in arm B. 12-month PFS was 55.6% (38.0-69.9) and 81.2% (62.9-91.1), respectively (p=0.08). Adj.HR (arm B *vs.* arm A) was 0.66, 95%CI (0.28-1.31), p=0.23. OS data, yet immature, did not show any significant difference between both arms (adj.HR arm B *vs.* A: 0.54 95%CI (0.20-1.49), p=0.23). From randomization, 28.6% G3-5 TRAEs in arm A were observed *vs.* 2.9% in arm B (p=0.005). **Conclusions:** The 6-month i.o. interruption for NSCLC patients with DC did not yield significant PFS or OS differences in this prematurely halted trial. Updated OS with a 3-year follow-up, quality of life and biomarker data, will be presented at the meeting. Clinical trial information: NCT03469960. Research Sponsor: BMS; IFCT.

9069 **Poster Session**

Spectrum of acquired *KRAS* mutations in driver mutation-positive non-small cell lung cancer.

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Background: With the emergence of effective targeted-therapies for *KRAS* G12C, and the development of promising agents for *KRAS* G12V and G12D among others, the identity of unique *KRAS* mutations in non-small cell lung cancer (NSCLC) has become increasingly relevant. Acquired *KRAS* mutations are a known mechanism of resistance observed across driver mutation-positive (DM+) NSCLC. The incidence and diversity of these acquired alterations, and whether they differ from those observed in *de novo KRAS*-mutated NSCLC, is unknown. **Methods:** NSCLC molecular profiles were obtained using next-generation sequencing (Caris Life Sciences) with paired whole-transcriptomic sequencing (Illumina NovaSeq) and immunohistochemistry (Caris Life Sciences). Demographic data were abstracted from medical records. *KRAS* mutation diversity was defined for *de novo KRAS*-mutated (*KRAS*mt) NSCLC (*KRAS* as only identified driver – *KRAS*mt_dn) and DM+ NSCLC with acquired *KRAS* mutations (concurrent *KRAS*mt with other known driver – *KRAS*mt_acq). Fisher's exact test was used to compare the distribution of unique *KRAS* mutations between the groups. Due to the unique biology of NSCLC with class II/III *BRAF* mutations, this subset was removed from the *KRAS*mt_acq subgroup for the final analysis. **Results:** A total of 5932 *KRAS*mt NSCLC samples were identified, among which 5879 were *KRAS*mt_dn and 53 were *KRAS*mt_acq (see table). The distribution of unique *KRAS* mutations was not significantly different between groups (p = 0.14). Within the *KRAS*mt_dn group, *KRAS* G12C was most common (40%), followed by G12V (19%), G12D (14%), G12A (7%) and Q61H/G13C (4% each). In the *KRAS*mt_acq group, *KRAS* G12C was most common (30%), followed by G12D (19%), G12V (17%), Q61H (11%), G12A (7%), and G13C (6%). The most common observed driver mutations in the *KRAS*mt_acq group were *EGFR* (38%) and *MET* (30%). In the *EGFR* group, *KRAS* G12D (25%), Q61H/G12C (20% each), G12V/G13C (10% each), and G12F/A/R (5% each) were observed. In the *MET* group, *KRAS* G12C (25%), G12D/V/A (19% each), Q61H (12%) and G12S (6%) were seen. Among 7 patients with a documented history of smoking in the *KRAS*mt_acq group, *KRAS* G12D and Q61H were most common (29% each), followed by G12V/F and G13C (14% each). **Conclusions:** While the distribution of unique *KRAS* mutations did not differ significantly between *KRAS*mt_dn and *KRAS*mt_acq groups, acquired *KRAS* mutations were seen across DM+ NSCLC subsets, among which the frequency of observed mutations appeared to vary. The functional and immunological significance of these mutations, and their impact on clinical outcomes, warrants further investigation. Research Sponsor: None.

	KRASmt_dn	KRASmt_acq	EGFR	MET	ALK	HER2	ROS1	BRAF Class 1
# of pts	5879	53	20	16	7	6	1	3
G12C	40%	30%	20%	25%	57%	50%	100%	-
G12D	14%	19%	25%	19%	-	33%	-	-
G12V	19%	17%	10%	19%	29%	-	-	67%
G12A	7%	7%	5%	19%	-	-	-	-
Q61H	4%	11%	20%	12%	-	-	-	-
G13C	4%	6%	10%	-	-	-	-	33%
G12F	2%	2%	5%	-	-	-	-	-
G12R	1%	2%	5%	-	-	-	-	-
G12S	2%	4%	-	6%	-	17%	-	-
Other	7%	2%	-	-	14%	-	-	-

9070 **Poster Session**

Patients with *EGFR* mutant (m) MET-altered NSCLC receiving tepotinib with an EGFR tyrosine kinase inhibitor (TKI): A case series.

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Background: Oncogenic activation of MET is a common mechanism of acquired resistance to EGFR TKIs in patients (pts) with *EGFR*m NSCLC, with *MET* amplification (amp) constituting the most frequent cause of bypass pathway activation. Currently, there are no approved targeted treatment options for these pts. Data from the Phase II INSIGHT (NCT01982955) and INSIGHT 2 (NCT03940703) studies indicate the combination of the selective MET TKI tepotinib plus an EGFR TKI has encouraging activity. We present a case series of pts with *EGFR*m MET-altered NSCLC receiving tepotinib plus an EGFR TKI outside of clinical trials. **Methods:** Access to tepotinib was provided to pts with *EGFR*m MET-altered NSCLC and resistance to EGFR TKIs through unsolicited compassionate use requests. All pts received tepotinib (500 mg [450 mg active moiety] once daily; first dose by Oct 2022) plus an EGFR TKI. Participating physicians provided case information up to January 2023. **Results:** 28 cases of pts with *EGFR*m NSCLC and MET alterations who received tepotinib plus an EGFR TKI were collated. 21 pts had *MET*amp after EGFR TKI treatment, 5 had MET overexpression, and 2 had *MET* exon 14 skipping. Pts were aged 41–86 years, 15 were Asian, 13 were white, 19 were female, 8 had smoking history, and all had adenocarcinoma histology. *MET*amp was detected by tissue biopsy in 17 pts, and liquid biopsy in 4 pts. Of 12 pts with *MET*amp detected by FISH, gene copy number ranged from 5.3–33.4, and *MET:CEP7* ratio from 0.7–15.1. EGFR TKIs received in combination with tepotinib were osimertinib (n = 21, 19 of whom received prior osimertinib), gefitinib (n = 6), dacomitinib (n = 1), afatinib (n = 1), with 1 pt received gefitinib followed by osimertinib. Tepotinib plus EGFR TKI was received by 9 pts as second-line, 9 as third-line, and 10 as fourth-or-later line. Median treatment duration was 8.8 months (range 1.3–20.6), with treatment ongoing in 13 pts (10 with current duration $\geq$10 months). Per the physician's assessment, 25/28 pts (89%) had clinical benefit, 16 of whom (57%) were considered to have a partial response (PR). Clinical benefit was reported in 18/21 (86%) pts with *MET*amp (12 PR, 57%), in 5/5 with MET overexpression (2 PR), and 2/2 with *MET* exon 14 skipping (2 PR). The most reported adverse event (AE) considered related to tepotinib was edema in 15 pts (most commonly peripheral edema). Grade 3 AEs related to tepotinib were reported in 5 pts (including Grade 3 edema in 2 pts), 1 of whom discontinued the combination due to Grade 3 pneumonitis. **Conclusions:** Tepotinib plus an EGFR TKI showed promising clinical activity in pts with MET-altered NSCLC who have progressed on a previous EGFR TKI, including those with several lines of prior treatment. Clinical benefit was observed irrespective of MET alteration type in this case series of pts treated outside of clinical trials, with a large proportion of patients continuing to benefit from ongoing treatment. Research Sponsor: The healthcare business of Merck KGaA, Darmstadt, Germany.

9071 **Poster Session**

Sexual dysfunction in women with lung cancer: Updates from the SHAWL study.

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Background: Despite its direct correlation with quality of life, sexual dysfunction is under-discussed and underreported in patients with lung cancer (LC). Sexual dysfunction is highly prevalent in patients with LC, with issues persisting over time; however, most data precede the approval of targeted therapies and immune checkpoint inhibitors. We report updated data from the SHAWL study, focusing on women's sex life satisfaction. **Methods:** This cross-sectional, international survey study was administered via the GO2 Foundation Lung Cancer Registry. We utilized the Patient-Reported Outcomes Measurement Information System (PROMIS) Sexual Function and Satisfaction Measures for data collection. Participants were recruited from June 2020 to June 2021. Eligibility criteria included age $>$ 18 years, self-identification as a woman, and an LC diagnosis within ten years. Participants were asked about sexual health pertaining to 30 days before survey completion, now referred to as "recent." **Results:** The survey was administered to 249 women (median age: 61 years). Most (67%) had stage IV LC and 47% were receiving targeted therapy; 66% were undergoing active treatment. Before LC diagnosis, 49% (117) of participants reported having no sexual health issues. Most women (54%, 128) indicated having had recent sexual activity, though 77% (183) reported moderate to severe sexual dysfunction. Indeed, only 7.5% (18) reported being quite or very interested in sexual activity, and only 6.7% (16) felt as if they always or often wanted to be involved in it. Out of the 128 women indicating recent sexual activity, the vast majority (72%, 91) also reported minimal to no satisfaction with their sex life, with 17% (22), 31% (39), and 24% (30) reporting none, a little bit, and some satisfaction, respectively. The most common reasons for lack of recent sexual activity were lack of interest (68%, 76) or vaginal dryness or pain (30%, 33). Most women (69%, 88) also reported rarely becoming sufficiently lubricated during sexual activity, with 54% (68) indicating that it was difficult to impossible to do so. Patients with stage IV diagnosis had a lower interest in and desire for sexual activity than those with non-metastatic LC. Patients not receiving active treatment reported similar rates of lack of interest and desire for sexual activity as those in active cancer therapy. Patients on targeted therapy had similar rates of sexual dysfunction as those receiving other LC treatments. **Conclusions:** The SHAWL study is the largest study evaluating sexual dysfunction and satisfaction in women with lung cancer in our current clinical environment. Sexual dysfunction, dissatisfaction, and lack of interest in sexual activity were highly prevalent in women with LC regardless of treatment status and type of therapy, suggesting that even after treatment completion, sexual issues persist. Sexual health should be integrated into thoracic oncology care for all patients with lung cancer. Research Sponsor: GO2 Foundation for Lung Cancer and University of Wisconsin Carbone Cancer Center.

9072 **Poster Session**

Outcomes of patients with advanced EGFR mutant lung cancer treated with first line (1L) osimertinib (osi) who would not have met eligibility criteria for the FLAURA trial.

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Background: Osi is a 1L therapy for EGFR mutant lung cancer based on the results of the FLAURA clinical trial. Patients on clinical trial are typically highly selected and the overall effectiveness of therapies may be lower in the real-world setting. We report the real-world outcomes of patients treated with first line osi and compare the outcomes of trial eligible and ineligible patients. **Methods:** Pharmacy records from January 2020 to October 2022 were used to retrospectively identify patients who received 1L osi for advanced EGFR mutant (exon 19 del. or exon 21 L858R) lung cancer in British Columbia, Canada. Patients were deemed ineligible for the FLAURA trial if they met one of five criteria: ECOG ^{3}2, unstable brain metastases (symptomatic or on steroids), hemoglobin $<$90, platelet $<$100, or creatinine clearance $<$50. Comparisons of overall survival (OS) and time to treatment discontinuation (TTD) were made between using Kaplan-Meier survival curves and log-rank testing. Hazard ratios (HR) are reported using Cox regression adjusting for baseline factors (Table). **Results:** Of 312 patients included, 133 (43%) were considered FLAURA-ineligible. Reasons for ineligibility were poor ECOG (n=120 [including ECOG 2=69, ECOG 3=48, and ECOG 4=4]), unstable brain metastases (n=21), anemia (n=7), thrombocytopenia (n=5), and low creatinine clearance (n=9). Median follow up was 22.7 months. At the time of analysis, 103/133 (77%) of ineligible patients had discontinued osi and 87/133 (65%) had died. 82/179 (45%) of eligible patients had discontinued osi and 53/179 (30%) were deceased. The median TTD in the ineligible group was 11.9 months (95% CI 10.5-15.5) vs 26.9 months (95% CI 21.9- 34.6) in the eligible group ($p<0.001$), HR 2.1 (95% CI 1.5-2.9, $p<0.001$). The median OS in the ineligible group was 15.8 months (95% CI 12.4 to 21.1) vs NR [not reached] (95%CI 28.5 to NR) in the eligible group ($p<0.001$), HR 2.6 (95% CI 1.8-3.7, $p<0.001$). Rates of dose reduction for toxicity were similar between ineligible (25%) and eligible (19%) patients (p=0.25). Second-line therapy was received by 28/102 (27%) of trial ineligible patients and 46/82 (56%) of trial eligible patients. **Conclusions:** Over 40% of the real-world population receiving 1L osi would have been ineligible for the FLAURA clinical trial. These patients had significantly inferior outcomes. This study provides benchmark data to better inform patient prognosis using real-world data. Research Sponsor: None.

	Trial Ineligible (n= 133)	Trial Eligible (n= 179)
Age (mean, years; range)	69 (37-92)	68 (33-95)
Male	52/133 (39%)	57/179 (31%)
Asian Ethnicity	61/133 (46%)	86/179 (48%)
Exon 19 mutation	65/133 (49%)	105/179 (59%)
Smoking History	50/133 (38%)	53/177 (30%)
De novo stage IV	113/133 (85%)	123/179 (69%)
Asymptomatic Brain Metastases	34/133 (26%)	34/179 (19%)
Lactate dehydrogenase elevated	46/132 (35%)	35/177 (20%)

9073 **Poster Session**

Efficacy and safety of sunvozertinib in treatment naïve NSCLC patients with EGFR exon20 insertion mutations.

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Background: Sunvozertinib (DZD9008) is a rationally designed, irreversible EGFR inhibitor targeting *EGFR* mutations with wild-type EGFR selectivity. Two pivotal second line studies (WU-KONG1 [NCT03974022] and WU-KONG6 [NCT05712902 and CTR20211009]) are ongoing in NSCLC patients with *EGFR* exon20 insertion mutations (exon20ins). Primary analysis of WU-KONG6 study demonstrated promising efficacy and safety of sunvozertinib in ≥ second line setting. Herein, we reported preliminary results of sunvozertinib in the first line setting. **Methods:** Two ongoing studies WU-KONG1 and WU-KONG15 (NCT05559645) enrolled treatment naïve advanced NSCLC patients with *EGFR* exon20ins. WU-KONG1 is a multinational phase I/II study, and WU-KONG15 is an investigator-initiated phase II study in China. *EGFR* mutation status was confirmed by local or central testing using tissue or cytological samples. Sunvozertinib was administered orally until disease progression or other discontinuation criteria were met. Patients who had at least one post-treatment RECIST assessment by investigators were evaluable for efficacy analysis, and all patients who received at least one dose of sunvozertinib were included in the safety analysis. **Results:** As of January 15, 2023, a total of 36 treatment naïve advanced NSCLC patients with *EGFR* exon20ins received sunvozertinib daily dosing at RP2Ds. Median age was 66.5 years, and 63.9% (23/36) were female. The baseline ECOG PS was 0 or 1. Majority of patients (33/36, 91.7%) had metastatic diseases at study entry, with 22.2% (8/36) having > 3 metastatic sites and 22.2% (8/36) having baseline brain metastasis (BM). The most frequent mutation subtypes included 769_ASV (13/36, 36.1%), 770_SVD (2/36, 5.6%) and others (21/36, 58.3%). In 26 efficacy-evaluable patients, 19 patients showed tumor response, with a best objective response rate of 73.1%, among them 14 patients had confirmed response, and another 3 patients were still on treatment and pending confirmation. In patients with BM, tumor response was also observed intracranially. Median duration of response had not been reached by the data cut-off date. Safety findings were consistent with what was observed in previous studies of sunvozertinib. The most common treatment emergent adverse events (TEAEs) included diarrhea, CPK increase, and skin rash. The majority of adverse events were CTCAE grade 1 or 2 and manageable with supportive measures. **Conclusions:** Consistent with second line results, sunvozertinib demonstrated promising efficacy and safety profile as monotherapy in the first line setting for patients with advanced *EGFR* exon20ins NSCLC. The updated data will be presented at the conference. A phase III, multinational, randomized study (WU-KONG28, NCT05668988) is ongoing to compare sunvozertinib to chemotherapy as first line treatment for *EGFR* exon20ins NSCLC. Clinical trial information: NCT03974022, NCT05559645. Research Sponsor: Dizal Pharmaceutical.

Detection of *MET* amplification (*MET*amp) in patients with *EGFR* mutant (m) NSCLC after first-line (1L) osimertinib.

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Background: *MET*amp is a common resistance mechanism to osimertinib in patients with *EGFR*m NSCLC and is associated with sensitivity to MET TKIs. Reported *MET*amp rates vary considerably depending on the type of biopsy and assay used. Here, we report a large comprehensive analysis of *MET*amp detected by TBx FISH (FISH+) and/or LBx NGS (L+) after 1L osimertinib. **Methods:** During prescreening of the INSIGHT 2 study (NCT03940703) of tepotinib + osimertinib in post 1L osimertinib patients (pts) with *EGFR*m NSCLC, *MET*amp was centrally assessed by TBx FISH (*MET* GCN ≥5 and/or *MET*/*CEP7* ≥2) and/or by LBx NGS (*MET* plasma GCN ≥2.3; Archer). **Results:** Of 472 pre-screened pts (64% female, 57% Asian, 97% adenocarcinoma), 350 provided TBx and 443 provided LBx. After excluding 36 TBx and 7 LBx 'not analyzed/not evaluable' samples, there were 314 TBx (163 from primary tumors, 151 from metastases) and 436 LBx samples with *MET*amp results (positive or negative). Overall, FISH+ *MET*amp was detected in 159/314 pts (50.6%), with similar FISH+ rates in the primary tumor (77/163, 47.2%) and metastases (82/151, 54.3%). FISH+ *MET*amp detection by region was: 43.6% (82/188) in Asia, 61.5% (72/117) in Europe, and 55.6% (5/9) in the US. When limiting analysis to sites without reported local prescreening, the overall FISH+ *MET*amp rate was 46.5% (93/200) and by region was: 43.5% (60/138) in Asia, 52.7% (29/55) in Europe, and 57.1% (4/7) in the US. In 159 FISH+ pts, median GCN was 11.8 (range 5.0–50.6) and median *MET/CEP7* ratio was 2.3 (range 0.8–12.7). Mean TBx turnaround time (TAT) from shipment to results was 6.8 days. Overall, L+ *MET*amp was detected in 51/436 pts (11.7%). In 35 L+ pts who were also FISH+, the median GCN was 16.6 (range 5.3–45.3) and median *MET/CEP7* ratio was 4.5 (range 1.0–12.7). 299 pts had both central TBx FISH and LBx NGS results (Table), of whom 152 (50.8%) were FISH+ and 38 (12.7%) were L+. LBx NGS identified *MET*amp with high specificity (negative percentage agreement [NPA] 98.0%) but low sensitivity (positive percentage agreement [PPA] 23.0%) compared with TBx FISH: only 3/38 L+ samples were FISH− but 117/152 FISH+ samples (77.0%) were L−. Clinical activity of tepotinib + osimertinib was comparable in FISH+ and L+ pts. **Conclusions:** In this large comprehensive analysis, FISH+ METamp was detected in ~50% of pts progressing on 1L osimertinib, while L+ METamp was detected in only 11.7% of pts. METamp, which is the most common mechanism of resistance post 1L osimertinib, can frequently be undetected by using LBx NGS only. Given high specificity but low sensitivity of LBx, L+ pts can receive a MET TKI while a negative METamp result by LBx should be confirmed by FISH. FISH allows optimal identification of METamp post 1L osimertinib, can be delivered in a clinically meaningful timeframe, and may allow more pts to benefit from an oral MET TKI. Clinical trial information: NCT03940703. Research Sponsor: the healthcare business of Merck KGaA, Darmstadt, Germany.

		TBx FISH		
Pts with central TBx and LBx results		FISH+	FISH−	Total
LBx NGS	L+	35	3	38
	L−	117	144	261
	Total	152	147	299

9075 **Poster Session**

Circulating tumor DNA (ctDNA) monitoring to inform maintenance outcomes in patients (pts) with advanced NSCLC treated with induction atezolizumab+carboplatin+nab-paclitaxel (A+CnP).

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Background: Chemoimmunotherapy (ChemoIO) is a prevalent first-line treatment for advanced NSCLC without driver mutations, with maintenance therapy recommended after induction. However, real-world data suggests variability in maintenance therapy's timing, intensity, and duration. Motivated by evidence that ctDNA monitoring can predict outcomes in pts receiving IO for advanced cancers, we hypothesized ctDNA monitoring could inform outcomes in advanced NSCLC prior to the start of maintenance therapy. **Methods:** This retrospective study included 98 pts from a completed phase III trial of A+CnP in squamous NSCLC (IMPower131; GO29437). Pts were treated with 4 or 6 cycles of induction A+CnP followed by maintenance atezolizumab. ctDNA monitoring utilized FoundationOne-Tracker, involving 1) comprehensive genomic profiling of pretreatment tumor tissue, 2) variant selection using an algorithm to filter out non-tumor variants, and 3) multiplex PCR of up to 16 variants to detect ctDNA and quantify plasma mean tumor molecules per mL (MTM/mL). Progression free-survival (PFS) and overall survival (OS) were estimated with Kaplan-Meier analysis and hazard ratios (HR) were calculated using multivariate Cox proportional hazard models adjusting for age, smoking history, PD-L1, and performance status. PFS and OS analyses were landmarked from C4D1 unless otherwise stated; pts with progression/death before the landmark date were excluded. **Results:** *TP53* (91%), *CDKN2A* (41%) and *PIK3CA* (32%) were frequently altered in baseline tissue; 51% had TMB $\geq$10 mut/Mb. A median of 10 variants (range 2-16) were tracked per pt. ctDNA was detected (ctDNA+) in 43% of C4D1 samples (median 15.2 MTM/ml, range 0.3-787.3). ctDNA+ at C4D1 was associated with a lower objective response rate (41%) compared to undetectable ctDNA (ctDNA-, 77%, $p < 0.001$). Pts with ctDNA- at C4D1 (56/96) had better PFS than their ctDNA+ counterparts (median PFS from C4D1 7.7 vs 2.8 months; HR: 3.07 [1.88-5.02]). Median OS from C4D1 was not reached for ctDNA- pts and was 8.3 months for ctDNA+ pts (HR: 4.31 [2.31-8.06]). In a C6D1 landmark analysis of 34 pts who were ctDNA+ at C4D1, prolonged induction (6 cycles vs 4 cycles) was not associated with any improvement in PFS (1.6 vs 2.2 months, HR 1.41 [0.58-3.39]) or OS (4.7 vs 9.8 months, HR 1.84 [0.71-4.76]). Additional analysis of plasma samples at baseline and on-treatment time points is ongoing. **Conclusions:** On-treatment ctDNA monitoring during induction chemoIO can inform outcome on subsequent maintenance therapy in pts with advanced NSCLC. For pts with ctDNA+, prolonged induction chemoIO was not associated with improved outcomes. ctDNA testing during induction chemoIO may offer an opportunity to identify pts at higher risk for disease progression and inform selection for novel personalized maintenance treatment strategies. Research Sponsor: Foundation Medicine Inc.; Genentech; Natera.

9076 **Poster Session**

Utility of ctDNA tumor fraction to inform negative liquid biopsy (LBx) results and need for tissue reflex in advanced non-small cell lung cancer (aNSCLC).

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Background: Negative LBx results can be challenging to interpret. Absence of a targetable alteration may accurately reflect the tumor genotype (true negative) or may represent a false negative due to insufficient ctDNA shed, concealing a targetable oncogenic driver. Reflex to tissue biopsy (TBx) profiling is thus advised, per FDA label, for negative LBx results. Here we investigate whether algorithmic quantification of ctDNA in a LBx sample can increase confidence in negative LBx results, reducing need for confirmatory TBx testing. **Methods:** This study used the nationwide (US-based) de-identified Flatiron Health-Foundation Medicine NSCLC clinico-genomic database (CGDB) from approximately 280 US cancer clinics (~800 sites of care), limited to patients (pts) with aNSCLC receiving any multi-gene LBx followed by TBx CGP. In parallel, we queried an institutional database of pts with both LBx (FoundationOneLiquid CDx, F1LCDx) and TBx (FoundationOneCDx, F1CDx) to calculate positive predictive agreement (PPA) and negative predictive value (NPV) of LBx compared to TBx for detection of 7 targetable NSCLC driver alterations: *KRAS* G12X, *EGFR*, *MET* exon 14, *BRAF* V600E mutations or *ALK*, *ROS1*, and *RET* rearrangements. Foundation Medicine's ctDNA tumor fraction (TF) on F1LCDx is a composite algorithm prioritizing aneuploidy at higher levels to avoid germline signal and prioritizing variant allele frequency of canonical alterations at lower levels to maximize dynamic range. **Results:** Of 1,734 LBx sent prior to 1st-line therapy in pts with aNSCLC, 59% (1,024) were negative for an NCCN biomarker. For 465 pts with TBx after negative LBx (median 2.4 weeks from LBx to TBx result), 179 (38%) had a driver detected on reflex to TBx. In 45 receiving matched targeted therapy, median real-world PFS was 25 months. For pts starting therapy after reflex to TBx (n = 233), median time from LBx result to start of therapy was 4.7 weeks. To understand whether reflex to tissue may be avoided in some cases, LBx (F1LCDx) sensitivity was studied across 2,138 pairs in the institutional database. PPA for the 7 driver alterations was 59% overall (679/1,157) and improved to 96% (433/453) when limited to cases with TF $\geq$1%. Similarly, NPV was modest overall (67%) but improved when limited to LBx specimens with TF $\geq$1% (96%). Studying TF in the CGDB cohort, 33 of 85 pts (39%) with reflex TBx after negative LBx had a LBx TF $\geq$1% and, given high NPV for driver alterations, might have avoided reflex to confirmatory TBx. **Conclusions:** Elevated TF ($\geq$1%) on F1LCDx informs assay sensitivity and identifies a subset of LBx results with high NPV where reflex to TBx, and the associated treatment delay, may be less valuable. Conversely, for pts with a negative LBx with low TF ($<$ 1%) on F1LCDx, reflex to TBx is an important follow-on step to identify potentially missed driver alterations with potential for durable benefit on targeted therapy. Research Sponsor: Foundation Medicine Inc.

9077 **Poster Session**

Treatment patterns and unmet need for patients with advanced non-small cell lung cancer and poor performance status: A real-world evidence study.

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Background: Performance Status (PS) is prognostic for poorer survival in oncology. Poor PS (pPS) may lead to inferior outcomes both as an independent factor and by limiting the range of available treatment options and the ability of patients to tolerate those regimens. Despite high real-world prevalence, patients with pPS are consistently underrepresented in clinical trials. Limited information is available regarding current treatment patterns for patients with pPS and advanced or metastatic non-small cell lung cancer (mNSCLC). **Methods:** We conducted a retrospective analysis using the nationwide de-identified Flatiron Health electronic health record (EHR)-derived database, selecting patients with mNSCLC diagnosed between 2017-2022 without *EGFR* or *ALK* genomic tumor aberrations. We estimated the prevalence of pPS (ECOG 2-3) within this cohort, and described common systemic treatment patterns by year and by PD-L1 status. For the subset of patients treated with pemetrexed/pembrolizumab/carboplatin (PPC), we estimated the association between pPS versus good PS (gPS - 0/1) and early discontinuation (< 4 cycles) or dose reduction (AUC < 4) of carboplatin using logistic regression controlling for observable confounders. **Results:** One quarter (24%) of the 22,575 patients in our sample had pPS. Relative to patients with gPS, patients with pPS were more likely to be older (mean age 72 vs. 69y, $p < 0.001$), to have stage IV cancer (62% vs 56%, $p < 0.001$) and less likely to have known PD-L1 status (60% vs. 63%, $p = 0.002$). The fraction of patients with no documented treatment was substantially higher among pPS versus gPS (37% vs. 21%). In the subset of patients with PS3, 53% of patients had no documented treatment. The most common treatment regimens among pPS patients were mono-immunotherapy (mono-IO - 19%) and PPC (15%). Use of mono-IO was positively correlated with higher PD-L1 expression (44% vs. 14% vs. 5.9% in PD-L1 high/low/negative, respectively). No documented treatment was negatively correlated with PD-L1 status (26% vs. 35% vs. 42%). Among patients with PS3, higher rates of no documented treatment were observed (39% vs. 50% vs 58% for PD-L1 high/low/negative, respectively). Anti-CTLA-4 combination use was low regardless of PS. pPS was associated with greater likelihood of early carboplatin discontinuation, (adjusted odds ratio, aOR 2.06), and dose reduction (aOR 1.75), both $p < 0.001$. **Conclusions:** One quarter of patients with mNSCLC have pPS. These patients are almost twice as likely to receive no treatment as those with gPS, and within the subset treated with the most common platinum containing regimen (PPC), pPS patients are also more likely to both initiate carboplatin at a reduced dose, and to discontinue it prior to completion. This suggests a substantial unmet need for this important subset of patients with mNSCLC. Research Sponsor: Genentech, Inc.

9078 **Poster Session**

Integrated efficacy and safety of brigatinib in patients with ALK TKI-naive advanced *ALK*+ NSCLC in the ALTA-1L and J-ALTA studies.

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Background: Brigatinib demonstrated efficacy and manageable safety in patients (pts) with anaplastic lymphoma kinase (ALK) tyrosine kinase inhibitor (TKI)-naive *ALK*+ non-small cell lung cancer (NSCLC) in phase 3 (ALTA-1L) and phase 2 (J-ALTA) trials. We present results of integrated efficacy and safety analyses of ALTA-1L and J-ALTA. **Methods:** ALTA-1L (NCT02737501) and J-ALTA (NCT03410108; conducted in Japan) were open-label, multicenter studies in pts with advanced or metastatic *ALK*+ NSCLC. Pts in ALTA-1L and in part 3 of J-ALTA were ALK TKI-naive. Stable or asymptomatic brain metastases were allowed in both studies. Pts received brigatinib 180 mg qd (7-day lead-in at 90 mg). Primary endpoints were blinded independent review committee (IRC)-assessed progression-free survival (PFS) in ALTA-1L and IRC-assessed 12-month PFS in the J-ALTA ALK TKI-naive cohort (both per RECIST v 1.1). Secondary endpoints included IRC-assessed objective response rate (ORR), duration of response, intracranial ORR, intracranial PFS, overall survival, and safety. Pooled efficacy and safety data from both studies are presented. **Results:** The pooled analysis population included 169 pts (ALTA-1L, N = 137; J-ALTA ALK TKI-naive cohort, N = 32). Median follow-up overall was 35.8 months (last pt last contact: ALTA-1L, January 2021; J-ALTA, July 2021). Most (66%) pts were aged $<$ 65 years, 24% had baseline brain metastases, 95% had stage IV disease at study entry, and 21% had received prior chemotherapy for locally advanced or metastatic disease. With brigatinib treatment, median PFS by IRC was 29.3 months (95% CI, 23.9–44.7). The confirmed ORR was 79% (95% CI, 72–85%), with 36 complete responses and 97 partial responses. Median duration of response was 38.1 months (95% CI, 22.9–not reached). Median overall survival was not reached; the 3-year survival rate was 74% (95% CI: 66–80%; 84 pts at risk). Intracranial ORR and intracranial PFS will be presented. Grade 3/4 treatment-emergent adverse events were reported in 74% of pts; the most common were increased blood creatine phosphokinase (31%), hypertension (18%), and increased lipase (16%). Any grade interstitial lung disease/pneumonitis was reported in 12 (7%) of pts. Adverse events led to treatment discontinuation in 11% of pts. **Conclusions:** Brigatinib treatment demonstrated clinically meaningful systemic and intracranial efficacy in this integrated analysis of pts with ALK TKI-naive advanced or metastatic *ALK*+ NSCLC in the ALTA-1L or J-ALTA trials. Safety results were consistent with the known profile for brigatinib, with no new safety findings. Clinical trial information: NCT02737501; NCT03410108. Research Sponsor: Takeda Pharmaceutical Company Limited, Inc., Lexington, MA, USA.

9079 **Poster Session**

A biomarker study of atezolizumab (atezo) + bevacizumab (bev) + carboplatin (carbo) + paclitaxel (pac) (ABCP) for patients with NSCLC harboring *EGFR* mutations (EGFRm) after failure of TKI therapy: NEJ043.

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Background: EGFRm NSCLC patients (pts) have limited treatment options after EGFR-TKI failure. We previously showed that the NEJ043 study investigating ABCP in EGFRm NSCLC pts after EGFR-TKI failure had a clinically meaningful efficacy (Furuya et al, ASCO 2022). Here we report the results of the biomarker study of NEJ043. **Methods:** NEJ043 study is a phase II study to evaluate the efficacy of ABCP in sensitizing EGFRm nonsquamous NSCLC pts after TKI failure. Pts received atezo (1200 mg), bev (15 mg/kg), carbo (AUC 6 mg/mL/min), and pac (175 mg/m^2) every 3 weeks up to 4 cycles followed by atezo plus bev until loss of clinical benefit. Before treatment initiation and three cycles of ABCP, peripheral blood mononuclear cells (PBMCs) were collected, and immunophenotypic data at each time point was obtained by flow cytometry. **Results:** 60 pts were included in the NEJ043 study and PBMCs were obtained from 31 pts. Pts with a higher percentage of $CD11b^+DR^{low}CD3^-CD14^+$ myeloid-derived suppressor cells (MDSCs) before ABCP had significantly longer PFS (median, 9.7 months (95% CI, 5.3-17.7) vs 5.6 months (95% CI, 3.9-8.1); HR 0.38; P = 0.0313). Further analysis of the immune cell phenotypes that changed between pre-treatment and the third course showed that pts with increased $CD62L^{low}CD8^+$ cells (median, 12.8 months (95% CI, 5.6-20.3) vs 5.7 months (95% CI, 4.4-8.1); HR 0.25; P = 0.003) and $PD\text{-}1^+CCR7^-CD45RA^-CD8^+$ cells (median, 8.5 months (95% CI, 5.6-13.8) vs 5.7 months (95% CI, 2.6-8.1); HR 0.37; P = 0.0324) had significantly longer PFS. **Conclusions:** Inhibition of MDSCs by ABCP, especially bev, may be important for EGFRm pts whose antitumor immunity is suppressed by MDSCs before treatment. Better PFS may be expected in pts in whom ABCP therapy induced $CD62L^{low}CD8^+$ effector T cells and $PD\text{-}1^+CCR7^-CD45RA^-CD8^+$ effector memory T cells. Clinical trial information: jRCTs031190066. Research Sponsor: Chugai Pharmaceutical Co., Ltd.

9080 **Poster Session**

Tislelizumab plus chemotherapy in patients with advanced brain metastases of non-squamous non-small cell lung cancer: A multicenter, prospective, open-label phase 2 study.

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Background: Patients (pts) with brain metastases (BM) were usually unrepresented in clinical trials assessing the efficacy of PD-(L) 1 inhibitors. Here, we investigated the efficacy and safety of tislelizumab (TIS) plus chemotherapy in NSCLC pts with asymptomatic untreated BM or with stable BM after local radiotherapy. **Methods:** This multicenter, prospective, open-label phase 2 study enrolled systemic treatment-naïve pts with stage IV non-squamous (nsq) NSCLC without EGFR or ALK mutations who had BM. Pts received TIS combined with pemetrexed and carboplatin for 4 cycles, followed by maintenance TIS and pemetrexed. RECIST v1.1 and RANO-BM were applied for assessment for systematic and brain disease, respectively. The primary endpoint was the investigator-assessed 1-year PFS rate per RECIST v1.1. **Results:** 36 pts were enrolled with 77.8% having stage IVB disease, 25.0% liver metastases and 41.7% bone metastases. 29 (80.6%) pts were with untreated, asymptomatic brain metastases, and the other 7 (19.4%) received radiotherapy for BM previously. As of 30 Nov 2022, the median follow-up was 12.3 months. 1-year systematic PFS rate was 36.8% (95% CI, 18.0-55.7), with median PFS of 7.5 months (95% CI, 5.1-NE). Systematic ORR was 50.0% (95% CI, 31.9-68.1%). Median OS was not reached, with 1-year OS rate of 70.5% (95% CI, 51.7-83.1). For intracranial efficacy assessment per RANO-BM, 1-year intracranial PFS (iPFS) rate was 56.6 % (95% CI, 31.7-75.5), with 45.5% (95% CI, 19.4, 68.5) and 100% in pts with untreated and pretreated BM, respectively. Intracranial ORR was 56.7% (95% CI, 37.4-74.5%), with 53.8% (95% CI, 33.4-73.4%) in pts with untreated BM and 75% (95% CI, 19.4-99.4%) in pretreated BM. No grade 5 toxicities were observed. Grade 3-4 TRAEs occurred in 33.3% (12/36) of pts. 13.9% of pts experienced irAEs; grade 3-4 irAEs occurred in 2 (5.6%) pts. **Conclusions:** TIS plus chemotherapy yielded promising systematic and intracranial PFS, and was generally well tolerated in nsq-NSCLC pts with untreated or pretreated BM. Clinical trial information: NCT04507217. Research Sponsor: None.

	Efficacy analysis set* (EAS)	
	EAS per RECIST v1.1 (n=32)	**EAS per RANO-BM (n=30)**
1-year PFS rate, % (95% CI)	36.8 (18.0, 55.7)	56.7 (31.7, 75.5)
Median PFS, months (95% CI)	7.5 (5.1, NE)	NR (8.2, NE)
ORR, % (95% CI)	50.0 (31.9, 68.1)	56.7 (37.4, 74.5)
DCR, % (95% CI)	90.6 (75.0, 98.0)	96.7 (82.8, 99.9)
1-year OS rate, % (95% CI)	70.5 (51.7, 83.1)	

*Efficacy analysis set included pts receiving ≥1 dose of TIS or chemotherapy, and having completed ≥1 post-treatment tumor assessment unless treatment was discontinued before the first tumor assessment due to disease progression or death; NR, not reached; NE, not estimable.

9081 **Poster Session**

Patient-reported outcomes of furmonertinib versus gefitinib in patients with locally advanced or metastatic, *EGFR* mutation-positive non-small cell lung cancer (FURLONG): A multicenter, double-blind, randomized phase 3 study.

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Background: Furmonertinib showed superior efficacy compared with gefitinib as first-line therapy in Chinese patients with *EGFR* mutation-positive non-small cell lung cancer (NSCLC), along with an acceptable safety profile without new signals in the FURLONG study. Here we present patient-reported outcomes (PROs). **Methods:** FURLONG is a multicenter, double-blind, double dummy, randomized phase 3 study done in 55 hospitals across mainland China. Eligible patients were randomly assigned (1:1) to receive either furmonertinib or gefitinib. The primary endpoint of IRC-assessed progression-free survival has been reported previously. PROs as prespecified secondary outcomes by the European Organization for Research and Treatment of Cancer (EORTC) Quality-of-Life Questionnaire Core 30 (QLQ-C30) and Quality-of-Life Questionnaire Lung Cancer 13 (QLQ-LC13), were analyzed in randomly assigned patients who had received at least one dose of study drug and completed at least one PRO assessment. Changes from baseline to randomized treatment discontinuation were analyzed with mixed model for repeated measures and time-to-event analyses. This study is ongoing for survival follow-up. **Results:** 357 patients received at least one dose of study drug, all of them completed at least one PRO assessment. Questionnaire completion rates were ≥95% at most time points. Baseline mean scores were similar in the furmonertinib and gefitinib groups. From baseline to randomized treatment discontinuation, statistically significant differences favoring furmonertinib for physical function, nausea/vomiting, appetite loss, diarrhea, alopecia, and other pain (any pain other than chest, arm, or shoulder pain) were observed. Time to deterioration in physical function, cognitive function, nausea/vomiting, appetite loss, diarrhea, cough, dyspnea, dysphagia, and alopecia were significantly longer with furmonertinib versus gefitinib (Table). **Conclusions:** Furmonertinib demonstrated favorable PROs as measured by the EORTC QLQ-C30 and QLQ-L13 versus gefitinib. These data presented the positive benefit risk profile of first-line furmonertinib and further support this novel third generation EGFR-TKI as a new standard of first line treatment in *EGFR* mutation-positive NSCLC. Clinical trial information: NCT03787992. Research Sponsor: Shanghai Allist Pharmaceuticals Co., Ltd.; China National Major Project for New Drug Innovation (2017ZX09304015).

	HR (95%CI)	*P* value
Physical function	0.63 (0.42, 0.94)	0.021
Cognitive function	0.73 (0.54, 0.98)	0.034
Nausea/vomiting	0.64 (0.41, 0.99)	0.042
Appetite loss	0.63 (0.43, 0.92)	0.016
Diarrhea	0.63 (0.46, 0.85)	0.002
Dyspnea	0.72 (0.53, 0.98)	0.034
Cough	0.67 (0.44, 1.00)	0.049
Dysphagia	0.54 (0.35, 0.83)	0.004
Alopecia	0.62 (0.42, 0.90)	0.011

9082 **Poster Session**

Mobocertinib efficacy in patients with NSCLC and *EGFR* exon 20 insertion mutations (ex20ins) identified by next-generation sequencing (NGS) of circulating tumor DNA (ctDNA).

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Background: *EGFR* ex20ins are distinct targetable driver mutations present in ~2% of all NSCLC. While most EGFR TKIs have limited effectiveness, mobocertinib is the first oral therapy approved for this unmet need. *EGFR* ex20ins are heterogeneous (> 60 variants), and PCR testing detects a limited number of variants, leading to undetected disease in ~50% of cases, whereas NGS can identify all such mutations. Testing plasma ctDNA is a noninvasive approach for detection of genomic variants, such as *EGFR* ex20ins. **Methods:** In the mobocertinib phase 1/2 study (NCT02716116), patients were enrolled based on *EGFR* ex20ins detected by various local tissue or liquid clinical trial assays (CTAs). Baseline plasma samples were collected and processed to extract cell-free DNA and were evaluated for *EGFR* ex20ins status using FoundationOne Liquid CDX (F1LCDX), an NGS-based plasma ctDNA test. Concordance between F1LCDX and the CTAs was demonstrated by testing patient samples from the phase 1/2 trial and paired tissue and plasma samples from commercially acquired and stage-matched patients with NSCLC (N = 305). Efficacy analyses by assay method were performed in *EGFR* ex20ins–positive platinum-pretreated patients (PPP; n = 114 [FDA approved population]; data cutoff: 1 Nov 2021) in the phase 1/2 trial. **Results:** Concordance between F1LCDX and CTAs was demonstrated with samples from the CTA-positive (n = 159) and CTA-negative populations (n = 87) tested by F1LCDX where tissue and plasma were assessable; the point estimate of positive percentage agreement (95% CI) was 68.6% (61.0–75.3), and the point estimate of negative percentage agreement was 100% (95.8–100). F1LCDX detected 34 individual *EGFR* ex20ins variant types. In the response evaluable population, patients who tested *EGFR* ex20ins positive by F1LCDX (n = 55) demonstrated confirmed ORR (34.5%) and disease control rate (74.5%), which was comparable to those observed among all PPP in the phase 1/2 trial (confirmed ORR: 28%; confirmed disease control rate: 78%). **Conclusions:** Mobocertinib has shown efficacy in PPP with *EGFR* ex20ins NSCLC. F1LCDX effectively identified patients with *EGFR* ex20ins who may benefit from mobocertinib, providing an additional noninvasive diagnostic option to guide treatment. Clinical trial information: NCT02716116. Research Sponsor: Takeda Development Center Americas, Inc., Lexington, MA, USA.

9083 **Poster Session**

Clinical and genomic predictors of response and toxicity to sotorasib in a real-world cohort of patients with advanced KRAS G12C-mutant non-small cell lung cancer.

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Background: With the accelerated approval of the KRAS G12C inhibitor sotorasib for patients with advanced *KRAS G12C*-mutant non-small cell lung cancer (NSCLC), there is a new need to explore efficacy and identify clinical and genomic factors associated with activity and toxicity among patients treated in routine clinical practice. **Methods:** Patients(pts) treated with sotorasib outside of the clinical trial setting at three institutions (MSK, Columbia, NYU) were examined to identify factors associated with real-world PFS (rwPFS), overall survival (OS), real-world (rw) response, and clinically significant toxicity (CTCAE v5.0 grade 3 or higher treatment-related adverse events [G3+ TRAE]). *TP53*, *STK11*, and *KEAP1* status were assessed by targeted NGS. Response and rwPFS were determined by investigator assessment of radiology reports. rwPFS and OS were estimated by Kaplan-Meier methods; log-rank tests were used for univariate group comparisons and Mantel-Haenszel method was used to determine hazard ratios (HRs). Fisher's exact test was used to determine associations between categorical variables. **Results:** 105 pts with advanced *KRAS G12C*-mutant NSCLC treated with sotorasib were identified. The response rate for patients treated was 28%, with median rwPFS of 5.3 months, and median OS of 12.6 months. *KEAP1* co-mutations were associated with shorter rwPFS and OS (rwPFS HR 3.19, $P = 0.004$; OS HR 4.10, $P = 0.003$); no significant differences in rwPFS or OS were observed among pts with or without *TP53* co-mutations (rwPFS HR 1.10, $P = 0.731$; OS HR 1.19, $P = 0.631$) or *STK11* co-mutations (rwPFS HR 1.66, $P = 0.098$; OS HR 1.73, $P = 0.168$). Dual *STK11*/*KEAP1* co-mutation status was associated with shorter OS compared to *STK11* wild-type (WT)/*KEAP1* mutant (MUT) status (OS HR 4.04, $P = 0.033$) and *STK11* MUT/*KEAP1* WT status (OS HR 5.41, $P = 0.012$). 16/105 (15%) pts experienced G3+ TRAEs. 15/16 (94%) patients with G3+ TRAE had previously been treated with immune checkpoint inhibitor (ICI). Among pts with prior ICI exposure (n = 86), last exposure within 12 weeks of sotorasib initiation was associated with G3+ sotorasib TRAEs ($P < 0.001$) and TRAE-related sotorasib discontinuation ($P = 0.014$); there was no association between prior irAE during ICI therapy and G3+ sotorasib TRAEs ($P = 0.757$). In total, 15/53 (28%) pts with last ICI exposure within 12 weeks of sotorasib initiation experienced G3+ TRAEs, most commonly hepatotoxicity. No cases of G3+ TRAEs were observed in 33 pts with last ICI exposure > 12 weeks prior to sotorasib treatment. **Conclusions:** Among patients treated with sotorasib in routine clinical practice, *KEAP1* co-mutations were associated with poor outcomes. Severe toxicity was almost exclusively associated with recent ICI exposure. These observations may help further guide sequencing of sotorasib and may help inform the next generation of KRAS G12C clinical trials. Research Sponsor: LUNGevity Foundation.

9084 **Poster Session**

Survival associations and driver oncogene overlap for copy-number amplifications of *ERBB2*, *KRAS* and *MET* in non-small cell lung cancer.

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Background: Next-generation sequencing (NGS) to detect targetable oncogenic driver mutations is standard of care in non-small cell lung cancer (NSCLC). However, the interpretation and clinical impact of copy number amplifications (CNA) of driver genes is less clear. *ERBB2*, *KRAS* and *MET* are oncogenic drivers with intersecting resistance mechanisms and evolving therapeutic landscapes. We examined the overlap between other oncogenic drivers and CNA of these genes, and the association of CNA with overall survival (OS), in a cohort of patients with NSCLC. **Methods:** NGS of DNA (592 genes or WES)/RNA (WTS) was performed for 5870 consecutive lung adenocarcinoma tumors submitted to Caris Life Sciences (Phoenix, AZ). The copy number of each exon was determined by calculating the average depth of the sample along with the sequencing depth of each exon. Driver oncogenes (Driver+/-) were defined as pathogenic fusions in *ALK*, *NTRK* (1,2 and 3), *RET* and *ROS1* or pathogenic SNVs/indels in *ALK*, *BRAF*, *EGFR*, *ERBB2*, *KRAS*, *MET*. Tumor mutational burden high (TMB-H) was defined as 10 mutations per MB. The χ^2 test was applied as appropriate ($p < .05$). **Results:** The cohort was 55% female; median age was 69 years (range 24-89) and similar across all cohorts. Incidence of CNA at different amplification thresholds was correlated with oncogene drivers. At CNA ≥6 for *ERBB2* and *KRAS*, but CNA ≥4 for *MET,* a significant tendency for mutual exclusivity with driver mutations was observed (log2 odds ratio *ERBB2*: -3.1, *KRAS*: -1.1, *MET*: -2.2, all $p < .001$). Tumors meeting these thresholds were designated CNA-High (*Gene*-H), versus CNA-Low (*Gene*-L). Only one tumor harboured two CNA-H genes (*KRAS* and *MET*). Independent of CNA status, the TMB-H frequency was decreased in Driver+ tumors (27% vs 52% in Driver-, $p < .001$). CNA-H tumors were associated with decreased OS (compared to CNA-L); for *ERBB2*-H, hazard ratio (HR) 1.74 (95% CI 1.44-2.10, $p < .001$), for *KRAS*-H HR 1.29 (1.16-1.65, $p < .001$), and for *MET*-H HR 1.46 (1.28-1.68, $p < .001$). Similar results were observed when stratified by driver mutation status (Table), with the exception of *KRAS*/ Driver- tumors. **Conclusions:** These data suggest tumors with high CNA of *ERBB2*, *KRAS* and *MET* represent clinically distinct entities and are significantly less likely to harbour concurrent driver oncogenes. The association between increased copy number and worse OS suggests amplified tumors are an important area for therapeutic development. Overall survival (collection to last contact) for *ERBB2*, *KRAS* and *MET* CNA-High versus CNA-Low tumors, by Driver mutation status. Research Sponsor: Caris Life Sciences.

	HR for death (CNA-High vs -Low)	Low CI	Upper CI	p-value
ERBB2				
Driver +	1.30	0.90	1.89	.16
Driver -	1.71	2.00	2.43	.003
KRAS				
Driver +	1.50	1.17	1.91	.001
Driver -	0.92	0.60	1.42	.669
MET				
Driver +	1.62	1.29	2.02	<0.001
Driver -	1.47	1.14	1.90	.003

9085 **Poster Session**

Impact on turnaround times (TAT) among non-squamous non-small cell lung cancer (NSCLC) patients across three time periods with varying biomarker testing techniques.

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Background: Biomarker testing and identification of actionable genomic alterations (AGAs) in NSCLC patients have led to targeted therapy use and improved outcomes, particularly in advanced stages. We sought to evaluate the impact of different testing paradigms on TAT, particularly with respect to treatment decision and time to initiation of treatment, across three time periods. **Methods:** A retrospective review of stage III or IV non-squamous NSCLC patients at the Princess Margaret Cancer Centre (Toronto, Canada) was conducted. Both *de novo* advanced and patients with metastatic progressions are included. Cohort 1 (C1; 01/2015 – 01/2017) underwent reflex *EGFR* (EntroGen) and ALK (5A4 immunohistochemistry, IHC) single gene testing. Cohort 2 (C2; 02/2017 – 09/2020) underwent reflex next generation sequencing (NGS; Trusight Tumor 15), ALK and *ROS1* testing. Cohort 3 (C3; 10/2020 – 01/2022) underwent reflex comprehensive NGS (161 genes, Oncomine OCA v3). Descriptive statistics are presented, including AGAs found and TAT from biopsy to result sign-out, and treatment related TAT. **Results:** Three cohorts of stage III and IV patients were identified, with C1 having proportionally more females (60%), never smokers (42%) with adenocarcinomas (98%). More patients with AGA were identified using NGS with larger panels (42%, 41%, 57%, respectively across C1 – C3). However, there is a longer median time from first oncology visit to treatment (14, 22, 27 days, respectively across C1-C3), and longer biopsy to treatment TAT trended towards more comprehensive testing (34, 38, 40 days, respectively across C1 - C3) in stage IV patients. **Conclusions:** As more comprehensive biomarker testing became available, more AGAs are identified with an increase in TAT from biopsy to sign-out and treatment start. Despite our institutional policy of reflex testing, future endeavours will be focus on ways to reduce TAT. Research Sponsor: Princess Margaret Cancer Center; Pfizer; PM Lung Cancer Molecular Diagnostics Program.

Cohort	C1	C2	C3
Patients with successful testing (n)	177	657	205
Median age (range)	70 years (46-93)	69 years (19-97)	70 years (33-91)
Female	106 (60%)	313 (48%)	102 (50%)
Never smoker	71 (42%)	193 (30%)	68 (34%)
Adenocarcinoma	173 (98%)	558 (85%)	184 (90%)
Stage IV patients with AGAs identified	52/123 (42%)	191/463 (41%)	*84/148 (57%)
Median time from biopsy to result sign-out	14 days (IQR: 10–19)	28 days (IQR: 22-33)	31 days (IQR: 27-38)
Median time from first oncology visit to treatment (stage IV only)	14 days (IQR: 2-28)	22 days (IQR: 14-36)	27 days (IQR: 15-38)
Median time from biopsy to treatment (stage IV only)	34 days (IQR: 22–52)	38 days (IQR: 26–52)	40 days (IQR: 22 – 60)

9086 **Poster Session**

Immune checkpoint inhibitors use and the incidence of hepatitis B virus reactivation or immune-related hepatitis in non-small cell lung cancer patients with chronic hepatitis B.

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Background: The safety and efficacy of immune-checkpoint inhibitors (ICIs) has not been thoroughly investigated in non-small cell lung cancer (NSCLC) patients with chronic hepatitis B (CHB) or occult hepatitis B infection (OBI). We analyzed incidence of hepatitis B virus (HBV) reactivation, immune-related hepatitis and jaundice in NSCLC patients treated with ICIs according to HBV DNA and hepatitis B serologic markers in real-world setting. **Methods:** A total of 1,277, consecutive NSCLC patients treated with ICIs from January 2015 to December 2020 at the Samsung Medical Center, Seoul, Korea were analyzed. Among them, 52 patients were hepatitis B surface antigen (+) (Group A, CHB), 759 patients were HBsAg (-)/anti-HBc IgG (+) (Group B, OBI), and 466 patients were HBsAg (-)/anti-HBc IgG (-) (Group C). Among 52 patients with CHB, 38 patients (73.1%) were receiving antiviral therapy. Primary endpoint was HBV reactivation, immune-related hepatitis and jaundice. Secondary endpoints include other immune-related adverse events, objective response rate, progression free survival (PFS) and overall survival (OS). **Results:** HBV reactivation was observed in two patients (0.2%) which was exclusively observed in Group A (CHB). Among CHB patients who were not receiving antiviral therapy, HBV reactivation was observed for 14.3% (2/14 patients). Incidence of immune-related hepatitis were 21.2%, 30.3% and 30.5% for Group A, Group B and Group C ($p > 0.05$), respectively, and incidence of immune-related of jaundice was 3.8%, 4.0% and 2.8% for Group A, Group B and Group C ($p > 0.05$), respectively. Incidence of $\geq$ grade 3 other immune-related adverse events, objective response rate, PFS, and OS were comparable among three group ($p > 0.05$ for all comparison). **Conclusions:** In this large, real-world cohort study, safety and efficacy of ICIs were comparable in patients with CHB or OBI, suggesting similar outcomes can be expected with ICIs in patients with CHB or OBI. HBV reactivation was observed in patients with CHB without antiviral therapy indicating antiviral prophylaxis might be required for them. For patients with OBI, risk of HBV reactivation was null. Research Sponsor: None.

9087 **Poster Session**

Phase II results of ivonescimab (AK112/ SMT112), a novel PD-1/VEGF bispecific, in combination with chemotherapy for first line treatment of advanced or metastatic non-small cell lung cancer (NSCLC) without actionable genomic alterations (AGA) in EGFR/ALK.

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Background: Since the initial approval of bevacizumab (bev) with chemo in NSCLC, the subsequent focus of bev use in combination with PD1 therapy for first line metastatic disease has largely focused on non-squamous (non-SCC) histology. Ivonescimab is a novel anti-PD-1/VEGF bispecific antibody. The bispecific approach to these targets has the potential to recalibrate the malignant immuno-architecture in favor of a more immune-responsive and anti-tumor microenvironment. Cooperative VEGF binding with the bispecific has been shown to elevate affinity of ivonescimab to PD-1 by more than 10-fold. Ivonescimab has a mean $T_{1/2}$ of 6-7 days while bev $T_{1/2}$ is 20 days. Therefore, we aimed to assess the efficacy and safety of ivonescimab combined with chemotherapy for first line advanced or metastatic NSCLC in patients (pts) with squamous (SCC) or non-SCC NSCLC. **Methods:** An open-label, multi-center phase II study evaluating the efficacy and safety of ivonescimab combined with chemotherapy in pts with advanced or metastatic NSCLC. Pts were enrolled into 3 cohorts based on prior therapy and presence of AGA. Data from pts with prior therapy for advanced or metastatic disease were presented in ASCO 2022 and here we report additional pts and longer-term data from pts with NSCLC without AGA receiving first line therapy for advanced/metastatic disease. Pts were treated with 10 or 20 mg/kg ivonescimab once every 3wks combined with carboplatin and pemetrexed (non-SCC) or carboplatin and paclitaxel (SCC). The primary endpoint was ORR per RECIST by investigator. **Results:** 135 pts with advanced or metastatic NSCLC received ivonescimab plus chemotherapy including 63 with SCC and 72 with non-SCC. Median age was 61 yrs (. 78% male, 3% and 97% pts had ECOG PS 0 and 1, respectively, and 20% pts had baseline brain metastasis. Median follow-up was 11.5 mo. Pts with SCC experienced a 75% ORR with median DOR 15.4 mo, 95% DCR, the 9-mo PFS and OS rate was 67% and 93%, respectively. Pts with non-SCC experienced a 55% ORR, DOR was not reached, 100% DCR, the 9-mo PFS rate and OS rate was 61% and 81%, respectively. The most common treatment related adverse events (TRAEs)$\geq$ 10% were epistaxis, proteinuria, rash, amylase increased, anemia, ALT increased, infusion related reaction, AST increased, pruritus, decreased appetite, and WBC decreased. Grade $\geq$3 TRAEs occurred in 28.1% TRAE leading to discontinuation occurred in 6.7% of pts. **Conclusions:** Ivonescimab, plus chemotherapy has shown promising anti-tumor activity in pts with advanced/metastatic NSCLC without AGA and can be administered safely in combination with platinum doublet chemotherapy to patients with SCC and non-SCC histology. Clinical trial information: NCT04736823. Research Sponsor: Akeso Biopharma, Inc.

9088 **Poster Session**

First line (1L) durvalumab in patients with PD-L1 positive, advanced non-small cell lung cancer (NSCLC) with a performance status of 2 (PS2): Primary analysis of the multicenter, single-arm phase II trial SAKK 19/17.

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Background: The safety and efficacy of 1L durvalumab in PS2 patients (pts) with advanced NSCLC is unknown. Important safety data leading to exclusion of pts with relevant respiratory symptoms have been published as an interim report. Here we present the primary analysis of 1L durvalumab in PS2 pts, unsuitable for combination chemotherapy and PD-L1 expression in ≥25% of tumor cells. **Methods:** In this single-arm, multicenter, phase II trial pts with PD-L1 positive (tumor proportional score, TPS ≥25%), advanced NSCLC with PS2, unsuitable for combination chemotherapy determined by the investigators, in the absence of known contraindications for immunotherapy and sufficient organ function, received a fixed dose of 1500 mg durvalumab every four weeks. The primary endpoint was overall survival (OS) at 6 months. The statistical hypothesis was to improve OS at 6 months from ≤35% to ≥53%. Adverse events (AEs) were assessed according to National Cancer Institute Common Terminology Criteria for AEs (NCI CTCAE) version 5.0. **Results:** Forty-eight pts were included (29 males, 19 females). Median age was 76 years (range, 37-87). OS at 6 months was 60% (95% CI: 45-74%). OS at 6 months after the exclusion of pts with initially relevant respiratory symptoms was 67% (95% CI: 46-84%, n = 27) compared to the subgroup of pts without this exclusion criteria who were recruited before the amendment (52%, 95% CI: 30-74%, n = 21). Median OS was 8.5 months (95% CI: 4.4-16.7). Objective response rate and median PFS were 17% (95% CI: 8-30%) and 2.5 months (95% CI: 1.8-7.1). Thirty-three deaths (69%) were observed to date. Ten early fatal events considered not treatment-related occurred during the first 5 weeks of treatment. Four out of the first 7 early fatal events (4/7; 57%) were respiratory failures in pts with advanced symptomatic primary lung tumors. Only 3 more early fatal events occurred after the protocol amendment excluding pts with severe respiratory symptoms. Thirty-nine patients (81%) had an AE grade ≥3 (G3). The most frequent AEs ≥G3 were lung infection (19%), dyspnea (15%) and hypertension (10%), respectively. Treatment-related AEs ≥G3 were reported in 9 pts (19%) and included colonic perforation in one patient (grade 5), colitis in 5 pts (10%), hepatitis and increased lipase in 3 pts each (6%). **Conclusions:** 1L durvalumab in PS2 pts with advanced PD-L1 positive (TPS ≥25%) NSCLC is effective and led to a promising 6-month OS of 60%. Four-weekly durvalumab can be safely offered to pts presenting without severe pulmonary symptoms who are not candidates for chemotherapy. Clinical trial information: NCT03620669. Research Sponsor: AstraZeneca.

9089 **Poster Session**

Safety, efficacy and biomarker data in patients with non-small cell lung cancer treated with the anti-IL1RAP antibody nadunolimab in combination with platinum doublet.

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Background: Interleukin-1 Receptor Accessory Protein (IL1RAP), expressed in various tumors, is essential for IL-1α and IL-1β signaling. IL-1α/IL-1β are implicated in tumor progression and therapy resistance, and chemotherapy can upregulate IL-1α in e.g. non-small cell lung cancer (NSCLC). Nadunolimab (CAN04), a fully humanized ADCC-enhanced IgG1 antibody, targets IL1RAP and blocks IL-1α/IL-1β signaling. Here, data are reported from clinical phase 1/2 trials in NSCLC pts given nadunolimab and platinum doublet. **Methods:** Pts with advanced NSCLC, 1st line or progressed on pembrolizumab, received nadunolimab at 1 (n=16), 2.5 (n=3) or 5 mg/kg (n=11) with cisplatin/gemcitabine (NCG), or at 2.5 mg/kg with carboplatin/pemetrexed (NCP) (n=5). Four additional pts, 3rd line or beyond, received NCG at 1 or 1.75 mg/kg nadunolimab. Primary objective was safety; efficacy was evaluated as a secondary objective and effects on serum and tumor tissue biomarkers explored. **Results:** The 30 1st or 2nd line pts given NCG had a median PFS of 7.2 months (95% CI 5.5-8.2), ORR of 53% (34-72) and DoR of 5.8 months (3.7-7.5). A dose-response trend was observed for PFS and DoR (Table). Twenty non-progressing pts continued nadunolimab as monotherapy post chemo; 8 of these remained in disease control for a further 12-131 wks. Nadunolimab monotherapy was well tolerated with ≥grade 3 adverse events reported less frequently. Two pts (non-squamous, 2nd line post pembrolizumab) showed complete responses, one observed after >40 wks of nadunolimab monotherapy. Furthermore, confirmed partial responses were observed in 3 of 5 pts given NCP, and 2 of 4 3rd line or beyond pts given NCG. NCG reduced several serum markers, e.g. CRP and tumor-promoting HGF, effects which were maintained by nadunolimab monotherapy. Additionally, a decrease of MCP-3 and 4 was observed during monotherapy. NCG also reduced IL-1- and tumor microenvironment (TME)-related markers in serum (angiopoietin 1, CXCL5, IL-8, TWEAK and VEGFA). Spatial analyses of protein and RNA markers in tumor biopsies are ongoing to verify potential effects in the TME. **Conclusions:** NCG shows promising efficacy in NSCLC with a trend for dose response, and long-term disease control by nadunolimab monotherapy post chemo with good safety. These observations are supported by changes in TME-related serum biomarkers. Preliminary data suggest similar efficacy with NCP, and in more heavily pretreated pts. Clinical trial information: NCT03267316, NCT05116891. Research Sponsor: Cantargia AB.

Dose (mg/kg)	n	PFS (mos)	95% CI	ORR (%)	95% CI	DoR (mos)	95% CI
1	16	5.6	3.9-7.4	50	24.7-75.3	4.7	3.6-7.5
2.5	3	7.6	NE	66.7	9.4-99.2	NE	NE
5	11	8.2	5.6-11.1	54.5	23.4-83.3	6.6	NE

9090 **Poster Session**

The impact of PD-L1 expression and co-mutations on outcome of KRAS-driven non-small-cell lung cancer.

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Background: Interest has surged for *KRAS* mutated (*KRAS*^{mut}) non-small-cell lung cancer (NSCLC) after approval of the covalent *KRAS*^{G12C} inhibitors sotorasib and adagrasib. It remains unclear, how prognosis of these tumors is influenced by co-mutations and which cases could benefit most from novel drugs alongside immunotherapy (IO) or chemo-immunotherapy (CHT-IO). **Methods:** This retrospective study included all NSCLC patients with *KRAS*^{mut} NSCLC treated in the Thoraxklinik Heidelberg from 01/2014 until 01/2021. For molecular profiling, PCR-based next-generation sequencing (NGS) was performed with a 40-gene panel, including *TP53*, *KEAP1* and *STK11*. Date of progression was verified through reevaluation of radiologic images by the investigators according to RECIST v1.1. Stratification was performed according to the type of *KRAS* mutation (G12C *vs.* other), presence of *TP53*, *STK11* and *KEAP1* co-mutations (*vs.* wild-type [WT] status), and the PD-L1 tumor proportion score (TPS $<$ 1 *aka* PD-L1^{neg}, *vs.* TPS 1-49, *vs.* TPS 50+ *aka* PD-L1^{high}). **Results:** Among 370 identified patients, no differences (all p-values $>$ 0.08) were observed between *KRAS*^{G12C} (n = 163) and *KRAS*$^{non\text{-}G12C}$ (n = 207) regarding clinicopathological features, like age (median 65 years), sex, smoking status, initial ECOG performance status, PD-L1 TPS, type of treatment in any line, number of treatment lines, and overall survival (OS, 19.4 months in median; details in the poster). In contrast, there was a strong association of PD-L1 TPS with OS (20.2 *vs.* 9.7 months for PD-L1^{high} vs. PD-L1^{neg}, p = 0.011) and progression-free survival (PFS, 5.7 *vs.* 1.9 months, p = 0.004) under IO. In addition, specifically within the PD-L1^{neg} subset, OS was longer for *KRAS*^{G12C} compared to *KRAS*^{other} patients (22.6 months *vs.* 12.1 months, p = 0.032). This was driven by the longer PFS under CHT-IO (9.7 *vs.* 4.5 months for *KRAS*^{G12C} *vs.* *KRAS*^{other}, p = 0.005), particularly in the absence of *TP53* mutations (8.5 vs. 4.0 months with p = 0.004 for *TP53*^{wt} patients; p $>$ 0.50 for *TP53*^{mut}) and *KEAP1* mutations (11.3 *vs.* 5.1 months with p = 0.01 for *KEAP1*^{wt} patients; p $>$ 0.70 for *KEAP1*^{mut}). Also, across all patients, *KEAP1*^{mut} cases showed a trend for shorter PFS under CHT-IO (2.7 vs. 8.0 months, p = 0.07) and IO (1.9 vs. 3.9 months, p = 0.081), as well as shorter OS (15.9 *vs.* 19.5 months, p = 0.068) compared to *KEAP1*^{wt}, in contrast to *STK11*^{mut} cases (p = 0.42-0.92 for the same comparisons). Overall, *KRAS*^{mut} NSCLC after chemotherapy and immunotherapy showed poor prognosis under standard therapies with a median PFS of 3 months, and a median OS of 6.8 months. **Conclusions:** In PD-L1^{neg} NSCLC, *KRAS*^{G12C} is associated with better outcome under CHT-IO and longer OS compared to *KRAS*^{other}, especially in the absence of *TP53* and *KEAP1* co-mutations. *KEAP1*, but not *STK11* mutations are associated with impaired benefit from (CHT-)IO in *KRAS*^{mut} NSCLC. Treatment of *KRAS*^{mut} NSCLC after chemo-immunotherapy represents an unmet medical need. Research Sponsor: Amgen GmbH; Thoraxklinik Heidelberg.

9091 **Poster Session**

RET testing and treatment patterns among patients with aNSCLC in US clinical practice.

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Background: Biomarker testing, including for rearrangement during transfection (RET), is recommended and important in selecting efficacious targeted therapy for patients with advanced non-small cell lung cancer (aNSCLC). This retrospective cohort study characterized RET testing and treatment patterns among aNSCLC patients in clinical practice. **Methods:** We used the nationwide Flatiron Health electronic health record-derived de-identified database to select patients diagnosed with aNSCLC (stage ≥IIIB) from 2017-2022. We measured rates of RET testing (test result ≤90 days after advanced diagnosis). We used logistic regression to identify baseline characteristics predictive of timely testing. Finally, we described treatment patterns for patients with RET+ aNSCLC before and after the US approval of RET inhibitors. **Results:** Among 26,329 aNSCLC patients, rates of RET testing ≤90 days after advanced diagnosis increased from 25% (2017 Q1) to 73% (2022 Q1). Patients were less likely to receive RET testing within 90 days if they were Black (multivariate odds ratio [OR] 0.8) or Hispanic (OR 0.8) compared to White, or had Medicare (OR 0.9; all $p<0.001$) compared to commercial insurance. Patients were more likely to receive RET testing within 90 days if they were in the highest socioeconomic quintile (OR 1.4), had *de novo* disease (OR 2.1), or no history of smoking (OR 1.3; all $p<0.001$). Between 2017 and 2022, there were increases in the use of next-generation sequencing (66% to 89%) and blood samples for biomarker testing (25% to 49%) and a decrease in mean days from diagnosis to test result (33 to 28) for the first RET test among those who had testing within 90 days. Among all patients with aNSCLC tested within 90 days (n=12,275), 73 were RET+ and received 1L treatment ≤90 days after advanced diagnosis. The most common 1L treatments before (n=35) and after (n=38) RET inhibitor approval were chemotherapy (40%) and RET inhibitor (42%), respectively (Table). **Conclusions:** RET testing has increased over time, but certain patient subgroups are less likely to receive timely RET testing and therefore may not be optimally treated. Among patients with RET+ aNSCLC identified after RET inhibitor approval, only 42% were treated with a RET inhibitor in the 1L setting. These results suggest both disparities in access to RET testing and unmet medical need among patients with RET+ aNSCLC. Research Sponsor: This study is sponsored by Genentech, Inc.

Treatment patterns of RET+ patients.

Treatment type	Patients who initiated 1L *before approval* of 1st RET inhibitor (n=35 of 73)	Patients who initiated 1L *after approval* of 1st RET inhibitor (n=38 of 73)
Chemotherapy only	14 (40%)	4 (11%)
Chemotherapy + Checkpoint inhibitor	10 (29%)	7 (18%)
Checkpoint inhibitor only	5 (14%)	4 (11%)
RET inhibitor	-	16 (42%)
Other targeted therapy	2 (6%)	3 (8%)
Clinical trial drug	4 (11%)	1 (3%)
Other	0 (0%)	3 (8%)

Explore ALK: Alectinib activity in patients with ALK+ metastatic non-small cell lung cancer—A national real world analysis (GFPC 03-2019).

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Background: Alectinib is a standard of care option in advanced *ALK*-rearranged (ALK+) non-small cell lung cancer (NSCLC) patients (pts), with efficacy established by phase 3 trials, in first-line and beyond. There are few efficacy data in unselected populations. **Methods:** The objective of this study was to evaluate the efficacy of alectinib in real-world setting. All ALK+ advanced NSCLC pts initiating alectinib, between December 13, 2017 (date of access in France) and June 27, 2020, whatever the line, were included in explore ALK study. Patient characteristics, alectinib duration of treatment (DOT), progression-free survival assessed locally (rwPFS), overall survival (OS) according to the prescription line of alectinib, the presence of brain metastases at alectinib initiation, response rate and tolerance were collected from the medical files. **Results:** The analysis included 223 pts: 46.2% were men, 84.7% had no smoking history or were former smokers, median age was 59 (22-101) years and 95% were adenocarcinomas. Alectinib was initiated as first-line treatment in 119 pts, with a PS of 0/1/>1 in 42%/31%/27% of cases, a median number of metastatic sites of 2 (cerebral, hepatic, bone in 33%, 24% and 32% of cases). In first-line setting, after a median follow-up of 33.7 months (95%CI, 32.2-37.5), the median of rwPFS and DOT were 28.1 (95%CI, 20.7-40.4) and 26.9 (95%CI, 20.2-31.3) months, respectively. The median OS was not reach (NR), the 3-year OS rate was 72.1%. The rwPFS was not significantly different depending on whether or not the patient has brain metastases, 28.1 (95% CI, 14.5-NR) and 30.5 (85% CI, 18.9-40.4) months, respectively. The best response was complete (CR), partial (PR) and stable (SD) in 21%, 58% and 17%. The cerebral response, evaluable in 30/39 of the pts, was CR, PR and SD in 26%, 46% and 23% respectively; 33% of pts had a grade 3 adverse event, resulting in a temporary interruption of treatment in 7.6% of cases and a permanent discontinuation in 5.9% of cases. At the time of progression, 48.1% of pts had a new biopsy (66% of tissue biopsy). Efficacy data for alectinib prescribed as second line and above are summarized in the table. **Conclusions:** In this large real-world, cohort of unselected advanced ALK+ NSCLC pts, alectinib initiated in 1st-line or beyond provides similar efficacy and safety results as obtained in phase III clinical trials. Research Sponsor: Roche.

Line of alectinib initiation	Median (95% CI)
2nd (n = 49)	
Duration of treatment	28,9 (17,7-40,6)
rw PFS	28,5 (16,5-49)
pts with cerebral metastasis (n= 23)	30,9 (17-49)
pts without cerebral metastasis (n = 26)	16,8 (9,9-NR)
OS	NR (NR-NR)
3-year OS rate	70.1%
3rd (n = 25)	
Duration of treatment	20,6 (17,7-31,2)
rw PFS	19,6 (13,9-31)
OS	NR (36-NR)
3-year OS rate	70.6%
4th (n = 12)	
Duration of treatment	18,7 (1,7-32,7)
rwPFS	17,4 (2,2-22,5)
OS	35,1 (7,8-NR)
≥5th (n = 18)	
Duration of treatment	14,7 (3,1-29,4)
rwPFS	11,7 (3,1-21)
OS	40,1 (7,9-NR)

9093 **Poster Session**

A phase I trial of sequential dosing of sonidegib and pembrolizumab in advanced solid tumors (aST) and non–small-cell lung cancer (NSCLC).

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Background: Pembrolizumab interrupts PD-1/-L1 interaction and is efficacious in many cancers. However, resistance invariably emerges in the majority of patients. Potential mechanisms include activation of compensatory pathways. The inhibition of sonic hedgehog signaling (sHH) was previously shown to induce intra-tumoral (IT) infiltration by CD4+, CD8+ and HLA-DR class II cells. Our preclinical data showed sHH inhibitor enhanced IT penetration by monoclonal antibodies and induced PD-L1 expression. We conducted a phase I study using a novel sequential pulse dosing of sonedegib followed by pembrolizumab in aST with an expansion cohort to determine the maximum tolerated dose (MTD), tolerability and preliminary efficacy. **Methods:** The dose escalation utilized a 3+3 design to determine the MTD and proceeded to expansion cohort upon determination of the MTD. Patients enrolled to each dose level were observed for dose limiting toxicities (DLTs) during the 1^{st} cycle. The expansion cohort consisted of NSCLC and head/neck squamous cell carcinoma (HNSCC) previously treated by anti-PD1/-L1. The recommended phase 2 dose (RP2D) was determined following the review of the toxicity profile of the combination from all cycles. The study treatment consisted of sonidegib oral daily from day 1 to 8 and pembrolizumab I.V. 200 mg on day 8 on an every 3-week cycle. The sonidegib dose levels explored were 400, 600 and 800 mg. Archival tumor and blood specimens were collected for correlative studies. Adverse events (AEs) were categorized and graded per CTCAE v5.0, and tumor response by RECIST v1.1. **Results:** The study enrolled a total of 33 patients and 29 received treatment (13 in escalation and 16 in expansion), including patients with NSCLC, HNSCC, skin cancer, gastric cancer and melanoma. The enrollment to the NSCLC cohort is complete and HNSCC continues. No DLT was encountered during dose escalation and the MTD was not reached. The highest planned dose level was selected to proceed to expansion (sonidegib 800mg days 1-8 in combination with pembrolizumab I.V. 200 mg on day 8 on an every 3-week cycle). The expansion cohort proceeded to enroll 15 patients evaluable for AEs (10 NSCLC and 5 HSNCC). Grade 3 and above treatment-related AEs across all patients were hyperglycemia, fatigue, dyspepsia, abdominal pain. The mature efficacy data will be reported at the meeting. **Conclusions:** The study successfully determined the RP2D of sonidegib when dosed sequentially with pembrolizumab in advanced solid tumors. The AE profile of the combination is similar to that for respective agents given individually. The efficacy data among anti-PD1/-PDL1-treated NSCLC will be reported at the meeting. Clinical trial information: NCT04007744. Research Sponsor: Sun Pharma.

9094 **Poster Session**

Characterization of diverse targetable alterations in ERBB2 and ERBB3 in 93,465 non-small cell lung cancers (NSCLC).

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Background: Recently, fam-trastuzumab deruxtecan-nxki was approved for NSCLC with selected activating *ERBB2* (HER2) mutations. Patritumab deruxtecan, a novel HER3 directed antibody drug conjugate, exhibits *in vitro* activity against HER3 mutations. We present a comprehensive landscape of *ERBB2*/*ERBB3* alterations (alt) that may predict sensitivity to HER2/HER3 targeted therapies in development. **Methods:** We queried an institutional database (Foundation Medicine) of tissue or liquid comprehensive genomic profiling (CGP) results from 93,465 patients with NSCLC (85,704 tissue and 7,761 liquid samples). *ERBB2* amp was defined as ≥ sample ploidy +3. Activating/likely activating alts were called using annotations including presence in COSMIC, functional knowledge of the gene affected, internal insights, and characterization in the literature. ctDNA tumor fraction (TF) on FoundationOneLiquid CDx was estimated using a composite algorithm. **Results:** Activating/likely activating alt in *ERBB2* and *ERBB3* were detected in 3.9% (n = 3337) and 0.8% (n = 696) of NSCLC tissue samples, respectively (*ERBB2*: 2.0% amp, 1.7% mutations [mut; SNVs or indels], 0.001% rearrangements [RE], and 0.2% multiple; *ERBB3*: 0.5% amp, 0.3% mut, and 0.004% multiple). Age at diagnosis, sex, and predicted ancestry were similar among patients with *ERBB2*alt and *ERBB2*wt tumors. *ERBB2* alt were more frequently observed in non-squamous NSCLC (4.3% vs 2.3% in SCC), largely driven by differential *ERBB2* mut frequencies (2.0% vs 0.4%). *ERBB2* mut were most common in the kinase domain (KD; 70%, 56% of which were exon 20 insertions [ex20ins]), followed by the extracellular domain (ECD; 20%) and transmembrane domain (TMD; 6%), while *ERBB3* mut were most common in the ECD (88%, most commonly V104L/M and G284R). *ERBB2* RE or splice mut affecting exon 16 were detected in 23 cases (0.03%). While *ERBB2* alt were mutually exclusive with other oncogenic drivers (*KRAS*, *ALK*, *BRAF*, *EGFR*, *MET*, *ROS1*, *RET;* each $p < 0.05$), *ERBB3* alt were found to co-occur with both *ERBB2* (8.5% vs 3.9% *ERBB2*wt, $p < 0.001$) and *MET* (8.6% vs 5.2% *ERBB2*wt, $p < 0.001$) alt. A similar distribution of *ERBB2* alt (1.6% amp, 2.4% mut, 0.4% multiple) was detected in liquid samples with elevated TF (≥10%; n = 1458); across all liquid samples, *ERBB2* mut frequency was comparable to tissue (1.5%) but frequency of amp was 0.5%. In our study, 26% of *ERBB2* mut tissue samples had activating/likely activating mut not included in the DESTINY-Lung01 trial, most notably 100% of both TMD mut (n = 99) and exon 16 alt (n = 25), as well as 35% of ECD mut (117/331) and 14% of KD mut (162/1145, including 6% of ex20ins). **Conclusions:** Diverse *ERBB2* and *ERBB3* alt in NSCLC may predict sensitivity to anti-HER2/3 therapies, but not all classes of alts are detected/reported by all profiling assays. Utilization of comprehensive testing to guide biomarker definitions, treatment selection, and clinical trial enrollment is imperative. Research Sponsor: Foundation Medicine, Inc.

9095 **Poster Session**

Updated molecular analysis of *MET* exon 14 skipping mutations (*MET*ex14) in non-small cell lung cancer (NSCLC).

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Background: *MET*ex14 is a heterogeneous family of mutations (mt) in NSCLC that can be effectively treated with approved targeted agents. Unlike some other drivers in NSCLC, *MET*ex14 occurs in both squamous and adenocarcinoma histology and in both smokers and non-smokers. Here, we present updated results from analysis of a large dataset to characterize the mutational landscape within *MET*ex14 NSCLC. **Methods:** NSCLC tissue samples were analyzed with DNA-based next-generation sequencing (NGS; 592 genes, NextSeq) or whole-exome sequencing (NovaSeq), RNA-based whole transcriptome sequencing (WTS, NovaSeq), and PD-L1 immunohistochemistry (Dako 22C3) at Caris Life Sciences (Phoenix, AZ). *MET*ex14 was detected by WTS. TMB-high was defined as ≥ 10 mt/Mb. Chi-square, Fisher's exact or Mann-Whitney U tests were used to determine statistical significance and corrected for multiple hypothesis testing ($q<0.05$). Immune cell estimates (quanTIseq) and pathway analysis (ssGSEA) were informed by WTS analysis. **Results:** A total of 711 *MET*ex14 cases were detected with 288 distinct *MET*ex14 mt. By histology, 79 (11.1%) were squamous (Sq), 478 (67.23%) were nonsquamous (nSq), and 24 (3.23%) were adenosquamous. The most common *MET*ex14 mt were D1028H (8.1%), D1028N (7.8%), c.3082+2T>C (5.0%), D1028Y (4.6%), and c.3082+1G>T (4.4%). Co-mutated *TP53* was common (43.4%) but varied by specific *MET*ex14 mt, observed in 60.0% of *MET* c.3082+3A>G vs 16.7% of *MET* G344R. Co-amplified CDK4 was found in 9.3%, with 42.9% in *MET* c.2924-1G>A vs 6.7% in *MET* c.3802+1G>T ($p<0.05$). High TMB was seen in 9%; median TMB ranged from 2 mt/Mb in *MET* c.3082+2T>A to 6.5 mt/Mb in *MET* c.3082+2T>G ($p<0.05$). PD-L1 ≥ 1% was seen in 80.8% compared to 56.2% in *MET*ex14-WT($p<0.05$), and median PD-L1 tumor proportion score (TPS) ranged from 0% in *MET* G344R to 75% in *MET* c.3082+2T>A ($p<0.05$). Co-mutations varied by histology: in Sq-NSCLC, 18.18% had *TP53* mt ($q<0.05$), 8.97% had *POT1* mt ($p<0.05$), 6.06% had *TERT* mt ($p<0.05$), 5.13% *CASP8* mt ($q<0.05$), and 2.53% *RNF43* mt ($p<0.05$), while in nSq-NSCLC, 45.51% had *TP53* mt, 3.38% had *POT1* mt, 0.87% had *TERT* mt, and 0% in *CASP8* and *RNF43* mt. Smoking status was available for 120 cases: 88% were smokers and 12% were nonsmokers. Wnt, Hedgehog, and Notch signaling were enriched in nSq ($q<0.05$) while upregulation of KRAS signaling, Epithelial-Mesenchymal Transition, and angiogenesis pathways were enriched in smokers with *MET*ext14 NSCLC ($q<0.2$). Higher estimates of neutrophils and lower estimates of M2 macrophages, NK cells, and CD8+ T-cells were observed in Sq-NSCLC. PD-L1, PD-1, HAVCR-2, IDO-1 and IFN-γ expression were higher in nSq than Sq-NSCLC ($q<0.05$). **Conclusions:** *MET*ex14 NSCLC is highly heterogenous, with variations in co-mutation, TMB, and PD-L1 expression. Although Sq- and nSq-NSCLC harbor *MET*ex14, the enrichment of oncogenic pathways and infiltrating immune cells differ between histology and smoking history. Research Sponsor: None.

9096 **Poster Session**

Long-term outcome for patients with advanced non–small-cell lung cancer treated by autologous cytokine-induced killer (CIK) cell immunotherapy in combination with sintilimab plus chemotherapy: NSCLC-CCICC-002.

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Background: Autologous cytokine-induced killer (CIK) cell immunotherapy in combination with Sintilimab demonstrated robust antitumor activity and safety in the phase Ib CCICC-002 study (NCT03987867) of Non–Small-Cell Lung Cancer. Long-term outcomes in patients are reported herein. **Methods:** Systemic therapy naïve patients received platinum-based doublet chemotherapy, Sintilimab (PD1 inhibiter), and CIK cells every 3 weeks for 4 cycles, then maintenance treatment with Sintilimab in squamous and with Sintilimab plus pemetrexed in non-squamous NSCLC until disease progression or unacceptable toxicity or two years. Kaplan-Meier estimates of overall survival (OS) and progression-free survival (PFS) were calculated. OS and PFS were based on immune-related response criteria by investigator assessment (data cut-off, January 31, 2023). **Results:** From May 2019 to Jan 2021, CCICC-002 enrolled 33 patients (19 squamous, 14 non-squamous NCSLC; 1 patient was excluded because the second biopsy revealed EGFR mutation) aged 46-73 years with median follow-up was 31.4 months (range, 7.6-44.4 months). Estimated 3-year OS was 51.8% in all patients; median OS was not reached (95% CI, 26.6 months-not reached) in all patients. In subgroups, median OS was 27.6 months (95% CI, 13.4 months-not reached) in squamous NCSLC and not reached (95% CI, 29.9 months-not reached) in non-squamous NCSLC, respectively. Median OS was not reached (95% CI, 27.6 months-not reached) in PD-L1 positive patients and 28.3 months (95% CI, 15.6 months-not reached) in PD-L1 negative patients, respectively. Estimated 3-year PFS rate was 27.5% and median PFS was 17.9 months (95% CI, 8.2-26.5 months) in all patients. Median PFS was 17.3 months (95% CI, 5.0-24.0 months) in squamous NCSLC and 22.4 months (95% CI, 5.7 months-not reached) in non-squamous NCSLC, respectively. Median response duration was 18.7 months (95% CI, 10.1-27.6 months). 30.3% of patients were ongoing at data cut-off, and the longest response was ongoing at 41.3 months. 1 of the 5 CMR (complete metabolic response by PET-CT) patients experienced disease progression during observation. Treatment-related AEs (TRAEs) occurred in 94.0% of patients and resulted in study discontinuation in 7.8%, and 15.2% experienced grade 3/4 TRAE. **Conclusions:** This long-term analysis of CCICC-002 represents the longest follow-up for CIK to date and confirms the durable antitumor activity and tolerability of CIK cells therapy in combination with Sintilimab plus chemotherapy in advanced NCSLC. Further studies are warranted to confirm these preliminary results. Clinical trial information: NCT03987867. Research Sponsor: Tianjin Medical University Cancer Institute and Hospital.

9097 **Poster Session**

A nation-wide genomic screening project for further development of targeted therapies in treatment-refractory non–small-cell lung cancer (LC-SCRUM-TRY).

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Background: Targeted therapies based on oncogenic drivers demonstrate dramatic and durable response in patients with non-small cell lung cancer (NSCLC). However, acquired resistance inevitably develop by diverse genomic resistance mechanisms. Genotype-matched targeted therapies to overcome treatment-resistance have not been established, except osimertinib against *EGFR* T790M mutation. **Methods:** We established a nation-wide genomic screening project in treatment-resistant NSCLC (LC-SCRUM-TRY; UMIN000041957) in September 2020 to identify the genetic resistant alterations, and to promote clinical therapeutic development. Enrolled patients have been screened for genetic alterations using a rapid next-generation sequencing (NGS) system, Oncomine Precision Assay (OPA) for tissue samples, and Guardant 360 (G360) or OPA for plasma samples. *MET* amplification was also evaluated by FISH for NSCLC post EGFR-TKI treatment. **Results:** As of January 2023, 129 institutions in Japan were participating, and 1252 patients had been enrolled. Sample types were tissue (84%), and plasma (16%), respectively. Turn-around-time (median [interquartile range]) of OPA and G360 was 5 (4-6), and 9 (8-10.5) days, respectively. Of these, a total of 711 (57%) were already identified to have oncogenic driver at enrollment (*EGFR*, 556 [43%]; *ALK*, 70 [6%]; *RET*, 22 [2%]; *ROS1*, 21 [2%]; *KRAS*, 15 [1%]; *ERBB2* exon 20 insertion [ex20ins], 8 [0.6%]; *MET* exon 14 skipping [ex14skip], 8 [0.6%]; *BRAF* V600E, 7 [0.6%]; *NTRK3*, 2 [0.2%]; others, 2 [0.2%]). Of 556 *EGFR*-mutated NSCLC, 537 (97%) were enrolled post EGFR-TKIs. *EGFR* mutation subtypes were exon 19 deletion (52%), L858R (41%), ex20ins (1%), others (6%), respectively. Of 537 EGFR-TKI resistant tumors, 326 (40%) had at least one genetic alteration related with drug resistance, including *EGFR* alterations (amplification [13%], C797S [4%], A750P [3%], E709X [2%], L792X [1%], L718Q [1%]), *MET* amp (16%), and other driver mutation/rearrangement (8%). Through this screening, 37 (7%) of patients resistant to EGFR-TKI were enrolled into clinical trials, with 16/102 (16%) patients with targetable alterations (*MET* amp or *EGFR* C797S). In addition, of 541 NSCLC without oncogenic drivers at enrollment, 116 (21%) were identified to have actionable oncogenic drivers with FDA-approved drug (KRAS G12C, 23 [4%]; ERBB2 ex20ins, 23 [4%]; RET, 13 [2%]; MET ex14skip, 13 [2%]; EGFR except ex20ins, [4%]; EGFR ex20ins, 10[2%]; ALK, 6 [1%]; ROS1, 5 [1%]). **Conclusions:** LC-SCRUM-TRY contributes to the clinical development of precision medicine to overcome drug resistance, especially for *EGFR*-mutated NSCLC resistant to EGFR-TKI. This screening platform also help to practice precision medicine for patients initially diagnosed as driver-negative. Clinical trial information: UMIN000041957. Research Sponsor: Amgen, Nippon Boehringer Ingelheim, Takeda, Haihe Biopharma, AstraZeneca, Eli Lilly Japan, Janssen, Novartis,Turning Point Therapeutics, Spectrum Pharmaceuticals.

9098 **Poster Session**

Retrospective clinical analysis of circulating tumor DNA (ctDNA)–based molecular response (MR) and baseline blood-based tumor mutational burden (bTMB) for monitoring response in phase 3 trial of bintrafusp alfa vs. pembrolizumab treatment of non-small cell lung cancer (NSCLC).

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Background: The clinical utility of ctDNA-based approaches, such as bTMB and MR, to monitor and predict response during chemo-immunotherapy was evaluated using longitudinal cohort samples from a Phase 3 study of bintrafusp alfa versus pembrolizumab as a first-line treatment in patients with PD-L1 expressing advanced NSCLC. **Methods:** ctDNA was collected at baseline and day 42 after treatment with bintrafusp alfa (Q2W, 1200mg) or pembrolizumab (Q3W, 200mg). The GuardantOMNI liquid biopsy (LBx) assay was used to detect somatic alterations in 497 genes and generate bTMB from baseline, and MR scores from baseline and day 42 (n = 424 samples). bTMB and somatic alterations influencing response were explored. MR scores were calculated using the validated Guardant Response algorithm. Associations between ctDNA metrics and PFS were assessed. **Results:** 418/424 samples passed sequencing QC; of these, somatic mutations were detected in 236/237 baseline samples and 177/181 day 42 samples. Of 212 NSCLC patients with eligible bTMB results at baseline, 104 (49.1%) patients received bintrafusp alpha and 108 (50.9%) received pembrolizumab. bTMB high (bTMB-H) is defined as $>$20mut/MB. In the bintrafusp alpha arm, PFS was significantly longer in patients with bTMB-H (median 8.3 months vs 2.7 months, p = 0.00086). In the pembrolizumab arm, PFS was also longer in patients with bTMB-H (median 5.65 months vs 5.5 months, p = 0.0898). Of 132 NSCLC patients with eligible MR results, 67 (50.8%) patients received bintrafusp alpha and 65 (49.2%) patients received pembrolizumab. In the bintrafusp alpha arm, molecular responders had significantly longer PFS (median 7.9 months vs 4.2 months, p = 0.00042). In the pembrolizumab arm, molecular responders also had significantly longer PFS (median 8.95 months vs 4.1 months, p = 0.00054). **Conclusions:** ctDNA analysis from plasma samples supported MR assessment in patients treated with ICI, indicating its utility as an adjunct to RECIST in monitoring of tumor response. Blood-based TMB-high was associated with immunotherapy treatment benefit. Analysis of b-TMB and MR allowed identification of patients with improved PFS in both treatment arms. Investigation of treatment specific TMB cut off selection and potential clinical utility of defined somatic mutations is ongoing. Clinical trial information: NCT03631706. Research Sponsor: This research was supported by the healthcare business of Merck KGaA, Darmstadt, Germany (CrossRef Funder ID: 10.13039/100009945).

9099 **Poster Session**

Patient-reported outcomes in patients with metastatic non-squamous non-small cell lung cancer from the PERLA trial comparing first-line chemotherapy plus dostarlimab or pembrolizumab.

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Background: PERLA (NCT04581824) is a global, randomized, Phase II, double-blind study assessing the efficacy and safety of chemotherapy (CT) combined with programmed death 1 (PD-1) inhibitors dostarlimab (dostCT) and pembrolizumab (pembCT) as first-line (1L) treatment (tx) for patients (pts) with metastatic non-oncogene-driven, non-squamous, NSCLC. DostCT had similar efficacy and safety to pembCT [1]. Exploratory analyses of patient-reported outcomes (PROs) from PERLA have been conducted. **Methods:** In PERLA, pts with ECOG status 0–1 were randomized 1:1 to receive ≤35 cycles (C) of dostCT or pembCT Q3W (CT was ≤35 cycles [C] of 500 mg/m^2 pemetrexed every 3 weeks [Q3W] and ≤4C of cisplatin or carboplatin). PROs were collected at baseline (BL), Q3W until C4, Q9W until C16, Q12W until end of tx and at 30-day safety follow-up. Change from BL in EORTC QLQ-C30 & QLQ-LC13 were analyzed using a longitudinal mixed model, with a ≥10-point change from BL considered clinically meaningful; scores were categorized as improved, stable, or worsened. Time to deterioration (TTD) in QLQ-C30 and selected QLQ-LC13 symptoms were estimated using Kaplan–Meier methods. **Results:** Analysis populations for dostCT/pembCT included 102/99 pts for QLQ-C30 and 96/90 pts for QLQ-LC13. Completion rates for QLQ-C30 and QLQ-LC13 were >80% up to C4 in both tx arms, decreasing after C7. At C13, 55.0% [n=33/60] and 54.2% [n=32/59] of dostCT pts, and 37.1% [n=23/62] and 35.7% [n=20/56] of pembCT pts completed QLQ-C30 and QLQ-LC13, respectively. Overall, least squares (LS) mean QLQ-C30 and QLQ-LC13 scores remained stable up to C13. Relative to BL, average pt functioning (e.g., physical, role) and cancer symptoms (e.g., pain, cough, dyspnea) were stable through C13 (~1 yr on tx); no clinically meaningful difference in LS mean QLQ-C30 or QLQ-LC13 scores were observed between tx arms. Across most QLQ-C30 and QLQ-LC13 subscales, >60% pts in both tx arms had stable or improved responses up to C13. At C13, meaningful improvements in chest pain and dyspnea were reported in a higher % of dostCT pts (34.4% [n=11/32] and 40.6% [n=13/32], respectively) than pembCT pts (10.0% [n=2/20] and 25.0% [n=5/20], respectively). TTD for QLQ-C30 and QLQ-LC13 subscales were comparable between tx arms, except for longer median TTD in dyspnea in dostCT pts (N=96) than pembCT pts (N=90) (4.24 vs 1.54 months; HR 0.64 [95% CI: 0.44–0.93]). **Conclusions:** HRQoL was similar and stable through C13 in both tx arms. These results supplement efficacy and safety data reported in PERLA and support further investigation of dostarlimab as an appropriate PD-1 inhibitor for use in combination with standard of care and novel therapies in metastatic NSCLC. References: 1. Peters, S *et al. IOTECH* 2022;16(S1):100162 Funding:GSK (213403). Editorial support provided by Fishawack Health, funded by GSK. Clinical trial information: NCT04581824. Research Sponsor: GSK (213403).

9100 **Poster Session**

RAMP 202: A phase 2 study of avutometinib (VS-6766) ± defactinib, in patients with advanced *KRAS* G12V mutant non–small cell lung cancer (NSCLC).

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Background: *KRAS* mutations (mt) occur in ~30% of lung adenocarcinomas, among which G12C is most common (40%), followed by G12V (22%) and G12D (16%). Approved treatments for advanced *KRAS* mt NSCLC (excluding G12C) are limited to chemotherapy and immune checkpoint inhibitors (ICIs). Avutometinib is a novel small molecule RAF/MEK clamp. Focal adhesion kinase (FAK) activation is a resistance mechanism to RAF/MEK inhibition. Defactinib, a small molecule FAK inhibitor, has shown synergistic antitumor activity with avutometinib in preclinical models. In prior studies, avutometinib ± defactinib has shown responses in patients (pts) with *KRAS* mt NSCLC, including *KRAS* G12V. **Methods:** RAMP 202 is a randomized, phase 2, adaptive, multicenter, open-label study evaluating the efficacy and safety of avutometinib ± defactinib in previously-treated *KRAS* mt NSCLC (NCT04620330). Key inclusion criteria include histologically confirmed NSCLC with known *KRAS* mt and ≥1 prior systemic therapy (platinum-based and immune checkpoint inhibitor or appropriate therapy for activating mutation). Part A evaluated the optimal regimen, either 4.0 mg avutometinib orally (PO), twice weekly, 3 weeks on, 1 week off (mono) or 3.2 mg avutometinib PO twice weekly + 200 mg defactinib PO twice per day, 3 weeks on, 1 week off (combo) in pts with *KRAS* G12V mt NSCLC. Primary endpoint was confirmed objective response rate (ORR) by blinded independent central review. The optimal regimen determined in Part A would subsequently be assessed for efficacy in Part B. Exploratory assessment of ORR is also planned in *KRAS*-other (non-G12V) NSCLC. **Results:** Of 35 pts with *KRAS* G12V enrolled to Part A, 16 pts received mono, and 19 received combo. Patients received up to 5 lines of prior systemic therapy (median 2), including prior platinum-based chemotherapy, ICIs, and bevacizumab. No confirmed responses were seen in the mono group. In the combo group, 2 pts (11%) experienced a confirmed partial response. The duration of each response was 7.9 and 8.5 months, with both ongoing at data cut. The majority of treatment-related adverse events (TRAEs, any grade) (N = 72) were mild to moderate. The most common Grade ≥3 TRAEs included blood CPK increase (11.1%), diarrhea (5.6%), anemia (5.6%), and rash (1.4%). Most AEs were manageable/reversible. **Conclusions:** In this heavily pretreated population of patients with *KRAS G12V* mt NSCLC, limited clinical activity was observed with combination therapy. While no new safety signals were identified, criteria to proceed to part B were not met, and further evaluation of avutometinib ± defactinib in *KRAS G12V* mt NSCLC will not be pursued. Additional trials evaluating rational avutometinib combinations (sotorasib, adagrasib, everolimus) are ongoing in patients with *KRAS* mt NSCLC. Clinical trial information: NCT04620330. Research Sponsor: Verastem Oncology.

9101 **Poster Session**

Association between duration of immunotherapy and overall survival in advanced non–small-cell lung cancer.

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Background: For patients (pts) with advanced non-small cell lung cancer (NSCLC) treated with front line immunotherapy-based treatment, the optimal duration of immune checkpoint inhibitor (ICI) treatment is unknown. We aimed to assess practice patterns surrounding ICI treatment discontinuation at two years, and to evaluate association of duration of therapy with overall survival by comparing pts who received fixed duration ICI therapy for 2 years vs those who continued therapy beyond two years. **Methods:** This study used the nationwide Flatiron Health electronic health record (EHR)-derived de-identified database, and included adult pts diagnosed with advanced NSCLC from 2016-2020, who received frontline immunotherapy-based treatment. Pts who were still on treatment without progression at 2 years were classified as "fixed duration" (treatment discontinuation at 2 years, between 700-760 days) vs "indefinite duration" (continued treatment beyond two years, $>$ 760 days). Overall survival from 760 days was analyzed using Kaplan-Meier methodology. Multivariable Cox regression adjusted for patient and cancer-specific factors was used to compare survival between fixed and indefinite-duration groups. **Results:** Our analytic cohort consisted of 113 pts in the fixed duration group and 593 in the indefinite duration group; median age was 69, 49% were female, and 71% were White. Pts in the fixed duration group were more likely to have a history of smoking and be treated at an academic center. There was no significant difference in overall survival between pts in the fixed duration and indefinite duration groups, either on univariable (HR 1.26, 95% CI 0.77-2.08) or multivariable Cox regression (HR 1.33, 95% CI 0.78-2.25). **Conclusions:** In a real world cohort of advanced NSCLC pts treated with front line ICI, only about 1 in 5 stopped treatment at two years rather than continuing treatment beyond two years. The lack of significant overall survival advantage for the indefinite duration cohort on adjusted analysis provides reassurance to pts and providers who wish to stop therapy at 2 years. Research Sponsor: None.

9102 **Poster Session**

The final analysis of a phase I/II study of nivolumab, ipilimumab combined with nintedanib in advanced non-small cell lung cancer.

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Background: Nintedanib (NT) is an oral triple kinase inhibitor that is active against NSCLC and inhibits the activity of the immunosuppressive cancer associated fibroblasts in the tumor microenvironment (TME). Targeting the TME with NT may represent an important synergistic approach in improving immunotherapy (IO) outcomes for NSCLC. We initiated a phase Ib/II trial to evaluate the combination of NT, nivolumab (N) and ipilimumab (I) in advanced (a)NSCLC. Based on the phase IB (dose escalation) results, the combination of N (3mg/kg/2w), I (1mg/kg/6w) and NT (150mg once daily) was declared as the recommended phase 2 dose (RP2D). Here we present the final analysis of the regimen in treatment naïve (TN), and IO pretreated (IP) aNSCLC. **Methods:** This is a single institution, non- randomized, parallel assignment phase I/II clinical trial of aNSCLC pts. Eligible pts were TN (Arm A) or with disease progression following IO (Arm B) with planned sample size of 40/arm. Enrollment into phase II was by the Bayesian two-stage design method with the primary objective of determining the overall response rate (ORR) in the intent to treat population. Key secondary objectives were overall survival (OS) and progression-free survival (PFS). Descriptive statistics were used to summarize demographic and safety data. The Kaplan- Meier method with log-rank test (5% level of significance, 95% CI and 2-sided test) was used for survival analysis. **Results:** 22 and 29 pts received the N+I+NT at the RP2D in Arm A and B, respectively. The median age was 67 [42;92] with 53% (27/51) females, 84% (42/51) Caucasian, ECOG 1 in 88% (45/51), and a current/prior history of tobacco use in 88% (45/51) pts. Adenocarcinoma histology was common (64%, 33/51) with PD-L1 $\geq$1% in 52% (22/42) pts. As of Oct 24, 2022, 18 and 26 pts were evaluable for response in Arm A and B, respectively. Clinical efficacy was observed in the TN and IP cohorts (Table). The most common treatment-related adverse events (TRAEs) were similar in both cohorts. TRAE of any grade in Arm A were nausea (8, 36%), diarrhea (8, 36%), fatigue (7, 32%), and in Arm B were nausea (10, 34%), fatigue (9, 31%), anorexia (8,27%). **Conclusions:** The combination of nivolumab, ipilimumab and nintedanib had a manageable toxicity profile and demonstrated promising antitumor activity in both TN and IP aNSCLC patients. Clinical trial information: NCT03377023. Research Sponsor: Drug support BI, BMS, Other support: Florida Department of Health James and Esther King Grant.

	TN/Arm A(N=22)	IP/ Arm B (N=29)
ORR, n,% (95% CI)	9, 40.9 (21.5,63.3)	6, 20.7 (8.7, 40.3)
Best overall response, n (%)		
Complete response (CR), cCR*	1 (4.5), 0	1 (3.4), 1
Partial response (PR), cPR**	8 (36.4), 5	5(17.2), 3
Stable disease (SD)	7 (31.8)	11(37.9)
Progressive disease (PD)	3 (13.6)	9(31.0)
Not evaluable /Not assessed	3 (13.6)	3 (10.3)
Disease control rate, % (95% CI)	72.7 [49.6,88.4]	58.6 [39.1,75.9]
Median PFS, mo (95% CI)	5.5(2.9, N.E.)	2.7 (1.5,6.9)
Median OS, mo(95% CI)	17.1 (5.5, N.E)	8.5 (5.7, 25.3)

*Confirmed CR, ** Confirmed PR.

9103 **Poster Session**

Anti-tumor activity of sunvozertinib in NSCLC with EGFR sensitizing mutations after failure of EGFR TKI treatment.

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Background: Sunvozertinib is a rationally designed, irreversible EGFR inhibitor targeting various EGFR mutations with wild-type EGFR selectivity. Clinical studies have showed its superior efficacy than current available therapies and favorable safety profile for treating NSCLC patients with EGFR exon20 mutations. Here we reported its anti-tumor activity in patients with EGFR sensitizing mutations (EGFRm) who failed from standard EGFR TKI treatment. **Methods:** This is a pooled analysis of three clinical studies in patients with EGFRm or HER2m NSCLC: WU-KONG1 (multinational phase I/II study, NCT03974022), WU-KONG2 (phase I study in China, CTR20192097), and WU-KONG15 (phase II study in China, NCT05559645). Patients were enrolled to receive sunvozertinib once daily at defined doses until discontinuation criteria were met. Patients who had EGFRm NSCLC, at least one measurable lesion at baseline, received at least one dose of sunvozertinib, and underwent at least one post-treatment RECIST assessment were evaluable for efficacy analysis. Patients with EGFRm or HER2m NSCLC who failed from standard systemic therapies and received at least one dose of sunvoertinib were included in the safety analysis. **Results:** As of October 17, 2022, a total of 32 patients who met efficacy evaluable criteria were included in the analysis. The doses of sunvozertinib ranged from 50 mg - 400 mg. Baseline characteristics: median age was 64.5 years old; 68.8% (22/32) were female; 75.0% (24/32) ECOG PS was 1; 34.4% (11/32) had more than three metastatic sites; 43.8% (14/32) had baseline brain metastases. Patients were heavily pretreated, with a median of 5 lines (range 1 - 16) of prior therapies. All patients had been treated with at least one type of EGFR TKI, including 68.8% (22/32) had been treated with a 3rd generation EGFR TKI. The majority of patients (29/32, 90.6%) had also been treated with chemotherapy. Anti-tumor activity was observed starting from 50 mg. Per investigators' assessment, the best objective response rate (BoR) was 21.9% (7/32). Anti-tumor activity was observed regardless of T790M mutation status. At the data cutoff date, the median duration of response and progression-free survival were 4.0 months and 5.9 months, respectively. Sunvozertinib was well-tolerated across all dose levels. The safety profile was similar to what has been previously reported. The longest treatment duration was more than 35 months (still ongoing). **Conclusions:** Sunvozertinib monotherapy demonstrated promising anti-tumor activity in heavily pretreated EGFRm NSCLC patients. Further clinical evaluation of sunvozertinib in this patient population is warranted. The updated data will be presented at the conference. Clinical trial information: NCT05559645 NCT03974022 and CTR20192097. Research Sponsor: Dizal Pharmaceutical.

9104 **Poster Session**

Association of alterations in multiple tumor suppressor genes with poor outcomes in patients with EGFR-mutant lung cancer.

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Background: Co-occurring alterations in tumor suppressor genes (TSG) have been described as determinants of disease heterogeneity in *EGFR*-mutant non-small cell lung cancer (NSCLC), however, detailed analyses of their impact on patient outcomes are limited. **Methods:** Patients with *EGFR*-mutant NSCLC treated with EGFR tyrosine kinase inhibitors (TKIs) at the Yale Cancer Center who had tumor genomic profiling either before EGFR-TKI therapy (pre-TKI) or at disease progression (post-TKI) were included. Whole exome sequencing (WES) of paired pre- and post-TKI tumor specimens were performed for a subset of patients. The cohort was divided into three subgroups based on alterations in *TP53* and five additional TSGs (*RB1*, *NF1*, *ARID1A*, *BRCA1* and *PTEN*): patients with tumors harboring a *TP53* mutation plus a mutation in at least 1 additional TSG ($TP53^{mut}$/TSG^{mut}), patients with tumors harboring a *TP53* mutation without an additional TSG mutation ($TP53^{mut}$/TSG^{wt}), and patients with $TP53^{wt}$ tumors. Clinical characteristics including progression-free (PFS) and overall survival (OS) were assessed. **Results:** One-hundred-one patients were included in this retrospective study. *TP53* mutations were identified in 65 (64%) tumors, of which 23 (35%) and 42 (65%) were classified as $TP53^{mut}$/TSG^{mut} and $TP53^{mut}$/TSG^{wt}, respectively. Among those cases with paired WES available (n = 34), frequencies of alterations in the six included TSGs did not significantly differ between pre- and post-TKI tumor specimens. In the full study cohort, the presence of a *TP53* mutation was associated with numerically worse PFS (HR 1.46, CI 0.97 – 2.21, p = 0.09) and OS (HR 1.68, CI 1.05 – 2.70, p = 0.04) on first-line EGFR-TKI. Strikingly, after dividing the $TP53^{mut}$ cohort into $TP53^{mut}$/TSG^{mut} and $TP53^{mut}$/TSG^{wt} cases, alterations in additional TSG were found to drive the poor outcomes: $TP53^{mut}$/TSG^{mut} cases had significantly worse PFS and OS on first-line EGFR TKI than $TP53^{mut}$/TSG^{wt}(mPFS 8.0 vs 10.6 months, p = 0.006; mOS 30.0 vs 33.3 months, p = 0.12) or $TP53^{wt}$ cases (mPFS 8.0 vs 12.6 months, $p < 0.0001$; mOS 30.0 vs 48.8 months, p = 0.001). There was no significant difference in PFS or OS between patients with $TP53^{mut}$/TSG^{wt} and $TP53^{wt}$ tumors. Similar outcome differences between the three groups were found in patients who received osimertinib in the second-line setting. **Conclusions:** The inferior outcomes associated with *EGFR/TP53*-mutant NSCLC tumors may be due to additional TSG alterations rather than *TP53* mutational status alone. Alterations in the investigated TSGs did not appear to emerge under EGFR-TKI therapy, which suggests that they are truncal. Our findings may have implications for understanding the biologic underpinnings of differential outcomes to EGFR TKIs. Research Sponsor: U.S. National Institutes of Health.

9105 **Poster Session**

Safety and efficacy of inetetamab in combination with pyrotinib in HER2 mutant patients with non-small cell lung cancer (NSCLC): An open-label, phase Ib trial.

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Background: Currently, limited targeted therapies are available for HER2 mutant NSCLC patients. Previous studies have shown the antitumor activity of pyrotinib in advanced NSCLC patients with HER2 mutations. Inetetamab is a recombinant humanized anti-HER2 monoclonal antibody. Whether inetetamab combined with pyrotinib could show manageable safety and more active antitumor activity remains unknown. This study was designed to evaluate the safety and efficacy of inetetamab in combination with pyrotinib in HER2 mutant patients with advanced NSCLC. **Methods:** This study was an open-label, phase Ib study. The HER2 mutant patients with locally advanced or metastatic NSCLC were assigned to receive inetetamab combined with pyrotinib. The study consisted of dose-escalation part and dose-expansion part. During dose-escalation period, the parallel "3+3" dose-escalation design was used to determine the dose-limiting toxicity (DLT). Inetetamab was administered every 3 weeks (8 mg/kg loading dose for cycle 1, followed by 6 mg/kg in subsequent cycles) with pyrotinib (dose-escalation part, 240mg QD, 320mg QD; dose-expansion part, 320mg QD). Primary endpoint of the study was DLT dosage and safety. The DLT was assessed during the 21-day DLT evaluation period after the first dose. Secondary endpoints included objective response rate (ORR), disease control rate (DCR), progression free survival and overall survival. **Results:** Between August 6, 2021, and August 25, 2022, 48 patients were enrolled. No DLT occurred during pyrotinib 240mg and 320mg escalation period. Therefore, pyrotinib 320mg was chosen as expansion dose. The most common treatment-related adverse events (TRAEs) were diarrhea (66.7% [2/3] in pyrotinib 240mg group, 95.6% [43/45] in pyrotinib 320mg group), rash (66.7% [2/3] in pyrotinib 240mg group, 22.2% [10/45] in pyrotinib 320mg group) and vomiting (0 in pyrotinib 240mg group, 24.4% [11/45] in pyrotinib 320mg group). TRAEs were generally Grade (G) 1-2. Only 7 patients reported G3 TRAE (1 in pyrotinib 240mg group, 6 in pyrotinib 320mg group). The preliminary efficacy was shown in the table below. The ORR and DCR of group receiving inetetamab with pyrotinib 240mg were 0% and 66.7%, respectively. The ORR and DCR of inetetamab with pyrotinib 320mg group were 36.6% and 85.4% respectively. The relationship between different mutation subtypes or co-mutations and efficacy will be updated during the conference reports. **Conclusions:** The preliminary data of inetetamab in combination with pyrotinib showed manageable safety and compelling antitumor activity in advanced NSCLC patients harboring HER2 mutations. Clinical trial information: NCT05016544. Research Sponsor: None.

Response	Inetetamab with Pyrotinib 240mg (n = 3)	Inetetamab with Pyrotinib 320mg(n = 41)
Partial response	0	15
Stable disease	2	20
Progressive disease	1	6
ORR	0	36.6%
DCR	66.7%	85.4%

9106 **Poster Session**

Dacomitinib for patients with non-small cell lung cancer harboring uncommon epidermal growth factor receptor mutations: Do mutation patterns matter?

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Background: Previous evidence has revealed the potential efficacy of dacomitinib in patients with advanced non-small cell lung cancer (NSCLC) carrying uncommon epidermal growth factor receptor (*EGFR*) mutations, but it remains unknown whether there are differences in its efficacy for different combination patterns of these uncommon mutations. **Methods:** The AFANDA cohort, an ambispective cohort including 121 NSCLC patients with uncommon *EGFR* mutations admitted from two tertiary hospitals in China, was employed for exploration. Meanwhile, a cohort of 63 patients with common mutations was included for comparison. Objective response rate (ORR), progression-free survival (PFS), and adverse events (AEs) were assessed between groups. **Results:** A total of 133 patients with advanced or recurrent NSCLC that received dacomitinib were eligible for analysis. Baseline characteristics were balanced between subgroups. A significant difference was observed between patients with common mutations (C group, n = 63), common mutation plus uncommon mutations (C+U group, n = 24), and uncommon mutations (U group, n = 46) regarding to PFS (mPFS: 7.07, 8.17, and 11.97 months; $p = 0.026$). Moreover, the highest ORR and DCR of the U group were observed among subgroups, although the differences were not statistically significant (ORR, 40.4%, 40.9%, and 61.4%; $p = 0.085$; DCR, 78.9%, 72.7%, 90.9%; $p = 0.134$). Furthermore, the multivariate analysis revealed that the mutation pattern was an independent prognostic indicator of PFS ($p = 0.049$), with the C+U group having the highest risk of progression (HR [hazard ratio]: 1.438, 95% CI [confidence interval]: 0.818-2.528) while the U group having the lowest one (HR: 0.666, 95% CI: 0.409-1.084). For toxicity analysis, no significant difference was observed regarding grade 3-4 AEs among subgroups (12.7%, 8.3%, 13.0%; $p = 0.827$). The drug resistance analysis did not reveal a significant difference concerning the secondary T790M mutation rate (26.3%, 0%, 13.3%; $p = 0.331$). **Conclusions:** Dacomitinib demonstrated different therapeutic efficacy for patients with NSCLC harboring different combination patterns of uncommon *EGFR* mutation, which should be considered in clinical trials' design and clinical application. Research Sponsor: None.

Multivariate Cox regression analysis.

		Multivariate Analysis		
Variates	**N**	**HR**	**95% CI**	***p* value**
Number of distant metastatic organs				**< 0.001**
<3/≥3	104/29	2.741	1.667-4.507	
Stage				0.060
III+IV/Recurrence	106/27	0.551	0.296-1.026	
Application line				**< 0.001**
1	71	Reference	/	/
2	21	1.629	0.886-2.998	0.116
≥3	41	4.607	2.830-7.498	**< 0.001**
Application dosage		0.655	0.447-0.960	**0.030**
15mg	15			
30mg	88			
45mg	28			
Others	2			
Mutation group				**0.049**
C	63	Reference	/	/
C+U	24	1.438	0.818-2.528	0.207
U	46	0.666	0.409-1.084	0.102

9107 **Poster Session**

Clinical and molecular features of long-term response to anti-PD-(L)1 therapy in patients with advanced non-small cell lung cancer.

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Background: PD-(L)1 blockade can generate long-term responses in subsets of patients (pts) with advanced non-small cell lung cancer (NSCLC), but the clinical and molecular features of long-term responders (LTR) are not well established. Whereas features predictive of initial response have been rigorously explored, long-term follow up in large cohorts is required to identify features distinguishing LTR from short-term responders (STR). **Methods:** We analyzed pts with advanced NSCLC treated with anti-PD-(L)1 therapy at three institutions (MSK, DFCI, MDACC) between 2011 and 2022; responses were assessed by RECIST. LTR was defined as partial response (PR) or complete response (CR) $\geq$ 24 months; STR was defined as PR/CR $<$ 12 months followed by progressive disease (PD). PD-L1 IHC, tumor mutational burden (TMB), next generation sequencing (NGS), and whole exome sequencing (WES) results from subsets of pts were analyzed. High TMB was defined by harmonized TMB z-score $\geq$ 0 ($\geq$ median TMB in each cohort: $\geq$ 7.9 for MSK, $\geq$ 10.5 for DFCI). **Results:** Among 3240 pts overall (MSK = 1536, DFCI = 1238, MDACC = 466), LTR was achieved in 267 (8.2%, 95% CI 7.3 to 9.2%) and STR was achieved in 213 (6.6%, 95% CI 5.7 to 7.5%), with similar rates from each site. 5-year overall survival (OS) was 83% among LTR and 20% among STR. In univariate analyses, non-squamous histology (non-SQ: odds ratio [OR] 2.13, p = 0.005), peripheral blood derived neutrophil to lymphocyte ratio (dNLR) $<$ 3.0 (OR 2.15, p $<$ 0.001), and high TMB (OR 2.25, p = 0.001) were associated with LTR compared to STR; high PD-L1 (PD-L1 $\geq$ 50%: OR 1.19, p = 0.494) was not. In multivariate analyses, non-SQ histology (OR 2.56, p = 0.047) and high TMB (OR 2.73, p = 0.001) remained independently associated with LTR over STR. Among LTR compared to patients with best response of PD, dNLR $<$ 3.0 (OR 1.72, p = 0.030), high PD-L1 (OR 5.23, p $<$ 0.001), and high TMB (OR 2.55, p = 0.001) associated with LTR. LTR showed deeper radiographic responses compared to STR (best response of -50% or greater: OR 3.88, p $<$ 0.01). Among 1798 pts with NGS, pathogenic *ARID1A* alterations were numerically higher among LTR compared to STR, but this was not significant when accounting for multiple hypothesis testing (14% vs 2%, p = 0.022, q = 0.196). Among 73 pts with available WES, both clonal (p = 0.037) and subclonal TMB (p = 0.010) were significantly higher among LTR compared to STR. **Conclusions:** We report outcomes from $>$ 10 years of advanced NSCLC pts treated with anti-PD(L)1 therapy in a large multicenter cohort, with ongoing response at 2 years associated with $>$ 80% 5-year OS. High TMB was a strong independent predictor of LTR over STR. Non-squamous histology, low dNLR, and depth of response also correlate with LTR, while no individual genomic alterations clearly distinguish LTR. These features may assist in identifying pts more likely to derive durable benefit from anti-PD(L)1 therapy without treatment intensification. Research Sponsor: U.S. National Institutes of Health.

9108 **Poster Session**

Tissue and plasma-based mechanisms of resistance to first-line osimertinib in EGFR-mutant NSCLC: A multi-institutional cohort.

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Background: Osimertinib (osi) is the preferred 1st line (1L) therapy for patients (pts) with EGFR+ NSCLC, but acquired resistance is universal. Identification of mechanisms of resistance (MoR) to 1L osi can inform subsequent therapies. We report a retrospective, multi-institutional cohort of pts with tissue biopsy (TBx) and/or liquid biopsy (LBx) upon 1L osi progression (PD). **Methods:** Pts with advanced EGFR+ NSCLC who had TBx and/or LBx (for ctDNA analysis) obtained at PD on 1L osi at 8 participating institutions were included. Molecular testing was performed using next-generation sequencing (NGS) and, in a subset, FISH per local standards. We retrospectively collected clinical characteristics, tissue histology, NGS/FISH results and subsequent therapies. **Results:** 193 pts (128 female; median age 64 yrs) had TBx (n = 129) and/or LBx (n = 122) upon PD on 1L osi, 58/193 had both tissue and ctDNA. Primary EGFR mutations included del19 (102), L858R (76), and other (15). Median time from osi start to first bx was 14 mos (range, 1-55). MoRs are summarized in the table. In all, 86/193 (45%) pts had a known MoR identified on TBx and/or LBx. Among 129 pts with TBx, histologic transformation (trans) and MET amplification (amp) were the most common MoR, each seen in 16% pts. Among 122 pts with LBx, secondary EGFR mutations were the most common MoR, seen in 15%. Among the 58 pts with both TBx + LBx, discordance between major MoRs was seen in 21/58 pts (36%), most commonly due to histologic trans detected on TBx only (n = 7) and discordant MET amp status (n = 8; 6 TBx+/LBx-, 2 TBx-/LBx+). No MoR was identified in 53% TBx and 75% LBx (including 14% Lbx where the original EGFR mutation was not detected in ctDNA). Results of TBx led to MoR-directed 2L therapy in 41/129 (32%) pts, while LBx results led to MoR-directed 2L therapy in 16/122 (13%). **Conclusions:** In this large, multi-institutional cohort, histologic trans (16%) and MET amp (16%) were the most common MoR to 1L osimertinib on tissue bx. In ctDNA, secondary EGFR mutations (15%) were the most frequent MoR. The results of TBx were more likely to impact second-line therapy than LBx. Our results underscore the importance of tissue biopsy (and limitations of liquid biopsy) after osimertinib PD, where tissue testing remains the gold standard. In addition, with more than half of patients having no identifiable MoR despite comprehensive testing, our results highlight the need for MoR-agnostic treatment strategies. Research Sponsor: None.

Major MoR	Tissue (N = 129) n (%)	ctDNA (N = 122) n (%)
Secondary EGFR Mutations	12 (10)	18 (15)
- C797S	7 (5)	10 (8)
- Other (G724S, L718Q/V, T790M)	5 (4)	8 (7)
MET Amp	20 (16)	7 (6)
MET Exon 14 Skipping		1 (1)
HER2/HER3 Amp	1 (1)	1 (1)
KRAS Amp/KRAS Mutation	4 (3)	2 (2)
BRAF V600E	3 (2)	3 (3)
Fusion (ALK, RET or BRAF)	2 (2)	3 (3)
PIK3CA	3 (2)	3 (3)
Histologic Trans	20 (16)	N/E
-SCLC	16 (12)	
-Squamous	3 (2)	
-SCLC + Squamous	1 (1)	
Multiple MoR Detected	5 (4)	6 (5)
No identified MoR	69 (53)	91 (75)

9109 **Poster Session**

Contemporary biomarker testing rates in both early and advanced NSCLC: Results from the MYLUNG pragmatic study.

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Background: The MYLUNG (Molecularly Informed Lung Cancer Treatment in a Community Cancer Network) consortium pragmatic study aims to identify and overcome barriers to timely and appropriate biomarker testing in patients (pts) with NSCLC. We previously reported retrospective real-world testing rates for 5 biomarkers from 2018-2020 in metastatic pts. We now report results from the prospective observational phase, including additional biomarkers in pts with both early and advanced NSCLC. **Methods:** This was a prospective, non-interventional cohort study of newly diagnosed pts with early stage (ES), locally advanced (LA), or metastatic NSCLC (mNSCLC) between 12/2020 and 9/2022 and enrolled from 12 community practices (69 sites) across The US Oncology Network. The proportion of pts with test results for 9 biomarkers at time of protocol initiation were examined: ALK, BRAF, EGFR, ROS1, PD-L1, KRAS, MET, NTRK, and RET. Timing of tests, use of single vs multigene NGS testing, clinical and socioeconomic factors, and reasons for not testing were collected in real time. **Results:** Of 1002 pts screened, 987 were enrolled and analyzed. There were 405 stage IB-IIIC pts [n = 284 stage IB-IIIA (ES cohort); n = 121 stage IIIB-IIIC (LA cohort)] and 582 stage IV pts (mNSCLC cohort). Descriptions for ES and LA vs mNSCLC pts respectively include median age 68 vs 69 yrs, 49% vs 52% female, 83% vs 77% white, 58% vs 79% adenocarcinoma histology, 71% vs 68% ECOG 0-1, and 33% vs 30% high school education level. Testing rates for ES vs mNSCLC cohorts are shown in the table below: prior to treatment initiation, 64% of ES and 83% of mNSCLC pts had at least one biomarker result; and 37% of mNSCLC pts had results for all 9 biomarkers. NGS testing occurred in 37% and 57% of the ES and mNSCLC cohorts respectively. Reasons for not testing included: barriers to ordering (42%, 25%), insufficient tissue (18%, 18%), clinical deterioration/crisis (5%, 12%), and other reasons (37%, 49%), respectively. **Conclusions:** As more genomic alterations are identified in NSCLC, we observed that many pts do not get full genotyping prior to treatment, and biomarker testing remains of utmost importance. Further analyses by distinct stages (e.g. LA), histology, social determinants, utilization of targeted therapies, and other reasons for not testing will be performed. These data will be used to evaluate future prospective interventions for MYLUNG, to help improve comprehensive biomarker testing for NSCLC. Research Sponsor: Amgen, AstraZeneca, Eli Lilly, Genentech, Mirati.

	Early Stage Stage IB-IIIA N = 284	mNSCLC Stage IV N = 582
Pts receiving treatment, n	273	555
Pts with biomarker result prior to treatment, n (%)[a]	174 (64)	461 (83)
ALK[b]	114 (66)	356 (77)
BRAF[b]	117 (67)	336 (73)
EGFR[b]	142 (82)	372 (81)
KRAS[b]	108 (62)	295 (64)
MET[b]	106 (61)	330 (72)
NTRK[b]	78 (45)	254 (55)
PD-L1[b]	151 (87)	390 (85)
RET[b]	106 (61)	306 (66)
ROS1[b]	114 (66)	345 (75)

[a]Denominator: pts receiving treatment [b]Denominator: pts with biomarker result prior to treatment.

9110 **Poster Session**

Efficacy and safety of SY-3505, a third-generation ALK TKI, in *ALK*-positive advanced non-small cell lung cancer: Results from a phase I/II, multi-center study.

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Background: SY-3505 is a potent, brain-penetrant, 3rd-generation (gen) anaplastic lymphoma kinase (ALK) tyrosine kinase inhibitor (TKI) with preclinical activity against both wild-type and most known resistance mutations of *ALK* occurring in 1st and 2nd-gen ALK TKI-resistant patients. Here we report the efficacy and safety results from the ongoing phase I/II study of SY-3505. **Methods:** Patients aged ≥18 years with histologically/cytologically confirmed, advanced, *ALK*-positive non-small cell lung cancer (NSCLC) and an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0-2 were recruited from 13 hospitals in China. In phase I study, patients received SY-3505 from 25-800mg once daily in dose-escalation phase, followed by dose-expansion at 500/600mg. Patients received alectinib only or ≥2 prior ALK TKIs were recruited in phase II study and treated with SY-3505 at 600mg once daily. The primary endpoint was investigator (INV)-assessed objective response rate (ORR) per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Secondary endpoints included disease control rate (DCR), duration of response (DoR), progression-free survival (PFS), overall survival (OS) and safety. **Results:** At data cut-off date of Feb.03, 2023, 92 *ALK*-positive NSCLC patients were enrolled in phase I/II, 82 were evaluable for efficacy, the ORR was 34.2% (95% confidence interval [CI] 24.0-45.5%), DCR was 74.4% (95% CI 63.6-83.4%). Herein the ORR and DCR of 59 patients in phase I for dose-escalation and dose-expansion was 32.3% (95% CI 20.6-45.6%) and 69.5% (95% CI 56.1-80.8%), respectively; median DoR and PFS was 11.1 (95% CI 5.28-not reached [NR]) and 6.20 (95% CI 3.08-10.3) months, respectively. Fifty-six patients received SY-3505 at 600mg once daily (two patients received non-alectinib 2nd-gen ALK TKI only, 22 received alectinib only and 32 received ≥2 prior ALK TKIs). Thirty-two (57.1%) patients experienced treatment-related adverse events (TRAEs) and two (3.6%) had grade ≥3 TRAEs. The most common TRAEs were diarrhea (42.9%), nausea (28.6%) and vomiting (26.8%), consistent with previous reported in phase I. Forty-seven patients were evaluable for efficacy, the ORR and DCR was 38.3% (95% CI 24.5-53.6%) and 83.0% (95% CI 69.2-92.4%), respectively. Median DoR and PFS were NR. Twenty-two patients had baseline central nervous system metastases, the ORR and DCR was 50.0% and 86.4%, respectively. **Conclusions:** SY-3505 was well-tolerated and showed significant and durable clinical activity in *ALK*-positive NSCLC patients who received at least one prior 2nd-gen ALK TKI, demonstrating a potential new treatment option for these patient population. Pivotal clinical study will be performed in future. Clinical trial information: NCT05257512. Research Sponsor: Shouyao Holdings (Beijing) Co., Ltd.

9111 **Poster Session**

A first-in-human phase I, dose-escalation and dose-expansion study of SY-5007, a highly potent and selective RET inhibitor, in Chinese patients with advanced *RET* positive solid tumors.

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Background: *RET* gene fusions have been identified as oncogenic drivers in 1-2% of non-small-cell lung cancer (NSCLC) and 10-20% of papillary thyroid carcinomas. Activating *RET* mutations occur in 50-60% of medullary thyroid cancer (MTC). Recently, selective RET TKIs, selpercatinib and pralsetinib, were approved for *RET* positive solid tumors by FDA. SY-5007 is a highly potent RET inhibitor that selectively targets *RET* fusions and mutations. This study is to investigate the safety, PK characteristics and preliminary efficacy of SY-5007 in Chinese patients with advanced *RET*-altered solid tumors. **Methods:** In this first-in-human phase I study, eligible patients previously treated and with positive *RET* were enrolled. In the dose escalation phase, following 3+3 design, the patients were administered orally with SY-5007 20 mg once daily, or 20, 40, 80, 120, 160, 200 mg twice daily in a 28-day cycle. The expansion doses (160 and 200 mg twice daily) were executed in a dose expansion phase to determine a recommended phase II dose (RP2D). Then three cohorts (*RET* fusion-positive NSCLC or thyroid cancers and *RET* mutant MTC) at RP2D were expanded in eligible patients. Primary endpoints included safety, tolerability, MTD, DLTs. Secondary endpoints included PK and preliminary antitumor activity of SY-5007 per RECIST v1.1. **Results:** As of Feb.06, 2023, a total of 60 patients including 55 *RET* fusion NSCLC and 5 *RET* mutant solid tumors were enrolled into dose escalation cohorts (n = 17) and dose expansion cohorts (n = 43).Totally, 55 (91.7%) patients experienced treatment-related adverse events (TRAEs) including increased aspartate aminotransferase (50.0%), increased alanine aminotransferase (41.7%), diarrhea (41.7%), etc. Grade ≥3 TRAEs were observed in 22 (36.7%) patients including hypertension (15%), diarrhea (5%), increased alanine aminotransferase (3.3%), etc. PK study showed SY-5007 was absorbed rapidly, exposure of SY-5007 increased in a dose-dependent manner at doses between 20 and 160 mg twice daily, and it was saturated at 160 mg twice daily. In 50 evaluable patients, the overall ORR and DCR was 62.0% (95% CI, 47.2-75.4) and 94.0 % (95% CI, 83.5-98.8), respectively. 29 patients (24 NSCLC, 4 MTC) received SY-5007 at 160 mg twice daily, 27 of 28 (96.4%) evaluable patients showed tumor regression, ORR and DCR was 72.4% (95% CI, 52.8-87.3) and 89.7% (95% CI, 72.7-97.8), respectively. For NSCLC patients, the ORR and DCR was 75.0% (95% CI, 53.3-90.2) and 91.7% (95% CI, 73.0-99.0), respectively. **Conclusions:** SY-5007 was well tolerated in patients. Preliminary antitumor activity was also observed in patients with advanced *RET*-fusion positive NSCLS and *RET* mutant MTC. The pivotal Phase II clinical study of SY-5007 in NSCLC patients is ongoing. Research Sponsor: Shouyao Holdings (Beijing) Co., Ltd. Clinical trial information: NCT05278364. Research Sponsor: Shouyao Holdings (Beijing) Co., Ltd.

9112 **Poster Session**

Phase 1 study evaluating the safety, tolerability, pharmacokinetics (PK), and efficacy of GEC255, a novel KRAS^{G12C} inhibitor, in advanced solid tumors.

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Background: The KRAS^{G12C} mutation occurs in 12-14% of NSCLC and in 3-5% of CRC patients and is recognized as an oncogenic driver mutation. Recently the discovery of a cryptic binding pocket within the effector region of the KRAS^{G12C} oncoprotein has led to the rapid clinical development of a new series of specific inhibitors. GEC255 is a novel small molecule which showed excellent target engagement ability and a favorable pharmacological profile. **Methods:** This is a phase 1, open-label, multicenter study (CTR20212486) to evaluate the safety, tolerability, pharmacokinetics (PK), and efficacy of GEC255 in patients (pts) with advanced solid tumors bearing KRAS^{G12C} mutation. The primary endpoint is safety and key secondary endpoints include PK and ORR. Key inclusion criteria: KRAS^{G12C} mutation identified through digital PCR, measurable or evaluable disease, ECOG PS $\leq$1, and life expectancy $>$ 3 months. Key exclusion criteria: previous administration of specific KRAS^{G12C} inhibitors, uncontrollable plasma cavity effusion. Phase 1a is an accelerated titration, dose-escalating study to determine the maximum tolerated dose (MTD) or recommended phase 2 dose (RP2D). Phase 1b is a dose expansion study which will enroll pts with NSCLC, CRC, and other solid tumors harboring the KRAS^{G12C} mutation. GEC255 will be administered PO QD until disease progression, intolerance, or withdrawal of consent. **Results:** 16 NSCLC pts (15 men, 1 woman, median age 58 y) were enrolled in Phase 1 dose escalation for the first 4 dose cohorts followed with dose escalation in chosen doses. No dose-limiting toxicity was observed and MTD has not been identified yet. GEC255 showed the linear increase in AUC exposure and C_{max} with increasing doses. T_{max} was 2-4 hours in all dosing groups and C_{trough} within the 24-hour period was higher than pERK IC_{90} even in low dose group. The half-life of GEC255 in 24h period is about 8-9h and there is no increase in AUC upon daily dosing for 28 consecutive days. Among the 16 pts, most pts (n = 13) had $\geq$1 prior lines of treatment (tx). A total of 15 patients had treatment-related adverse events and most AEs are G1 or G2 (93.3%); the most frequent AEs are diarrhea (56.3%), ALT increase (37.5%), rashes (25%), and anemia (25%). Tumor response was evaluated in 13 pts. 10 pts (76.9%) had objective response (complete or partial response) and 12 pts (92.3%) had disease control (objective response or stable disease). In 600mg dose group, the ORR was 83.3% and DCR was 100% (n = 6). 7 pts are continuing to receive GEC255. **Conclusions:** GEC255 has been well tolerated at the doses tested and has shown encouraging anticancer activity to advanced NSCLC patients with KRAS^{G12C} mutation pts. MTD has not been determined, and enrollment into the dose exploration is ongoing. (http://www.chinadrugtrials.org.cn/index.html). Clinical trial information: CTR20212486. Research Sponsor: GenEros Biopharma Research Center, Hangzhou, Zhejiang, China.

9113 **Poster Session**

First-in-human, multicenter phase I study of TGRX-326 in patients with advanced ALK-positive non-small cell lung cancer.

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Background: TGRX-326, a deuterated derivative of lorlatinib (LOR), is a potent 3rd generation ALK and ROS1 dual TKI with high potency against multiple ALK-resistant mutations. Deuteration of the key metabolic site of the molecule allows to achieve a higher exposure than with LOR and this may result in alleviated toxicities and better efficacy. **Methods:** The study comprised 3 phases: dose escalation (D-ESCAL), dose expansion (D-EXP) and cohort expansion (C-EXP). In D-ESCAL and D-EXP, ALK+ pts prior failed on 2nd gen ALK-TKIs or ROS1+ pts resistant to crizotinib (CRZ) were enrolled; in C-EXP, ALK+ pts progression after CRZ (C-EXP-A1),progression after ≥1 2nd gen TKIs (C-EXP A2), ROS1+ progression after CRZ (C-EXP-B) and pts with ALK TKI naïve (C-EXP-C) were enrolled. **Results:** Up to Jan 13, 2023, 185 pts (median age 53 years, 45.9% male) were enrolled; Median treatment and follow-up was 5.5 and 6.7 months, respectively. There were no DLT observed and no MTD identified in D-ESCAL (5-125mg QD, n=19). Based on the safety, efficacy and PK exposure data of 42 pts in D-ESCAL and D-EXP, 60 mg QD was selected as the RP2D for C-EXP,the average AUC_{tau} of 60mg QD reached to 5443ng*hr/mL. Treatment-related adverse events (TRAEs) occurred in 87.5% patients (162/185), the most common TRAEs were hypercholesterolemia (74.1%), hypertriglyceridemia (68.1%), weight gain (36.2%), peripheral edema (15.7%), peripheral neuropathy (14.1%). As for R2PD, 132 of 155 (85.2%) experienced TRAEs, Grade ≥3 TRAEs occurred in 19.7%, most frequent were hypertriglyceridemia (11%) and hypercholesterolemia (8.4%). Dose interruptions and dose reductions associated with TRAEs were reported in 10 (5.4%) and 5 (2.7%) pts respectively. Confirmed response were observed in 142 ALK+pts enrolled in C-EXP, results are shown in the Table (Efficacy of B-ROS1+ pts will be reported separately). Eleven ALK mutations were detected in 16 pts (either alone or in combination); 50.0% pts achieved PR. Out of 6 pts who were positive for G1202R, 50.0% experienced PR. **Conclusions:** TGRX-326 was well tolerated in pts with advanced ALK+ NSCLC and showed promising clinical antitumor activity irrespectively of ALK+ resistance to CRZ and 2nd gen TKIs, especially among those with brain metastases. Impressive activity was seen in ALK TKI naïve NSCLC. TGRX-326 demonstrated antitumor activity against multiple ALK mutations including G1202R. Clinical trial information: NCT05441956. Research Sponsor: Shenzhen TargetRx, Inc.

	C-EXP A1	C-EXP A2	C-EXP A2	C-EXP A2	C-EXP C
Prior TKI	CRZ	1 ALK TKI[a]	2 ALK TKIs[a]	≥3 ALK TKIs[a]	None
Nr of pts	15	40	37	17	33
ORR, n (%)	9(60.0)	14(35.0)	14(37.8)	5(29.4)	24(72.7)
DCR, n (%)	15(100.0)	29(72.5)	31(83.8)	16(94.1)	30(90.9)
Nr of pts with IC target lesions	5	5	13	8	8
IC-ORR,n (%)	3(60.0)	4(80.0)	7(53.8)	6(75.0)	6(75.0)
IC-DCR, n (%)	5(100.0)	4(80.0)	11(84.6)	8(100.0)	8(100.0)

IC: intracranial;[a]Lines of therapy.

9114 **Poster Session**

SKB264 (TROP2-ADC) for the treatment of patients with advanced NSCLC: Efficacy and safety data from a phase 2 study.

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Background: TROP2 (trophoblast cell surface antigen 2) is commonly overexpressed in non-small cell lung cancer (NSCLC) and associated with poor prognosis. SKB264 is a novel anti-TROP2 ADC developed using sulfonyl pyrimidine-CL2A-carbonate linker to conjugate its payload, a belotecan-derivative topoisomerase I inhibitor, to achieve an average Drug-to-antibody Ratio (DAR) of 7.4. The design was to achieve a more effective balance between stability in circulation and release of the ADC payload in tumor cells. Here we report clinical efficacy and safety results of SKB264 in the treatment of patients (pts) with NSCLC from a Phase 2 expansion cohort. TROP2 expression level by immunohistochemistry was assessed retrospectively. Correlation analyses between response and TROP2 level will be provided. **Methods:** This is a Phase 1/2, multicenter dose-escalation/expansion study in pts with relapsed or refractory locally advanced/metastatic NSCLC and other tumor types (NCT04152499). All NSCLC pts received SKB264 at 5 mg/kg IV Q2W. Tumor assessments based on RECIST 1.1 were performed every 8 weeks by investigators. **Results:** As of February 9th, 2023, 43 pts (63% male, 88% ECOG PS 1, median age 58 yrs [44-74]) were enrolled. Median follow-up was 11.5 months (mo; 95% CI, 10.4-12.2). Median treatment duration was 5.7 mo (range, 0.5-14.1). Among 39 response-evaluable pts, the ORR was 44% (17/39, 15 confirmed and 2 pending confirmation), median DoR was 9.3 mo (range, 1.3+ to 11.2+), 6-month DoR rate was 77%. For EGFR wild type subgroup (previously received median 2 lines of therapy including anti-PD-1/L1), the ORR was 26% (5/19), DCR was 89% (17/19), median PFS was 5.3 mo, and 9-month OS rate was 80.4%. For subgroup with TKI resistant EGFR mutant NSCLC (50% also failed at least one line of chemotherapy), the ORR was 60% (12/20), DCR was 100% (20/20), median PFS was 11.1 mo, and 9-month PFS rate was 66.7%. 67.4% (29/43) of pts had Grade $\geq$ 3 treatment-related adverse events (TRAEs). The most common Grade $\geq$3 TRAEs (occurred in $\geq$5% of pts) were neutrophil count decreased (32.6%), anemia (30.2%), white blood cell count (WBC) decreased (23.3%), stomatitis (9.3%), rash (7.0%), and lymphocyte count decreased (7.0%). Grade 4 TRAEs occurred only for neutropenia and WBC decreased. Most of the hematology toxicity occurred within the first two months of treatment and resolved after treatment with granulocyte colony stimulating factor or erythropoietin without blood transfusions. 23.3% (10/43) of the pts experienced dose reduction due to TRAEs. No neuropathy or drug-related ILD/pneumonitis was reported. No TRAEs led to treatment discontinuation or death. **Conclusions:** SKB264 at 5 mg/kg Q2W demonstrated encouraging anti-tumor activity and manageable safety profile in pts with relapsed or refractory locally advanced/metastatic NSCLC. TRAEs were mainly hematologic. Phase 3 studies of SKB264 in pts with advanced NSCLC have been planned. Clinical trial information: NCT04152499. Research Sponsor: Sichuan Kelun-Biotech Biopharmaceutical Co., Ltd.

9115 **Poster Session**

Implementation strategies for monitoring adherence in real time (iSMART): A pilot randomized trial.

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Background: Helping patients to manage symptoms and adhere to oral anticancer agents (OACAs) is a major challenge in oncology. OACAs cause side effects that can lead to suboptimal adherence if not optimally managed, contributing to decreased effectiveness. Low-cost, text messaging approaches have shown promise, but have not been robustly studied in oncology. Guided by principles from implementation and behavioral science, we developed and tested the effect of an augmented intelligence chatbot on OACA adherence and symptom burden in patients with advanced lung cancer. **Methods:** We conducted a two-arm pilot randomized trial (NCT04347161) to evaluate the effect of the chatbot on OACA adherence and symptom burden compared to usual care. The chatbot engages patients via text messaging and applies natural language processing and machine learning to learn from interactions. Core functionalities include: 1) motivational daily adherence reminders, 2) longitudinal symptom monitoring with self-management support, and 3) bidirectional communication with clinical teams. Participants included English-speaking patients with advanced lung cancer treated with any of 9 OACAs targeting EGFR, ALK, or ROS-1. The primary outcome was 12-week adherence, measured using the microelectronic monitoring system (MEMS) and defined dichotomously if the patient achieved $\geq$95% adherent days or not. Secondary outcomes were assessed at baseline and 12 weeks using validated survey instruments, including symptom burden using the Edmonton Symptom Assessment System Total Distress Score (range 0-90), health-related quality of life (HRQOL) using EQ-5D-3L (range 0-100), and usability using Health-ITUES (range 1-5). We used multivariable logistic regression adjusting for stratification variables to test the chatbot's effect on adherence (intent-to-treat analysis) and evaluated mean differences (by arm) in secondary outcomes using Fisher's exact test. **Results:** From February 2021 to August 2022, 75 patients across 4 sites enrolled (median age 65 years, 64% female, 88% White, 21.3% high school education or lower); 50.7% (n=38) were randomized to intervention. Compared to usual care, we observed no significant differences in adherence in the intervention arm (78.8% vs 81.8%; aOR=1.7 95% CI: 0.3-9.4). However, in contrast to those in usual care, participants in the intervention arm had significantly greater decreases in symptom burden (mean difference: -2.7 vs 2.6; $p<0.05$) and increases in HRQOL (mean difference: 4.1 vs -4.8; $p<0.05$) from baseline to 12 weeks. Overall chatbot usability was high (mean score=3.9). **Conclusions:** In this pilot randomized trial, an augmented intelligence chatbot successfully reduced symptom burden and improved HRQOL but did not significantly alter OACA adherence. Chatbots are a potentially scalable strategy for improving symptom management that warrant study in larger randomized trials. Clinical trial information: NCT04347161. Research Sponsor: Lung Cancer Research Foundation grant supported by funds from Pfizer.

9116 **Poster Session**

Characteristics of long-term survivors with EGFR mutant (EGFRm) metastatic non-small cell lung cancer (mNSCLC).

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Background: Although osimertinib has become standard first-line (1L) therapy for patients (pts) with *EGFR*m mNSCLC, a subset treated with earlier-generation *EGFR*-targeted TKIs and chemotherapy have had long-term survival. We sought to characterize clinical features of long-term survival in pts with *EGFR*m mNSCLC treated prior to the osimertinib era. **Methods:** Data were abstracted from electronic medical records at 12 cancer centers participating in the Academic Thoracic Oncology Medical Investigator's Consortium (ATOMIC). We included patients with mNSCLC with sensitizing mutations in *EGFR* who started 1L systemic therapy before 2015. Survival distributions and predictors were assessed using Kaplan-Meier estimates and a multivariable Cox proportional hazards model including time-dependent brain metastasis (met) development, age, 1L therapy (targeted vs. chemotherapy), sex, race, and smoking status. Multivariable logistic regression was used to evaluate baseline predictors associated with 5+ year survival vs. not for those with known survival status at 5 years after start of 1L. **Results:** We identified 304 patients (69% female, 56% White, 29% Asian, mean age 61.2). First-line targeted therapy was given in 70% of patients. With a median follow-up of 81.5 months, median overall survival was 63.5 months (95% CI 59.4-71.9). 135 (44%) pts survived 5+ years; among those with baseline next-generation sequencing (NGS), presence of a baseline pathogenic *ERBB2* variant was higher in 5+ year survivors (4/51 [8%], 2x amplification, y772_A775dup, S310F) v others (1/65 [2%], amplification). Among 161 pts with baseline brain imaging, both baseline and on-treatment development of brain mets were associated with worse survival (HR 1.29, 95% CI 1.21-1.37; HR 1.59, 95% CI 1.47-1.72; both $P < 0.001$). Excluding 22 patients lost to follow-up before 5 years, a history of smoking (OR 2.99, 95% CI 1.35-6.90, $P = 0.008$) and baseline brain metastases (OR 3.57, 95% CI 1.64-8.13, $P = 0.002$) were associated with death before 5 years. **Conclusions:** Long-term survivors with *EGFR*m mNSCLC treated before the osimertinib era were more likely to be nonsmokers and have no baseline brain metastases. This highlights a subset of *EGFR*m patients who had excellent outcomes with older treatment strategies and may not benefit as much from intensification approaches. Additional baseline mutational data will be presented at the conference. Research Sponsor: AstraZeneca; LUNGevity.

9117 **Poster Session**

Association between real-world, upfront, next-generation sequencing and overall survival (OS) in advanced non–small-cell lung cancer (aNSCLC) in the United States.

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Background: Multiple biomarker testing strategies exist as the treatments of aNSCLC rapidly evolve. While upfront NGS is considered optimal, this practice has not been universally adopted. Surprisingly, the impact of NGS vs non-NGS approaches on OS is unclear, with the largest study to date demonstrating lack of benefit. We aim to identify the genomic testing strategy associated with the most optimal OS in aNSCLC using data from a large, contemporary electronic health record (EHR) database. **Methods:** This retrospective study used Flatiron EHR data. Patients diagnosed with aNSCLC between 11 Apr 2019 and 31 Dec 2021 who received systemic therapy were identified and followed from the date of diagnosis to 31 May 2022 or death. Testing methods reported within the patient's chart were extracted. Methods assessed included NGS (defined as any test type with 'NGS' as test name) and non-NGS (defined as PCR, FISH, IHC, and other sequencing methods not containing 'NGS'). Upfront testing was defined as tests received on or prior to the date of initiation of first-line (1L) therapy. Kaplan-Meier analyses were used to estimate and compare real-world overall survival (rwOS) by testing strategies. Among those with actionable genetic mutations, we also explored rwOS by timing of targeted therapy (TT) initiation. **Results:** Of a total 13,139 patients, mean age was 69, 49% female, 64% white, 33% Medicare insured, and 88% treated in community setting only. Median follow up time was 9 months. The percentage of patients with upfront NGS increased from 29% in 2019 to 66% in 2022. Median OS (mOS) was longest in patients with upfront NGS compared to those with upfront non-NGS genomic tests ($p < 0.05$), those with NGS after 1L ($p < 0.05$), and those with no NGS test ever ($p < 0.05$) (see table). 19% of patients with upfront NGS vs. 15% of those with upfront non-NGS received TT in 1L; 23% of patients with NGS vs. 19% of those with upfront non-NGS received TT at any line of therapy. In patients with actionable genetic mutations, mOS decreased with later initiation of TT; mOS was not reached (NR) (34.6 – NR) in patients who initiated TT in 1L, 34.7 (29.1 – NR) months in those with 2L TT, and 24.3 (20.3 – 30.1) months in those who initiated TT in 3L. **Conclusions:** This is the first and largest study to demonstrate that upfront NGS testing leads to better OS when compared to upfront non-NGS genomic testing, later NGS, or no-NGS in aNSCLC. In line with these results, we also found an OS benefit associated with earlier TT initiation. These results highlight the significant impact of upfront NGS testing and underscore for the need for both education and wider accessibility of NGS testing. Research Sponsor: Novartis, Inc.

	Upfront NGS testing (n = 6,210)	Upfront non-NGS genomic testing (n = 2,697)	NGS testing after 1L initiation (n = 2,824)	No NGS tested ever (n = 2,152)
Median OS (CI) in months	20.9 (19.8-21.9)	17.5 (16.1-19.2)	18.2 (16.6-19.4)	16.9 (15.3-18.6)

9118 **Poster Session**

Clinical, pathologic, and genomic hallmarks of *KRAS*-amplified non-small cell lung cancer.

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Background: *KRAS*-mutant non-small cell lung cancers (NSCLCs) have unique clinicopathologic and genomic features, and novel therapies are in development to target many *KRAS*-mutant tumor types. Whether *KRAS* amplification also defines a unique, potentially targetable, molecular subset of NSCLC is currently unknown. **Methods:** Clinicopathologic and genomic data were abstracted from multiple independent cohorts of pts whose cancers underwent tumor genomic profiling at the Dana-Farber Cancer Institute (Cohort 1), AACR Project GENIE v.13, The Cancer Genome Atlas (TCGA), and 212 other studies (Cohort 2). Patient (pt) outcomes were examined according to *KRAS* amplification status (*KRAS* amplified vs *KRAS* non-amplified). Whole transcriptome sequencing and quantitative proteomics data from TCGA and the Cancer Cell Line Encyclopedia (CCLE) were used to correlate *KRAS* amplification with KRAS RNA levels and protein expression. **Results:** Among 15,341 pts with NSCLC, *KRAS* amplification was identified in 355 (2.3%) cases (median number of copies [range]: 11 [7-87]); the prevalence was similar in adenocarcinomas and squamous cell carcinomas. Compared to *KRAS* non-amplified cases, pts with *KRAS*-amplified NSCLC were more likely to be men (52.4% vs 45.6%, $p = 0.01$), have a history of smoking (82.1% vs 64.2%, $p < 0.01$), and higher median pack-years (35 vs 23.5, $p < 0.01$). However, median age was similar between the two groups (66 vs 66, $p = 0.88$). *KRAS* amplification was also associated with higher aneuploidy (median fraction of genome altered 30.4% vs 14.3%, $p < 0.01$), tumor mutational burden ($p < 0.01$ across different platforms), and increased median PD-L1 expression (20% vs 5%, $p = 0.01$). Of the 355 NSCLC samples with *KRAS* amplification, 152 (43%) had no concurrent oncogene driver mutations. In unbiased mutation enrichment analyses, *KRAS*-amplified tumors were enriched in concurrent mutations in *KRAS*, *PALB2*, *POLE,* and *SLC34A2* ($q < 0.1$), while *KRAS* non-amplified tumors were enriched for oncogenic *EGFR* mutations ($q < 0.1$). Transcriptomic and proteomic profiling from the TCGA and CCLE cohorts demonstrated that *KRAS* amplification was associated with significantly increased KRAS mRNA ($p < 0.01$) and protein expression ($p < 0.01$), compared to *KRAS* non-amplified samples. In pts with available clinical outcomes data in the combined cohort (N = 9,335), the median overall survival (OS) from the date of diagnosis was significantly shorter in *KRAS*-amplified vs *KRAS* non-amplified cases (adjusted HR: 1.40, $p < 0.01$). *KRAS* amplification was confirmed to confer significantly worse survival outcomes in pts with both *KRAS* wild-type (N = 6,695, adjusted HR 1.37, $p = 0.02$) and *KRAS*-mutant (N = 2,640, adjusted HR 1.34, $p = 0.02$) NSCLC. These results were independently replicated in Cohort 1 and Cohort 2. **Conclusions:** *KRAS* amplification defines a novel molecular subset of NSCLC characterized by distinct clinicopathologic and genomic features and worse survival. Research Sponsor: None.

9119 **Poster Session**

FDA analysis of toxicity profiles of oral TKIs recently approved for non-small cell lung cancer based on receipt of prior immune checkpoint inhibitor therapy.

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Background: Immune checkpoint inhibitors (ICIs) targeting PD-(L)1 are standard front-line therapy for advanced non-small cell lung cancer (NSCLC). Molecularly targeted tyrosine kinase inhibitors (TKIs) are standard of care for subsets of oncogene-driven NSCLC. Published literature suggests the possibility of increased toxicity in patients who receive ICIs followed by *EGFR* or *ALK* TKI treatment. However, the toxicity profile in patients who receive ICIs followed by TKIs with other genomic targets has not been well described. **Methods:** Marketing applications for TKIs in patients with NSCLC submitted to the Office of Oncologic Diseases between Jan 2019 to Dec 2022 were reviewed. Datasets were analyzed for demographics, treatment-emergent adverse events (TEAE), and prior anti-cancer therapies for TKI-treated patients in the primary efficacy population. Drug classes for which $< 5\%$ of patients received prior ICI were excluded. Grade 3-4 TEAE, serious adverse events (SAE), discontinuation TEAE and TEAE of interest (hepatotoxicity, rash, and interstitial lung disease [ILD]) were summarized. **Results:** 9 applications were identified and 2 were excluded. The remaining applications involved TKIs targeting *EGFR* exon 20 insertion, *KRAS G12C*, *MET* exon 14 skipping, and *RET* fusion alterations. Analyses included 867 patients; 61% received prior ICI therapy. Patient characteristics and results of analyses are presented in the table. In our pooled analysis, the incidence of Grade 3-4 AEs, SAEs, and hepatotoxicity were slightly higher in the prior ICI group, while the incidence of discontinuation TEAE, ILD, and rash were similar between groups. Analysis for hepatotoxicity was limited to reported AEs (did not include analysis of laboratory data). Review of toxicity data across individual drug classes did not show major differences compared to the overall results. **Conclusions:** Our analysis of safety data for newer TKIs with varied genomic targets does not appear to show excessive toxicity in patients with NSCLC who received prior ICI compared to those who did not. In future clinical trials evaluating TKIs in this population, inclusion of patients who have received prior ICI therapy should be considered when appropriate. Research Sponsor: None.

TEAE summary for TKIs in patients with NSCLC based on receipt of prior ICI (N=867).

	Prior ICI Therapy (N = 528)	No Prior ICI Therapy (N = 339)
Demographics		
Sex	54% F	56% F
Age (years), median (range)	63 (25-89)	65 (23-90)
Race	67% White	48% White
	25% Asian	46% Asian
	4% Black	2% Black
Ethnicity	3% Hispanic or Latino	1% Hispanic or Latino
Region	60% U.S.	29% U.S.
	19% Asia	44% Asia
	19% Europe	25% Europe
Prior Radiotherapy	59%	45%
Drug Class	35% *RET*	44% *RET*
	14% *MET* exon 14 skipping	33% *MET* exon 14 skipping
	42% *KRAS G12C*	4% *KRAS G12C*
	9% *EGFR* ex20 ins	19% *EGFR* ex20 ins
Toxicity		
Grade 3 or 4 TEAE, %	71	63
SAEs, %	56	45
Discontinuation AE, %	12	12
Hepatotoxicity, %	4	1
ILD, %	4	6
Rash, %	26	25

9120 **Poster Session**

Stimulator of interferon gene (STING) expression as a biomarker for overall survival in PDL1-negative, TMB-low non-small cell lung cancer (NSCLC) treated with immune checkpoint inhibitors (ICIs).

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Background: cGAS-STING (CGS) is an intracellular DNA sensing pathway that when activated, stimulates interferon and other immune-related signaling pathways. While increased expression of CGS-related genes has been associated with better survival in NSCLC, studies investigating this phenomenon in tumors less likely to respond to ICIs such as PDL1-negative, TMB-Low NSCLC are lacking. Here we report the role of CGS pathway in NSCLC tumors that are both PDL1-negative and TMB-Low. **Methods:** DNA (592-gene or whole exome) and RNA sequencing (whole transcriptome) was performed for NSCLC specimens (n=7264) submitted to Caris Life Sciences (Phoenix, AZ). PDL1 negativity was defined as $<$1% TPS score (22C3) & TMB-Low as $<$10 mutations/Mb. Hierarchical Agglomerative Clustering (HAC) was performed on STING pathway genes (CXCL10, CCL5 and GZB) and tumors were grouped into STING-high (n=3070), STING-intermediate (n=1609) and STING-low (n=2585) groups. Microenvironmental cell populations (MCP)-counter analysis was used to estimate cellular composition of immune cells. Statistical significance was determined using chi-square/ Fisher's exact/Mann-Whitney U tests and adjusted for multiple comparisons ($q<0.05$). Kaplan Meier method was used to estimate the overall survival (OS) derived from insurance claims of IO treated pts with NSCLC (n=400). Pts were stratified into groups above or below the median expression of the *STING* gene (*TMEM173)*. **Results:** Compared to STING-low, tumors that were STING-high had enrichment in immune cell infiltrates including CD8+ T cells (4.4-fold) and B-cells (5.9-fold); Additionally, STING-high cohort had significantly higher expression of immune checkpoint (IC) genes including *CD274*(2.5-fold), *CD80* (2.7-fold, all $q<0.05$). STING-high tumors also had a higher prevalence of *TP53* mutations (mts) and a lower prevalence of *STK11* and *KEAP1* mts (Table). Median overall survival (OS) was 21.1 months in the *STING*-high cohort (n=200) vs 11.9 months in the *STING*-low cohort (n=199) in IO treated pts (HR = 0.62, $p<0.000.1$) **Conclusions:** To our knowledge this is the largest real-world dataset indicating that enrichment of both the *STING* gene, and gene signatures associated with the STING pathway represent valuable transcriptomic biomarkers to stratify pts with PDL1-negative and TMB-Low NSCLC who benefit more from IO therapies. Conversely, novel IO combination strategies need to be employed in STING-low tumors to enhance outcomes. Research Sponsor: None.

Alterations	Overall STING- HIGH (n=3070)	Overall STING-LOW (n=2585)
***STK11* (% Prevalence)**	15.4	21.3
***KEAP1* (% Prevalence)**	10.6	15.8
***TP53* (% Prevalence)**	56.5	50

9121 **Poster Session**

Nivolumab and ipilimumab in advanced non small cell lung cancer previously treated with PD1 axis inhibition.

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Background: Nivolumab combined with ipilimumab is currently one of many first line treatment options for patients with advanced non-small cell lung cancer (NSCLC). The benefit of this regimen in patients with NSCLC previously treated with a programmed death 1 (PD1) axis inhibitor is unclear. **Methods:** We conducted a phase II study (NCT03262779) of nivolumab and ipilimumab in patients with PDL1 unselected advanced NSCLC with either primary resistance (cohort 1) or acquired resistance (cohort 2) to prior PD1 axis inhibitor therapy. Nivolumab 3 mg/kg was administered intravenously every 2 weeks, and ipilimumab 1 mg/kg every 6 weeks, and continued until disease progression or treatment limiting toxicity. If $>$ 1 response or prolonged stability ($>$ 24 weeks) using immune related response criteria were observed in the first 10 patients treated on cohort 1, an additional 30 patients would be accrued (simon 2-stage). A total of 10 patients would be accrued to cohort 2 (exploratory cohort). The primary endpoint was objective response rate (ORR) by RECIST v1.1 in cohort 1. Secondary endpoints included, ORR in cohort 2, progression free survival (PFS) and overall survival (OS) in both cohorts. **Results:** Among 10 patients with primary resistance to PD1 axis inhibitor therapy, no objective responses were observed (8 patients had progressive disease (PD) and 2 patients had unconfirmed stable disease (SD) as best response). Among 10 patients with acquired resistance to PD-1 axis inhibitor therapy, ORR was 10% (1 patient with confirmed complete response, 5 patients with confirmed SD including 4 patients with SD lasting more than 9 months, 3 patients with unconfirmed SD, and 1 patient with PD). Durable clinical benefit (DCB, response or SD for at least 6 months) rate was 50%. Median duration of benefit in the 5 patients with DCB was 11.9 months. Nine of the 10 patients in cohort 2 developed initial resistance to PD-1 axis inhibitor monotherapy (rather than combination chemo-immunotherapy), all received immunotherapy as part of their last line of therapy. The remaining patient developed resistance while on maintenance chemoimmunotherapy after initial response to chemoimmunotherapy; best response to trial therapy in this patient was unconfirmed SD. Median PFS/ OS in cohort 1 were 1.8 months/ 6.8 months, and in cohort 2, 6.7 months/ 31.8 months. Grade 3 treatment-related adverse events (TRAEs) occurred in 4 patients across both cohorts, including colitis (2 pts), diabetes (1 pt), pneumonia (1 pt) and elevated lipase (1 pt). There were no grade 4/5 TRAEs. Two patients discontinued trial therapy due to toxicity (colitis), both in cohort 2. **Conclusions:** Combination immunotherapy with nivolumab and ipilimumab does not overcome primary resistance to PD1 axis inhibitor therapy; however, can overcome acquired resistance to PD1 axis inhibitor therapy. Translational studies from tumor and serial peripheral blood collections are ongoing. Clinical trial information: NCT03262779. Research Sponsor: BMS; U.S. National Institutes of Health.

9122 **Poster Session**

A decision-making tool for first-line treatment in advanced non–small-cell lung cancer based on plasma proteome biomarkers.

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Background: Initial treatment selection for advanced NSCLC patients without driver mutations is mainly based on evaluating PD-L1 expression levels in the tumor tissue. However, PD-L1 assays are only moderately predictive. In addition, the guidelines for the PD-L1≥50% subpopulation are not definitive, enabling the usage of immune checkpoint inhibitors (ICI) either as a monotherapy or combined with chemotherapy. Here we aim to provide a decision-making tool for the first-line treatment of advanced NSCLC patients based on plasma derived biomarkers obtained before treatment initiation. **Methods:** Pre-treatment plasma samples were collected from 545 NSCLC patients receiving ICI-based therapy. Clinical benefit was evaluated based on progression-free survival (PFS) at 12 months as a threshold. Deep plasma proteomic profiling was performed using aptamer technology. Based on the proteomic profiles, a computational model, termed PROphet, was developed and evaluated in a blinded manner on the validation subset (n = 272). The model output, clinical benefit probability, was used to stratify the patients into two groups, PROphet-positive or -negative. **Results:** The model displayed good performance with a high correlation between the predicted clinical benefit and the observed clinical benefit rate (R^2= 0.97), outperforming a PD-L1-based prediction model (R^2= 0.35). Patients classified as PROphet-positive achieved significantly longer overall survival (OS) than PROphet-negative patients, with a median OS of 25.9 versus 10.8 months (hazard ratio, HR = 0.51; 95% confidence interval, CI = 0.37-0.70; p-value $<$ 0.001). Next, we examined the clinical utility of combining the PROphet output with PD-L1 levels by comparing different treatment modalities. Focusing on PD-L1≥50%, patients with PROphet-positive results displayed similar OS and PFS when receiving ICI monotherapy or ICI-chemotherapy (OS HR = 0.77; CI = 0.42-1.43; p-value = 0.4096), suggesting that these patients may consider monotherapy, thus avoiding chemotherapy-related toxicity. Conversely, PD-L1≥50% patients with a PROphet-negative result displayed a significantly longer OS and PFS when receiving ICI-chemotherapy in comparison to ICI monotherapy, with a median OS that was not reached versus 11.10 months in the combination therapy and monotherapy groups, respectively (HR = 0.29; CI = 0.14-0.59; p-value $<$ 0.001). These patients should consider combination therapy, avoiding a treatment that is suboptimal for them. Results for PD-L1 1-49% and $<$ 1% provide additional clinical information for each subgroup. **Conclusions:** Plasma proteomic profiling can provide biomarkers that accurately predict the benefit of ICI-based treatment. The model output complements tissue PD-L1 expression levels as a tool to assist therapeutic decisions. Research Sponsor: OncoHost LTD.

9123 **Poster Session**

Amplification of wild-type *RET* and clinical response to selpercatinib for non–small-cell lung cancer (NSCLC).

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Background: *RET* rearrangements and *RET* kinase domain mutations represent targetable genomic alterations in various cancer types. However, the frequency and characteristics of *RET* amplification in cancer and its potential role as a targetable oncogenic driver are not well-characterized. **Methods:** In a pan-cancer cohort of patients at the Dana-Farber Cancer Institute (DFCI) whose tumors underwent next-generation sequencing (NGS), we evaluated the frequency of wild-type (wt) *RET* amplification (defined as ≥6 copies) in the absence of *RET* rearrangements or activating mutations. We validated our findings using merged data from the TCGA, GENIE, and China Pan-Cancer datasets. **Results:** The frequency of wt *RET* amplification across all cancers was 0.08% (28/34,463) in the DFCI cohort and 0.16% (145/91,466) in the validation cohort. In NSCLC, the frequency of *RET* amplification was 0.10% (5/4773) in the DFCI cohort and 0.13% (15/11,622) in the validation cohort. Other cancer types with *RET* amplification included hepatobiliary cancer, prostate cancer, and breast cancer, among others. For 22 *RET*-amplified cases with available copy number data, the median *RET* gene copy number was 7 (range 6-36). Among 20 *RET*-amplified NSCLCs, 10 had no other known driver mutations, and 10 had concurrent driver mutations (including *MET* exon 14 skipping, *MET* amplification, *KRAS* G12C/S/D, *EGFR* L858R, *EGFR* exon 20 insertion, and *EGFR* exon 19 deletion). In cases with available smoking status, 5 out of 6 patients with *RET*-amplified NSCLC had a history of tobacco use. A 69-year-old man with unresectable stage III NSCLC had disease recurrence after chemoradiation and durvalumab. Both the initial and recurrent biopsy samples showed focal high-level *RET* amplification (22 and 28 copies, respectively); genomic and RNA sequencing showed no other driver mutations or *RET* rearrangements. He experienced partial response to the selective RET inhibitor selpercatinib with decrease of both intracranial and systemic tumor burden. **Conclusions:** Amplification of wt *RET* represents a novel, targetable, rare molecular subset of NSCLC and other cancers. Research Sponsor: None.

9124 **Poster Session**

Multi-center real-world data curation and assessment of tumor growth rate and overall survival in advanced NSCLC treated with PD-(L)1 immune checkpoint inhibitor therapy.

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Background: While Immune Checkpoint Inhibitors (ICI) have become the standard-of-care for advanced non-small cell lung cancer (NSCLC) for certain patient populations, durable responses only occur in a small subset of patients. Therefore, there is an unmet need to identify patients that will respond before and during treatment to optimize treatment strategies. Multiple studies have shown promise that quantitative imaging biomarkers can predict response to ICI therapy. Studies have also shown that tumor growth parameters derived from time series data can provide early indications of long-term response. However, most studies to date have investigated single institution or clinical trial datasets, which are inadequate to capture the broad spectrum of real-world diversity of ICI treatments. In this study, we aimed to build a generalizable, well-validated imaging biomarker for treatment response. **Methods:** We have curated a retrospective dataset including serial imaging data of 1,215 advanced NSCLC patients who received ICIs from nine institutions across the US and Europe, capturing the diversity of the imaging data, such as CT scanner models, image acquisition parameters, reconstruction algorithms, as well as diversity in patient population, performance status, and treatment settings. Expert lesion annotations and manual volumetric segmentations were performed on all visible lesions (ranging from 1-18 lesions per subject, totaling 6,441 lesions) across the serial imaging data (ranging from 1-18 follow-up scans per subject), which enables lesion and organ-specific tumor burden assessment. We stratified overall survival based on volumetric response and tumor growth rate using a model defined by the sum of exponential growth (g) and decay (d), $vol(t) = vol(0)*(e^{gt} + e^{-dt} - 1)$. **Results:** Survival analysis showed that the 3-month volumetric response (N = 875) was significantly associated with overall survival (OS) for the lowest quartile (Q1; log-rank p-value, $P = 2.1e^{-4}$) and highest quartile (Q4; $P = 9.8e^{-8}$) compared to the middle quartiles (Q2+Q3). The median overall survival (OS) stratified by the volumetric response was 547.7, 450.9, and 332.0 days in the Q1, Q2+Q3, Q4 quadrants, respectively. Among patients having a minimum of 2 follow-up scans in the first 18 weeks (N = 264), we found that patients with the tumor growth parameter (g) in the highest quartile had significantly lower OS compared to the patients in the Q2+Q3 quadrants ($P = 7.2e^{-5}$). **Conclusions:** Our results demonstrate the potential of large multi-center real-world imaging datasets in investigating novel early response assessment methodologies, such as volumetric tumor burden quantification and tumor growth modeling. In our further work, we will investigate response patterns at individual lesion levels and correlations with overall patient-level response. Research Sponsor: Onc.AI.

9125 **Poster Session**

Phase II randomized trial of first-line pembrolizumab and vorinostat in patients with metastatic NSCLC (mNSCLC): Final results.

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Background: Histone deacetylase inhibitors enhance tumor immunogenicity through various mechanisms including induced expression of MHC and T cell chemokines. A previous phase I trial demonstrated the combination of pembrolizumab (P) with vorinostat (V) in advanced/metastatic (m)NSCLC was well tolerated with signals of activity in ICI-pretreated pts. To further investigate the combination, we conducted a first-line, phase II trial. **Methods:** Pts with treatment-naïve mNSCLC and tumor PD-L1 expression ≥ 1% were eligible. Pts were randomized, open-label, 1:1 to receive P 200 mg IV q3 wk as monotherapy [Arm A] vs P 200 mg IV q3 wk plus V 400 mg PO daily [Arm B]. The primary endpoint was overall response rate (ORR). Secondary endpoints included DOR, PFS and OS. Tumor biopsies were collected both pre- and on-treatment (day 15-21) for exploratory correlative analysis including gene expression and changes in the tumor microenvironment. **Results:** Between 7/2017 – 2/2022, 86 pts were enrolled, with 83 pts evaluable for response (40 in Arm A and 43 in Arm B). Median age was 69 (range 44 - 87), 47% female, and ECOG PS 0/1 in 9%/91%. PD-L1 TPS was ≥50% in 20/40 (50%) of pts in Arm A, and in 23/46 (50%) of pts in Arm B. The most common TRAEs in Arm A included diarrhea (15%) and fatigue (10%). 3 pts in Arm A experienced grade ≥ 3 irAEs (including 1 each of grade 3 hepatitis, pneumonitis, and rash). The most common TRAEs in Arm B included fatigue (41%), nausea (44%), diarrhea (35%) and increased creatinine (33%). 3 pts in Arm B experienced grade ≥ 3 irAE (2 grade 3 pneumonitis and 1 grade 4 myopericarditis). In Arm B, 22/45 (49%) of pts had a dose-reduction in vorinostat, most commonly due to grade 2-3 fatigue or nausea. Efficacy results by intention-to-treat are summarized in the Table below. For evaluable patients only, ORR was 44% in Arm B (19/43) and 28% in Arm A (11/40) (p=0.18). RNA-sequencing of a subset of patients showed a significant increase in interferon-γ pathway activity in both Arms. However, between the two Arms, interferon-γ pathway activity was enhanced to greater extent in Arm B, which may have contributed the higher overall response rate. **Conclusions:** To our knowledge, this is the first randomized trial investigating the combination of HDAC inhibition and anti-PD1 therapy in NSCLC. Although the combination arm had a numerically higher ORR compared to P monotherapy, the result did not meet the primary endpoint for significance. While there were no new safety signals with the combination therapy, reduction or interruption in V dose occurred frequently, which may have contributed to lack of survival differences between arms. Clinical trial information: NCT02638090. Research Sponsor: Merck Sharp & Dohme LLC; Department of Defense.

Best response:	Arm A N= 40	Arm B N = 46	P value
PR/CR	11 (28%)	19 (41%)	p=0.266
SD	15 (38%)	15 (33%)	
PD	14 (35%)	9 (20%)	
NE		3 (7%)	
DCR	26 (65%)	34 (74%)	p=0.508
Median PFS	4.5 mo	4.3 mo	p = 0.8

9126 **Poster Session**

Subcutaneous amivantamab (ami) in patients (pts) with advanced solid malignancies: The PALOMA study—Updated safety and identification of the recommended phase 2 dose.

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Background: Ami, an EGFR-MET bispecific antibody, is approved for pts with advanced *EGFR* exon 20 insertion non-small cell lung cancer after progression on platinum-based chemotherapy. Intravenous (IV) delivery is associated with infusion-related reactions (IRRs) in 67% of pts, requiring splitting the first dose over 2 days (Park *Ann Oncol* 2021;32[suppl_5]:S981). PALOMA (NCT04606381) is an ongoing phase 1b dose escalation study of subcutaneous (SC) ami ± rHuPH20 (a hyaluronidase that aids SC agent absorption) in pts with advanced solid tumors who may benefit from *EGFR*- or *MET*-directed therapy. Preliminary results showed SC ami was well tolerated, improved time and ease of administration, and meaningfully reduced IRRs (Krebs *Cancer Res* 2022;82:12_Supplement, CT198). We present updated safety results and identification of the recommended phase 2 dose (RP2D) for ami SC Q2W administration. **Methods:** PALOMA enrolled pts with various advanced solid tumors. Objectives were to evaluate administration feasibility, safety, and PK of low and high concentration formulations of ami SC (50 mg/mL ami ± rHuPH20 [Part 1; Cohorts 1a/b] and 160 mg/mL ami ± rHuPH20 [Part 2; Cohorts 2a/b, Cohort 3a, Cohort 5a]). Cohorts 1a/b and 2a/b received 1050 mg (1400 mg, ≥80 kg), Cohort 3a received 1600 mg (2240 mg, ≥80 kg), and Cohort 5a received 2560 mg (3360 mg, ≥80 kg). Cohorts 1-3 were dosed weekly for the first 4 weeks and Q2W thereafter. Cohort 5a was dosed weekly for the first 3 weeks and Q3W thereafter. **Results:** As of Jan 3, 2023, 81 pts were enrolled (16 pts in Part 1, 65 pts in Part 2) and majority had NSCLC (71; 88%). Median age was 64 years, 44 (54%) pts were female, and most pts were White (44; 54%) or Asian (34; 42%). Across all doses, IRRs were reported by 13 (16%) pts; all of grade 1-2. The most frequent manifestations of IRRs were chills (7%), pyrexia (7%), and asymptomatic tachycardia (4%). Treatment-emergent AEs (TEAEs) of rash were reported by 59 (73%) pts, with no grade ≥3. In total, 3 (4%) pts discontinued ami SC due to toxicity (2 pneumonitis, 1 asthenia). Grade ≥3 related TEAEs were reported by 3 (4%) pts (hypoalbuminemia, lymphopenia, hypertension). Full ami SC dosing on day 1 was feasible (≤7 min), obviating the need for split dosing. PK analysis confirmed that ami SC 1600 mg (2240 mg, ≥80 kg) Q2W resulted in similar exposure to the approved IV dose (1050 mg [1400 mg, ≥80 kg] Q2W). Compared to IV, ami SC resulted in lower C_{max} and equal or higher C_{trough} and $AUC_{0\text{-}336h}$ at Cycles 2 and 4. Based on these data, ami SC 1600 mg (2240 mg, ≥80 kg) was selected as the RP2D for ami SC Q2W administration. **Conclusions:** Ami SC was well tolerated with meaningful reductions in administration time and TEAEs. Ami SC provided a quantitative and qualitative improvement in the symptoms of IRRs vs historical IV rates. The identified RP2D for ami SC on the Q2W schedule achieved similar exposure as the approved IV dose. Clinical trial information: NCT04606381. Research Sponsor: Janssen R&D, LLC.

9127 **Poster Session**

Changes in PD-L1 and tumor mutational burden between paired samples and relationship to immune checkpoint inhibitor outcomes in non-small cell lung cancer.

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Background: Programmed cell death receptor ligand 1 (PD-L1) tumor proportion score (TPS) and tumor mutational burden (TMB) are key biomarkers of response to immune checkpoint inhibitors (ICI) in non-small cell lung cancer (NSCLC). How often PD-L1 and TMB values change across samples within individual patients (pts) and the impact of this variation on ICI outcomes are limited. **Methods:** Pts with NSCLC and multiple PD-L1 or TMB assessments at the Dana-Farber Cancer Institute were included. Clinicopathologic and genomic data were analyzed in association with PD-L1 and TMB changes. In patients with > 2 samples, each sample was paired with the subsequent and each pair was analyzed independently. Minor and major changes in PD-L1 were defined as absolute changes of 10-49% and 50-100%, respectively. **Results:** The PD-L1 cohort included 402 sample pairs (median ΔPD-L1: 0; range: -90,+95%) and the TMB cohort included 413 sample pairs (median ΔTMB: 0 mut/Mb; range: -20.6,+24.5). Concordance between pairs was high for both PD-L1 ($R = 0.53$, $P < 0.01$) and TMB ($R = 0.80$, $P < 0.01$). Samples taken within < 1 year had higher concordance for PD-L1 than samples taken ≥ 1 year apart ($P < 0.01$), but length of time between biopsies did not impact TMB concordance. Minor or no changes in PD-L1 were observed in 82.3% of pairs; the frequency of major increases was 9.7% and major decreases was 8%. After dividing TMB into tertiles, 72.6% sample pairs showed no tertile change, 16% increased to a higher tertile, and 11.4% decreased to a lower tertile. PD-L1, but not TMB, decreased with intervening ICI ($P = 0.02$), but PD-L1 and TMB did not change significantly with other intervening systemic therapies. Acquired copy number losses of the *CD274* gene (encoding for PD-L1) were enriched in pairs with a major PD-L1 decrease ($Q < 0.05$). Similarly, acquired loss of chromosome 9p (which contains the *CD274* locus) correlated with a reduction in PD-L1, while 9p gains correlated with an increase in PD-L1 ($P = 0.02$). A total of 142 pts had multiple PD-L1 scores assessed before ICI initiation. Among pts with at least one PD-L1-positive sample (TPS $\geq 1\%$), the presence of another sample that was PD-L1 negative ($< 1\%$) correlated with worse outcomes to ICI compared to pts with no PD-L1-negative samples: response rate was 11% vs 39% ($P < 0.01$), median progression-free survival (mPFS) 2.7 vs 8.0 months ($P < 0.01$), and median overall survival 13.6 vs 21.2 months ($P = 0.05$), respectively. Among pts with at least one PD-L1 TPS $\geq 1\%$ and one $< 1\%$, cases where the last PD-L1 TPS before ICI was $\geq 1\%$ achieved longer mPFS than if the pre-ICI sample was PD-L1 negative (3.6 vs 1.8 months, $P = 0.03$). **Conclusions:** Although PD-L1 and TMB generally had high intrapatient concordance across samples, significant changes in values occurred in some patients. Variations in PD-L1 influenced ICI outcomes, warranting an assessment proximal to ICI initiation whenever feasible. Research Sponsor: None.

9128 **Poster Session**

Results from a first-in-human phase 1B study of a complement factor H inhibitor (GT103) in patients with non-small cell lung cancer (NSCLC).

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Background: GT103 is a first-in-class IgG3 monoclonal antibody that was derived from a single human B cell and inhibits complement factor H (CFH). CFH is implicated in cancer immune evasion and overexpression portends a poor prognosis in multiple malignancies. CFH regulates C3 convertase in the alternative pathway of the complement cascade, limiting downstream opsonization and membrane attack complex formation. Monoclonal antibody inhibition of CFH facilitates complement-dependent tumor cell lysis, modulates the adaptive immune response, and inhibits tumor growth. **Methods:** GT103 is being evaluated in a multi-institutional, first-in-human, phase Ib study in patients with advanced stage, refractory NSCLC. A standard '3+3' dose escalation schema was used across four dose levels, with treatment given until disease progression or unacceptable toxicity. Dose limiting toxicity (DLT) observation period included cycle 1 and radiographic disease assessment was performed every 6 weeks. We have previously reported that no DLT was seen at the highest two dose levels of 3 mg /kg or 10 mg/kg administered IV every 3 weeks. Two expansion cohorts have now been opened at 10 mg/kg IV every 2 week and 15 mg/kg every 3 weeks dose levels allowing up to 6 patients at each dose level. We herein present updated clinical outcomes and analysis of correlative biomarkers. **Results:** As of February 3, 2023, twenty-five patients have been treated, with a median follow up of 230 days. Five of the 21 patients in the dose escalation cohort demonstrated stable disease by RECIST criteria. In the 10 mg/kg dose level, one patient has experienced prolonged disease stabilization and has received 12 cycles to date with tumor reduction on CT. The DLT period is ongoing for two patients enrolled in the 10 mg/kg IV every 2 weeks and two patients in the 15 mg/kg every 3 weeks expansion cohorts. Soluble C5b-9 (s C5b-9) is a candidate pharmacodynamic biomarker for GT103 and was measured at baseline and at day 15 from patients in all four dose escalation levels (0.3, 1, 3, 10 mg/kg). An increase in sC5b-9 was found in 13 of 21 patients at day 15. A marked doubling of the baseline sC5b-9 level was demonstrated in a subset of patients by day 15 indicative of biologic activity. **Conclusions:** GT103 is well tolerated in heavily pretreated advanced NSCLC population. Early clinical activity has been demonstrated to date with stable disease seen in 24% of patients. Updated clinical results and correlative data will be presented. A separate phase 2 study of combination GT103 with pembrolizumab is planned for patients with refractory NSCLC. Trial Registration: The study was approved by Duke University IRB with approval number Pro00104564. Clinical trial information: NCT04314089. Research Sponsor: Grid Therapeutics.

9129 **Poster Session**

Clinical and genomic landscape of *EGFR*-mutant lung cancers (LCs) with squamous and adenosquamous differentiation.

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Background: Outcomes to first-line therapy with osimertinib in patients (pts) with EGFR-mutant (EGFR+) squamous (sq) or adenosquamous (adenosq) LC have not been well described. Pts also undergo adenocarcinoma to squamous transformation (transformed) after treatment with EGFR tyrosine kinase inhibitor (TKI). The clinical and genomic characteristics of pts with EGFR+ sq and adenosq LC are largely unknown. **Methods:** We clinically and genomically characterized all pts with EGFR+ LC with baseline sq or adenosq histology and transformed histology at Memorial Sloan Kettering Cancer Center. Next-generation sequencing was performed with the MSK-IMPACT. We compared clinical outcomes (time to discontinuation (TTD), overall survival (OS), and post-progression survival after osimertinib discontinuation (PPS)) among the different cohorts. **Results:** A total of 51 pts were identified: 14 with baseline sq/adenosq treated with first-line (1L) osimertinib; 8 transformed cases post 1L osimertinib; 13 with baseline sq/adenosq treated with early generation TKI; 3 transformed cases post early generation TKI; the remainder of pts had early-stage EGFR+LC with baseline sq/adenosq. Median age was 63, and 57% were female. Eighteen (35%) were former or current smokers. Among pts with baseline sq/adenosq histology who were treated with 1L osimertinib, median TTD was 11.1 months (95%CI 7.7, not reached (NR)), and median OS was 24.3 months (95%CI 11.1 months, NR). Compared to a non-overlapping time-matched cohort with baseline adenocarcinoma treated with 1L osimertinib (N = 55), TTD was numerically shorter in the sq/adenosq cohort (11 vs. 17 months, HR 1.8, p = 0.076), and median OS was significantly shorter (24 vs. 33 months, HR 2.64, p = 0.03). PPS was shortest in baseline sq/adenosq (5 months, HR 2.94, p = 0.023), but similar in transformed (11 months, HR 0.89, p = 0.8) compared to adeno (11 months). The sq/adenosq cohort had significantly higher proportion of L858R EGFR (48% vs 31% $p < 0.001$) and atypical EGFR mutations at baseline (17% vs 7.3%, $p < 0.001$) compared to the adenocarcinoma cohort. PIK3CA mutations were enriched at baseline in the sq/adenosq cohort. In the transformed cases, RB1 alterations were present in 13% at baseline. There was a similar distribution of type of EGFR mutations in the non-overlapping pts in the AACR GENIE EGFR+ LC cohort with sq/adenosq histology (N = 4, 50% L858R, 25% atypical). **Conclusions:** Pts with EGFR+ sq/adenosq LCs exhibit inferior TTD and OS with 1L osimertinib compared to adenocarcinoma controls. Sq/adenosq LCs appear to be molecularly distinct with enrichment in EGFR L858R and atypical EGFR mutations. Transcriptomic profiling of a subset of samples will be presented. Our findings highlight the need for novel therapeutic strategies among pts in this high-risk subgroup. Research Sponsor: U.S. National Institutes of Health.

9130 **Poster Session**

Evaluating generalizability of practice-changing randomized clinical trials in non-small cell lung cancer using machine learning-based in-silico trials.

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Background: Results of randomized clinical trials (RCTs) of anticancer agents are not generalizable to many real-world patients. Advances in machine learning (ML) and increasing availability of curated real-world data offer opportunities to assess generalizability by simulating trials "in-silico". Our objective was to assess the generalizability of survival outcomes reported in 2 practice-changing phase III trials in first-line (1L) advanced non-small cell lung cancer (aNSCLC). **Methods:** Our cohort included patients from the nationwide Flatiron Health EHR-derived de-identified database diagnosed with stage IIIB-IV or recurrent aNSCLC between 2011 and 2020. First, we trained and validated supervised ML models (gradient boosted, random forest, support vector machine and penalized Cox) to predict 1-year survival for patients with aNSCLC; the Lung Cancer Prognostic Index (LCPI), a published disease-specific prognostic index, was used as a comparator model. We used 130 demographic, vital sign, laboratory, and biomarker features at aNSCLC diagnosis to build models. Second, we used the best-performing ML model to create 4 prognostic risk groups. Third, we simulated 2 seminal trials for 1L treatment of aNSCLC, using inverse probability of treatment-weighted survival analyses, coarsely reproducing inclusion/exclusion criteria across ML-derived risk groups. We compared median overall survival (mOS) using Kaplan-Meier curves from the start of 1L treatment to death in in-silico trials (ISTs) vs. RCTs. **Results:** Our cohort included 61,339 patients with aNSCLC. The best-performing gradient boosted model outperformed the LCPI (AUC 0.784 vs 0.688). In ISTs, survival benefits of novel treatments varied across risk groups and were generally lower in ISTs compared to RCTs (Table). IST results in high- and very high-risk patients were inconsistent with RCT survival results. For example, for KEYNOTE-024, mOS in the pembrolizumab arm was 30.0 months, whereas in the IST, mOS among patients receiving pembrolizumab varied from 1.3 months in very high-risk patients to 41.5 months in low-risk patients. RCT results overestimated treatment effects for high-risk aNSCLC patients. **Conclusions:** ML-based ISTs can reveal heterogeneity in real-world survival outcomes associated with novel oncology treatments and elucidate populations for whom RCT results generalize poorly. Research Sponsor: None.

		IST: mOS (mos) Treatment vs Control (difference in mOS) by Risk Group				
Trial	RCT: mOS (mos) Treatment vs Control (difference in mOS)	All (n = 61,069)	Very High (n = 9,630)	High (n = 22,123)	Medium (n = 18,166)	Low (n = 11,420)
KEYNOTE-024 (2016)	30.0 vs 14.2 (15.8)	10.9 vs 5.0 (5.9)	1.3 vs 1.7 (-0.4)	5.6 vs 4.9 (0.7)	21.6 vs 9.4 (12.2)	41.5 vs 17.0 (24.5)
KEYNOTE-189 (2018)	22.0 vs 10.7 (11.3)	14.0 vs 4.9 (9.1)	1.9 vs 1.5 (0.4)	6.6 vs 4.4 (2.2)	19.3 vs 9.2 (10.1)	43.1 vs 25.5 (17.6)

9131 **Poster Session**

A phase 2a study evaluating the efficacy and safety of sutetinib in patients with advanced non–small-cell lung cancer (NSCLC) harboring uncommon EGFR mutations.

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Background: Although non-small cell lung cancer (NSCLC) patients with tumor harboring classical Epidermal Growth Factor Receptor (EGFR) mutations have numerous therapeutic choices, uncommon EGFR mutation NSCLC patients have limited treatment options. Sutetinib is a selective tyrosine kinase inhibitor (TKI) targeting uncommon EGFR mutations. **Methods:** In this multicenter, open-label phase 2a study, treatment-naïve adults with NSCLC harboring uncommon EGFR mutations (G719X, S768I, L861Q) received oral sutetinib monotherapy at 80 or 64 mg/day (Chinese trial register CTR20190681). The primary endpoint was objective response rate (ORR) per RECIST v1.1. Secondary endpoints included duration of response (DoR), overall survival (OS), safety and tolerability. Adverse events (AEs) were graded according to the CTCAE v5.0. **Results:** Sutetinib was administered to 30 NSCLC patients at 80 (n = 15) or 64 (n = 15) mg/day. Median age was 60 years old (range 47-74 years). Twenty patients (66.7%) were females, 10 patients (33.3%) had a history of smoking. Patients had an ECOG PS of 0 (10.0%) or 1 (90.0%). Tumors had a G719X (36.7%), L861Q (30.0%), or S768I (20.0%) EGFR mutation, or a combination of these uncommon EGFR mutations (13.3%). None had EGFR T790M, L858R, exon 19 deletions, or exon 20 insertions. The ORR was 71.4% (20/28), including 92.9% (13/14) and 50.0% (7/14) in the 80 and 64 mg/day cohorts, respectively. The disease control rate (DCR) was 96.4%, including 100.0% (14/14) and 92.8% (13/14) in the 80 and 64 mg/day cohorts, respectively. All responses were partial responses. The median DoR was 12.5 months (20.3 and 9.2 months in the 80 and 64 mg/day cohorts, respectively). One-year OS was 84.7% (92.9% and 75.0% in the 80 and 64 mg/day cohorts, respectively). As of 15 January 2022 (database lock), 11 (36.7%) patients were still receiving sutetinib treatment. Grade ≥3 treatment emerged AEs were similar in the 80 mg/day (80.0%, 12/15) and 64 mg/day (73.3%, 11/15) cohorts. The most frequently reported grade ≥3 Treatment-related AEs (TRAEs) were diarrhea (36.7%), abnormal liver function (13.3%), and rash (10.0%). One grade 4 TRAE was observed: hypokalemia in the 64 mg/day cohort. **Conclusions:** Sutetinib demonstrated a high response rate with durable antitumor activity in patients with NSCLC harboring uncommon EGFR mutations. The toxicities are expected and comparable to other EGFR TKIs. A multi-center phase 2b study is ongoing in the United States and China to further evaluate Sutetinib in uncommon EGFR mutation NSCLC. Clinical trial information: CTR20190681. Research Sponsor: Suzhong Pharmaceutical Group Co., LTD.

9132 **Poster Session**

Artificial intelligence algorithm developed to predict immune checkpoint inhibitors efficacy in non–small-cell lung cancer.

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Background: Many non-small cell lung cancer (NSCLC) patients with high PD-L1 IHC expression and/or high TMB level do not respond to immune-check point inhibitors (ICIs). Discovery of novel predictive biomarkers for ICI response in NSCLC continues to be a critical unmet medical need, given the expense, potential toxicity, and therapeutic delay due to ICI treatment without benefit. **Methods:** We developed a supervised deep learning algorithm (Deep-IO) to predict therapeutic response to ICIs in NSCLC patients from standard histology whole slide hematoxylin and eosin (H&E) images, which was trained based on ICI objective response rate. We utilized a convolutional neural network (CNN) implemented in Pytorch. The efficiency of the Deep-IO was evaluated through classification performance metrics and the area under the receiver operating characteristic curve (AUROC). The algorithm was trained and tested on 85218 tiles (size: 512x512 pixels) in 446 advanced stage NSCLC patients from the Dana Farber Cancer Institute (DFCI), all treated with ICI monotherapy. **Results:** The objective response rate, comprising complete and partial response, was 26% (n = 114) in the overall cohort. The DFCI patient cohort was randomly split into a training set (N=379, 85%) and a test set (N=67, 15%). The classifier's predicted class (responder vs non-responder) probabilities at the tiles level were averaged for each patient. Quantitative evaluation of whole section test dataset shows that the developed model achieves the accuracy of 0.72, weighted average (WAVG) precision of 0.77, WAVG recall of 0.72 and WAVG F-score of 0.74 on classifying ICI non-responders from responders. Comparing with PD-L1 expression (TPS%) and TMB (mu/Mb), Deep-IO had superior predictive power for ICI response (AUROC=0.75) in the test set. The combined Deep-IO+PD-L1 scores resulted in a significantly greater AUROC value of 0.82 compared to single tests and a 32% improvement in specificity (0.88 vs. 0.56) compared to PD-L1 evaluation alone (Table). **Conclusions:** This proof-of-concept study shows that an artificial intelligence–powered H&E image classifier can predict ICI effectiveness in NSCLC. Deep-IO outperformed both established predictive biomarkers. We will assess Deep-IO in additional external NSCLC data sets for validation and confirmation. Research Sponsor: None.

Biomarker	AUROC	Specificity	Sensitivity	PPV	NPV
Deep-IO+PD-L1	0.82	0.88	0.70	0.58	0.92
Deep-IO	0.75	0.55	0.93	0.34	0.97
PD-L1	0.67	0.56	0.80	0.31	0.92
TMB	0.61	0.25	0.97	0.25	0.99

9133 **Poster Session**

Investigating racial inequities of circulating tumor DNA (ctDNA) use in patients with non-small cell lung cancer: A real world analysis.

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Background: The use of ctDNA has emerged as an invaluable adjunct to tissue-based molecular testing, though it remains unclear if racial inequities associated with ctDNA implementation exist. We sought to assess disparities in frequency of actionable alterations detected and utilization of those results for treatment decisions in a diverse urban population of NSCLC patients. **Methods:** We performed a retrospective study of NSCLC patients who received Guardant ctDNA testing from 11/2015-10/2022. Kaplan Meier curves with log-rank tests were used to assess time-to-treatment initiation or treatment change from date of ctDNA collection among race/ethnicity subgroups (Hispanic, Black, White). Univariate associations between race/ethnicity subgroups, NCCN actionable mutation detection, and variant allele frequency, were assessed using Chi-Square and Kruskal-Wallis tests for categorical and continuous variables, respectively. **Results:** We identified 258 subjects. The race/ethnicity distribution in order of prevalence was Hispanic (33.0%, n = 85), Black (32.6%, n = 84), White (24.8%, n = 64), and Asian/other/unknown (9.7%, n = 25). Median turnaround time for ctDNA result was 8 days (range 2-24 days) from collection date. Median time-to-treatment initiation or change was 25 days for the combined cohort, and 24 days for patients with treatment naïve metastatic disease. Time-to-treatment initiation or change was similar among race/ethnicity subgroups in the combined cohort, as well as those specifically with metastatic disease not yet initiated on treatment at time of ctDNA testing ($p = 0.52$ and $p = 0.43$, respectively). Similar proportions of all race/ethnicity subgroups had an NCCN actionable mutation detected ($p = 0.92$) and similar variant allele frequencies ($p = 0.68$). An NCCN actionable mutation was detected in 35.3% (n = 91) of patients, the most common being EGFR (n = 53) and KRAS G12C (n = 17). CtDNA results helped avoid the need for repeat tissue biopsy in 25.6% (n = 66) of patients. Of the 68% (n = 175) of patients with paired tissue and liquid biopsies, 24.0% (n = 42) of patients had discordant results, and 8.6% (n = 15) had additional alterations detected on liquid biopsy. **Conclusions:** In our diverse cohort, we observed a similarly high detection rate of actionable mutations and early time-to-treatment based on ctDNA results across all race/ethnicity subgroups. In addition, ctDNA helped avoid need for repeat tissue biopsy in 25% of patients and yielded additional alterations not detected on tissue in nearly 10% of patients with discordant results. Our findings suggest that broad based molecular testing utilizing ctDNA is not only feasible, but also that it enables faster time-to-treatment in a racially diverse urban population. Continued efforts are necessary to ensure timely molecular testing among all patients, and to identify any racial inequities that may exist.
Research Sponsor: None.

9134 **Poster Session**

Amivantamab and lazertinib in treatment-naïve *EGFR*-mutated advanced non–small-cell lung cancer (NSCLC): Long-term follow-up and ctDNA results from CHRYSALIS.

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Background: CHRYSALIS (NCT02609776) evaluated the combination of amivantamab (ami) and lazertinib (laz) in treatment-naïve patients (pts) with epidermal growth factor receptor (*EGFR*)-mutated NSCLC. As previously reported, all 20 pts achieved a partial response (overall response rate of 100%) but interpretation of long-term outcomes was limited by the length of follow up (Cho *Ann Oncol* 2020; 31:suppl_4, 1258O; Cho *J Thorac Oncol* 2022;17:S126, P1.16-01). Herein, we present long-term results from this treatment-naïve cohort. **Methods:** The treatment-naive cohort enrolled pts with *EGFR* exon 19 deletion (ex19del) or L858R mutated advanced NSCLC. All pts received 1050 mg IV ami (1400 mg if ≥80 kg) and 240 mg oral laz. Response was assessed by the investigator per RECIST v1.1. Circulating tumor DNA (ctDNA) was analyzed from plasma samples prior to initiation of treatment, at Cycle 3 Day 1, and at end of treatment (EOT). **Results:** Of the 20 pts enrolled in the treatment-naive cohort (median 62.5 years, 55% women, all Asian), 11 had *EGFR* ex19del and 9 had L858R NSCLC. As of Nov 15, 2022, the median follow-up and duration of treatment were 33.6 and 33.5 months, respectively. Ten (50%) pts were progression-free and remained on treatment, including 7 of 11 (64%) with ex19del and 3 of 9 (33%) with L858R. The median duration of response (DOR), median progression-free survival (PFS), and median overall survival (OS) were not estimable. The estimated landmark PFS rate was 85% at 12 months, 65% at 24 months, and 51% at 36 months. Of note, 2 (10%) pts were treated beyond progression. The longest ongoing pt has a duration of treatment of 37.2 months and DOR of 35.7 months. Treatment-related dose interruptions, reductions, and discontinuations of either ami and laz occurred in 7 (35%) pts, 8 (40%) pts, and 1 (5%) pt, respectively. The safety profile was consistent with prior reports, with predominantly on-target EGFR- or MET-related adverse events. Among the 10 pts who discontinued treatment, 4 submitted samples for ctDNA analysis at both baseline and EOT. There was 1 pt with new *PIK3CA* mutations, 1 with low-level *HER2* amplification, 1 pt with a new *CCNE1* and *EGFR* amplification, and 1 pt with no new mutations detected. Updated data on ctDNA at EOT may be available at the time of congress presentation. **Conclusions:** At a median duration of treatment of 33.5 months, median DOR, PFS, and OS have not been reached in treatment-naïve pts receiving ami+laz, with 50% remaining progression-free and on treatment. No new safety signals were identified. The ongoing phase 3 MARIPOSA study (NCT04487080) is further investigating ami+laz vs osimertinib vs laz in previously untreated, *EGFR*-mutated, advanced NSCLC. Clinical trial information: NCT02609776. Research Sponsor: Janssen R&D, LLC.

9135 **Poster Session**

Final results from a phase II trial of CIMAvax-EGF and nivolumab as second-line (2L) therapy after platinum-based chemotherapy in advanced non-small cell lung cancer (NSCLC).

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Background: CIMAvax-EGF (C-E) is a recombinant anti-human epidermal growth factor (EGF) depleting immunotherapy which has previously shown increased survival as maintenance after platinum-based chemotherapy in patients (pts) with advanced NSCLC. The primary objective of this single-arm phase II trial was to evaluate the 12-month overall survival (OS) in pts receiving C-E in combination with Nivolumab(N) as 2L therapy for advanced NSCLC. **Methods:** Pts with previously treated, immunotherapy-naive advanced NSCLC received 2.4 mg C-E IM every 2 weeks(w) for 4 doses (loading phase) in combination with N 240mg IV every 2 w, then continued monthly maintenance C-E combined with N 240mg IV every 2 w. Enrollment to this arm was terminated before estimated sample size was met due to poor accrual as immunotherapy became incorporated into 1st line therapy. We present OS and progression-free survival (PFS) data [determined using a Kaplan-Meier test with 90% confidence intervals (CI)] of pts who were able to complete the loading phase per protocol (PP). **Results:** 21 out of 23 enrolled pts were included in the PP analysis. Among the 21 pts, 17 (81.0%) had non-squamous(nsq) histology, 12 (57.1%) were KRAS wildtype (9.5% unknown status), 13 (61.9%) had PD-L1 tumor proportion score 0%. 43% pts (n=3) with known KRAS mutation (n=7) had co-mutated STK11. Disease control rate was 47.6% (n=10) defined as pts who had stable disease or partial response as best response per RECIST v1.1. The 21 PP pts had a 29% 3-year(yr) OS rate (90% CI 14, 45; intention-to-treat [ITT] population in 23 pts with 26% 3-yr OS rate, 90% CI 13, 42). Median(m) OS for PP pts was 11.9 months, 90% CI 8.0 – 23.9 months (ITT mOS 10.4 months, 90% CI 6.8-13.6). Pts with squamous histology had a better 3-yr OS rate compared to those with nsq histology [50% (90% CI 10, 81) vs 24% (90% CI 9, 41), respectively]. Pts with PD-L1 expression $\geq$1% had higher 3-yr OS [38% (90% CI 12, 63)] and 3-year PFS [38% (90% CI 12, 63)] compared to pts with no PD-L1 expression (3-yr OS 23% [90% CI 8, 44] and 3-yr PFS 8% [90% CI 1, 25]). mOS, 1-yr and 3-yr OS for EGFR/ALK/KRAS wildtype pts was higher [31.7 months (90% CI 5.9, NR), 67% (90% CI 4, 84), 50% (90% CI 24,71), respectively) compared to KRAS mutated NSCLC [10.1 months (90% CI 6.5, 12.1), 29% (90% CI 6, 56), 0% (90% CI 1, 41), respectively]. **Conclusions:** NSCLC pts who were able to complete the PP combination of C-E plus N at the minimum had numerically better OS compared to historical study cohorts with N as 2L monotherapy. Among pts who completed PP treatment, pts with KRAS wildtype NSCLC had the longest mOS observed. C-E is currently being investigated in combination with pembrolizumab as maintenance therapy after completing 1L chemoimmunotherapy for NSCLC with PD-L1 $<$ 50% and as 1L therapy in combination with pembrolizumab for EGFR/ALK wildtype NSCLC and PD-L1 $\geq$ 50%. Clinical trial information: NCT02955290. Research Sponsor: Roswell Park Alliance Foundation.

9136 **Poster Session**

Real-world outcomes of first-line immune checkpoint inhibitors with or without chemotherapy in *KRAS* G12C altered NSCLC according to PD-L1 status.

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Background: There is a considerable debate whether treatment approaches should be tailored in advanced KRAS G12C-mutated NSCLC. Increasing evidence suggests that *KRAS* G12C-mutated NSCLC is associated with genomic heterogeneity that may impact clinical outcomes. Herein, we report a multimodal, real world outcomes analysis of 1L patients with advanced *KRAS* G12C-mutated NSCLC stratified by treatment type and PD-L1 status. **Methods:** Deidentified multimodal real-world data (RWD) of 1576 advanced, 1L NSCLC patients across the US were retrospectively analyzed from the Tempus database. Selection criteria included: Tempus xT targeted NGS, known PD-L1 status, absence of *EGFR*, *ALK* and *ROS1* mutations, and treatment with chemotherapy (CT) + pembrolizumab (P), or P only. Patients were stratified by the presence or absence (wt) of *KRAS* G12C alterations. Median OS (mOS) was estimated using Kaplan-Meier methods. Subgroup analyses were performed using Cox model stratified by *KRAS* G12C status, PD-L1 status, and pathogenic alterations of *STK11* and *KEAP1*. **Results:** In this study, two cohorts were assessed, *KRAS* G12C (n = 201) and *KRAS* G12C wt (n = 1375). Characteristics and demographics were balanced between both cohorts. Among TPS $<$ 50 patients treated with CT + P, *KRAS* G12C (n = 109, 54%) had a mOS of 11.64 months (m) versus 16.81m (HR = 1.32, p = 0.06) for *KRAS* G12C wt (n = 864, 62.8%). Among TPS $<$ 1 patients treated with CT + P, *KRAS* G12C (n = 46, 22%) had a mOS of 11.18 m versus 16.44 m (HR = 1.67, p = 0.01) for *KRAS* G12C wt (n = 489, 35%). Among TPS $\geq$50 patients treated with P only, *KRAS* G12C (n = 45, 22.3%) had a mOS of 30.03m compared to 25.03m (HR = 0.94, p = 0.83) in *KRAS* G12Cwt (n = 236,17.1%). TPS $<$ 50 subgroup was enriched for select co-mutations with *KRAS* G12C (*STK11*, 24.5%; *KEAP1*, 10.7%) vs. TPS $\geq$50 (*STK11*, 3.8%; *KEAP1*, 5.1%). When evaluating the impact of co-mutations in the *KRAS* G12C with TPS $<$ 50, *STK11* (n = 30) mOS was 10.59m (HR = 1.01, p = 0.81) and *KEAP1* (n = 13) mOS was 7.63m (HR = 2.14, p = 0.03). **Conclusions:** This largest RWD analysis to date demonstrates that 1L *KRAS* G12C NSCLC patients with TPS $<$ 1% and $<$ 50% receiving standard CT + P have the shortest survival among all evaluated sub-groups. Novel *KRAS* G12C targeted combination therapies in development for this patient population may offer the promise of better outcomes. Research Sponsor: Tempus Labs and Mirati Therapeutics.

		CT + P	CT + P	P	P
PD-L1 Status		*KRAS G12C*	*KRAS G12C*wt	*KRAS G12C*	*KRAS G12C*wt
TPS < 1	*mOS (m)*	11.18 (n = 46)	16.44 (n = 489)	16.31 (n = 3)	15.71 (n = 38)
	HR [95% CI] p-value	1.67 [1.12 - 2.50] p = 0.01		1.57 [0.34 - 7.06] p = 0.56	
TPS 1-49	*mOS (m)*	16.91 (n = 63)	19.58 (n = 375)	NA (n = 10)	23.70 (n = 66)
	HR [95% CI] p-value	1.12 [0.73 - 1.73] p = 0.59		0.35 [0.05 - 2.69] p = 0.32	
TPS < 50	*mOS (m)*	11.64 (n = 109)	16.81 (n = 864)	16.31 (n = 13)	15.72 (n = 104)
	HR [95% CI] p-value	1.32 [0.99 - 1.77] p = 0.06		0.72 [0.22 - 2.35] p = 0.58	
TPS ≥50	*mOS (m)*	NA (n = 34)	18.02 (n = 171)	30.03 (n = 45)	25.03 (n = 236)
	HR [95% CI] p-value	0.60 [0.29 - 1.22] p = 0.16		0.94 [0.54 - 1.64] p = 0.83	

9137 **Poster Session**

Risk factors for venous thromboembolism (VTE) among patients with *EGFR*-mutated advanced non-small cell lung cancer (NSCLC) receiving amivantamab plus lazertinib versus either agent alone.

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Background: Amivantamab (ami), an EGFR and cMET bispecific antibody with immune cell-directing activity, and lazertinib (laz), a CNS-penetrant 3rd-generation EGFR tyrosine kinase inhibitor have shown clinical activity in biomarker-selected patients (pts) with advanced NSCLC. Antitumor activity has been suggested to be improved when the agents are given in combination (Leighl *Ann Oncol* 2021;32: suppl_5, 1192MO). We examined the incidence of VTE, a common adverse event (AE) among pts with lung cancer, for those receiving ami monotherapy, laz monotherapy, and ami+laz to investigate if there is elevated risk and understand potential predisposing risk factors. **Methods:** CHRYSALIS (NCT02609776; ami monotherapy and ami+laz), CHRYSALIS-2 (NCT04077463; ami+laz), and LASER201 (NCT04075396; laz monotherapy) are ongoing open-label studies of locally advanced/metastatic NSCLC. Two descriptive, univariate risk analyses were performed, with the primary analysis including all treatment-emergent VTE events (grouped term) and a secondary analysis that excluded VTE events occurring after progression of disease (PD) or within 30 days prior to PD. **Results:** This analysis included 560 pts who received ami monotherapy, 536 ami+laz, and 252 laz monotherapy, predominantly in the TKI-relapsed setting. The incidence of VTE events of any grade was numerically higher in pts who received ami+laz (21%) than those who received ami (11%) or laz (11%) monotherapy. The median time to onset of the first VTE event was 84.5 days for ami, 79 days for ami+laz, and 170 days for laz. The majority (64%) of ami+laz pts had VTE events in the first 4 months. The most common VTE events by preferred term were pulmonary embolism and deep vein thrombosis. The incidence of grade $\geq$3 VTE events was comparable among pts receiving ami (5%), ami+laz (6%), and laz (6%), and there were no grade 5 VTE events for ami+laz. The overall incidence of serious VTE AEs was low (ami, 3%; ami+laz, 5%; laz, 4%). There were 6 discontinuations due to VTE, 1 (0.2%) ami, 2 (0.4%) for ami+laz, and 3 (1.2%) laz. In the primary analysis, age $\geq$60 years was a significant risk factor ($P < 0.05$). In the secondary analysis, age $\geq$60 years, ECOG performance status of 1 (vs 0), and response to therapy (partial response or better) were significant risk factors ($P < 0.05$). **Conclusions:** Lung cancer diagnosis is a known risk factor for VTE. In a review across clinical trials, single-arm cohort data suggest there is a numerically higher incidence of VTE for ami+laz compared with each monotherapy. Age $\geq$60 years, ECOG performance status, and response to treatment are potential risk factors. The relationship between response and VTE is emerging and may reflect possible immune or inflammatory-mediated mechanisms. Further efforts to understand VTE-associated risk factors in randomized clinical trials are ongoing. Clinical trial information: NCT02609776, NCT04077463, NCT04075396. Research Sponsor: Janssen R&D, LLC.

TPS9139 **Poster Session**

A phase III, multicenter, double-blinded, randomized, active-controlled study on the efficacy and safety of QL1706 with chemotherapy (CT) as first-line therapy for PD-L1–negative advanced or metastatic non–small-cell lung cancer (NSCLC).

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Background: PD-(L)1 immunotherapy plus platinum-doublet chemotherapy has been the standard 1L treatment for EGFR/ALK wild-type advanced NSCLC pts. However, pts with PD-L1 negative achieve minimal benefit from the PD-(L)1 immunotherapy plus CT. PD-(L)1 plus CTLA-4 blockade with CT in 1L treatment of PD-L1 negative NSCLC derived an improved median overall survival (OS) versus CT alone in CheckMate-9LA study (*Luis Paz-Ares et al., Lancet Oncol 2021*) and POSEIDON study (*M L. Johnson et al., JCO 2022*). QL1706 is a novel bifunctional antibody, containing a mixture of anti-PD-1 IgG4 and anti-CTLA-4 IgG1 antibodies produced in a fixed ratio (2:1) from the same single cell and manufactured together as one product (MabPair). QL1706 monotherapy or plus CT showed impressive safety and efficacy in advanced NSCLC both in phase I and phase II studies (data have been submitted for publication). Of note, QL1706+CT exhibited promising antitumor activity in advanced PD-L1 negative NSCLC. The phase III study aims to compare the efficacy of QL1706+CT versus anti-PD-1 (tislelizumab) + CT (approved in China for 1L treatment of mNSCLC) as 1L treatment in advanced PD-L1 negative NSCLC. **Methods:** The phase III, multicenter, double-blinded, randomized, active-controlled study is enrolling pts aged 18-75 years with ECOG PS of 0-1, previously untreated, PD-L1 negative (TPS $<$ 1%), EGFR/ALK wild-type, and pathologically identified stage IIIB-IV NSCLC. Eligible pts will be randomized (1:1) to receive 4-cycle treatment of QL1706 (5 mg/kg, Q3W) plus CT or tislelizumab (200 mg, Q3W) plus CT followed with maintenance treatment of QL1706 or tislelizumab monotherapy (squamous), or in combination with pemetrexed (non-squamous), until disease progression, intolerable toxicity, or for up to 2 years of immunotherapy. Stratification factors include histology (squamous vs non-squamous), brain metastasis (yes vs no), and sex (male vs female). Co-primary endpoints are progression-free survival (PFS) and OS. Secondary endpoints include objective response rate (ORR), disease control rate (DCR), duration of response (DOR) assessed by investigator per RECIST v1.1, 6 mo- and 12 mo-PFS, 6 mo- and 12 mo-OS, and safety. Exploratory endpoints include PK characteristics, immunogenicity, PFS2 (defined as time from randomization to progression after first subsequent therapy or any-cause death), and efficacy (iPFS, iORR, iDCR, iDOR) by investigator per iRECIST, biomarker analysis of tumor mutation burden. The study planned to enroll 650 pts to obtain approximately 493 PFS events (HR = 0.69; Power = 94%) and 445 OS events (HR = 0.75; Power = 83%) across the QL1706+CT and tislelizumab+CT arms for the final analyses of PFS and OS, respectively. The alpha was split between PFS (α = 0.005) and OS (α = 0.02). Enrollment began from Feb 2023. Clinical trial information: NCT05690945. Research Sponsor: Qilu Pharmaceutical Co., Ltd.

TPS9140 **Poster Session**

A phase 1a/1b study of aurora kinase A inhibitor VIC-1911 as monotherapy and in combination with sotorasib for the treatment of *KRAS G12C*-mutant non–small-cell lung cancer.

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Background: Activity of direct covalent $KRAS^{G12C}$ inhibitors in NSCLC is limited by mutational and adaptive resistance. AURKA has roles in centrosome maturation and cytokinesis. AURKA amplification/overexpression is reported in multiple tumors, including NSCLC, and AURKA signaling may mediate adaptive resistance to KRAS inhibition. VIC-1911 is a highly selective, orally active small molecule inhibitor of AURKA. VIC-1911 demonstrated monotherapy activity *in vitro* in $KRAS^{G12C}$-mutant human NSCLC cells with intrinsic and acquired resistance to the $KRAS^{G12C}$ inhibitor sotorasib, and combination VIC-1911 and sotorasib showed synergy in the same cell lines. Combination VIC-1911 and sotorasib delayed the emergence of adaptive resistance *in vitro*. These findings suggest that 1) AURKA activation is present in both intrinsic and acquired resistance to sotorasib in $KRAS^{G12C}$-mutant NSCLC and 2) the combination of VIC-1911 and sotorasib is a potential therapeutic approach for $KRAS^{G12C}$-mutant NSCLC with intrinsic or acquired resistance to sotorasib monotherapy. In addition, *in vivo* data suggest both sotorasib and adagrasib are synergistic in combination with VIC-1911 in human $KRAS^{G12C}$-mutant NSCLC cell line xenograft models. **Methods:** A non-randomized, open-label Phase 1a/1b study of VIC-1911, an aurora kinase A inhibitor, administered as monotherapy and in combination with sotorasib for the treatment of advanced $KRAS^{G12C}$-mutant NSCLC is in progress. Participants $\geq$18 years, with locally advanced or metastatic $KRAS^{G12C}$-mutant NSCLC, prior treatment with at least 1 line of PD-1/PD-L1 inhibitor therapy with or without platinum-based chemotherapy and have adequate organ function are eligible. Both $KRAS^{G12C}$ inhibitor naïve and experienced patients are eligible. VIC-1911 monotherapy is given at oral doses of 25 – 90 mg twice daily in dose escalation and at the VIC-1911 maximum tolerated dose (MTD) in the expansion cohort in patients who are refractory/relapsed on prior $KRAS^{G12C}$ inhibitor therapy. The combination regimen includes dose escalation with VIC-1911 at oral doses of 75, 150 or 200 mg twice daily on days 1-4, 8-11 and 15-18 every 28-day cycle plus sotorasib 960 mg daily in patients who are refractory/relapsed or naïve to prior $KRAS^{G12C}$ inhibitor therapy. In dose escalation, a 3+3 schema is followed with dose limiting toxicity (DLT) criteria for toxicity and a sample size $\leq$ 36. For expansion cohorts, the sample size is based on Simon 2-stage optimal design, with a sample size $\leq$ 104. VIC-1911 and sotorasib dose modification criteria are provided. Supportive medications are allowed and early stopping rules for toxicity will be followed. VIC-1911 pharmacokinetics will be assessed. Pharmacodynamics will be determined from ctDNA and tumor biomarker analysis. Clinical trial information: NCT05374538. Research Sponsor: VITRAC Therapeutics, LLC.

TPS9141 **Poster Session**

STAR-121: A phase 3, randomized study of domvanalimab (DOM) and zimberelimab (ZIM) in combination with chemotherapy vs pembrolizumab (pembro) and chemotherapy in patients with untreated metastatic non-small cell lung cancer (mNSCLC) with no actionable gene alterations.

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Background: Although immune checkpoint inhibitors have improved clinical outcomes in mNSCLC, the majority of patients will experience progression and shorter survival. Thus, an urgent need exists for more effective treatment options in mNSCLC. DOM is an anti-TIGIT IgG1, Fc-silent monoclonal antibody designed to inhibit the interaction between TIGIT and its ligand, CD155, thereby reducing immunosuppression of T cells and natural killer cells and promoting antitumor activity. ZIM is an anti–PD-1 IgG4 monoclonal antibody with demonstrated antitumor activity in vivo and preliminary clinical activity in multiple tumor types. Preliminary studies have shown that dual blockade of TIGIT and PD-(L)1 increases antitumor activity relative to PD-(L)1 inhibition. In ARC-7, a randomized phase 2 study in PD-L1–high, first-line NSCLC, DOM and ZIM in combination recently demonstrated a higher objective response rate (ORR) and longer median progression-free survival (PFS) than ZIM monotherapy. We hypothesize that DOM and ZIM in combination with chemotherapy will improve clinical outcomes in patients with untreated mNSCLC without *EGFR* or *ALK* aberrations regardless of PD-L1 expression. **Methods:** STAR-121 is a phase 3, global, open-label, randomized study to evaluate the safety and efficacy of DOM and ZIM plus chemotherapy vs pembro plus chemotherapy as first-line therapy for patients with mNSCLC with no *EGFR* or *ALK* aberrations or other known actionable gene alterations. Approximately 720 patients will be randomized into 3 groups (A, B, or C) in a 4:4:1 ratio and stratified by baseline PD-L1 tumor proportion score ($<$ 50% vs $\geq$50%), histology (squamous vs nonsquamous), and geographic region (East Asia vs non–East Asia). Eligible patients are aged $\geq$18 with untreated mNSCLC with no *EGFR* or *ALK* aberrations. Group A will receive DOM 1200 mg + ZIM 360 mg + platinum-doublet chemotherapy (PT), group B will receive pembro 200 mg + PT, and group C will receive ZIM 360 mg + PT. DOM, ZIM, and pembro will be administered until disease progression (PD) as assessed by blinded independent central review (BICR) per RECIST 1.1 or intolerable toxicity or for up to 35 doses. Study treatment will be administered IV every 3 weeks. PT will be chosen by investigators based on tumor histology and administered for the first 4 cycles, after which, pemetrexed can be continued for patients with nonsquamous histology until PD or intolerable toxicities. The primary endpoints are PFS by BICR and overall survival. Key secondary endpoints are ORR and duration of response by BICR, safety, and quality of life. This study is currently enrolling globally. Clinical trial information: NCT05502237. Research Sponsor: Gilead Sciences, Inc.

TPS9142 **Poster Session**

A phase 2 multi-arm study of magrolimab in combination with docetaxel in patients with locally advanced or metastatic solid tumors: ELEVATE Lung and UC.

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Background: Patients (pts) with solid tumors that progress on standard chemotherapy and/or immune checkpoint inhibitors experience limited efficacy with existing standard of care options. These pts have a significant unmet need, and novel agents that safely enhance treatment efficacy are needed. Magrolimab is a monoclonal antibody that blocks CD47, a "don't eat me" signal often overexpressed on solid tumor cells. Magrolimab blockade of CD47 induces macrophage-mediated phagocytosis of tumor cells and has shown preclinical activity and promising clinical efficacy in hematologic malignancies. Certain chemotherapies, including taxanes, enhance prophagocytic signals on tumor cells, leading to potential synergistic antitumor activity when combined with magrolimab. This study is evaluating the safety, tolerability, and efficacy of magrolimab with docetaxel in metastatic non-small cell lung cancer (mNSCLC), small cell lung cancer (mSCLC), and urothelial cancer (mUC). **Methods:** This open-label study includes a safety run-in and 3 phase 2 cohorts. Pts eligible for the safety run-in must have had $\geq$1 (mNSCLC, mSCLC) or 2 and not more than 3 (mUC) prior lines of systemic anticancer therapy in a locally advanced/metastatic setting and will be treated with magrolimab + docetaxel. In phase 2, pts must have either mNSCLC treated with platinum-based chemotherapy and/or an immune checkpoint inhibitor (ICI), mUC treated with prior systemic chemotherapy and/or an ICI, or mSCLC treated with platinum-based chemotherapy with or without an ICI in a locally advanced/metastatic setting. Pts refractory to prior taxane therapy or who have received a taxane within 12 months of study start are excluded. Pts who had prior treatment with CD47/SIRPα-targeting agents were also excluded. Magrolimab is administered intravenously (IV) as a 1-mg/kg priming dose on cycle 1 day 1 (C1 D1) to mitigate on-target anemia followed by 30 mg/kg on D8 and D15. Magrolimab 30 mg/kg is administered on C2 D1, D8, and D15 and 60 mg/kg on D1 for C3+. The recommended phase 2 dose (RP2D) is determined in the safety run-in, with de-escalation if prespecified dose-limiting toxicity criteria are met. Once the RP2D is determined, the phase 2 cohorts will follow the same dose schedule. Docetaxel 75 mg/m^2 is administered IV on D1 of each cycle. Reasons for treatment discontinuation may include unacceptable toxicity, disease progression, or pt/investigator choice to discontinue. The primary endpoints are incidence of adverse events by CTCAE v5.0 (safety run-in, phase 2) and investigator-assessed objective response rate by RECIST 1.1 (phase 2 cohorts). Secondary endpoints are magrolimab concentration vs time and antidrug antibodies (safety run-in, phase 2), progression-free survival and duration of response by RECIST 1.1, and overall survival (phase 2 cohorts). Planned enrollment is $\approx$116 pts. Clinical trial information: NCT04827576. Research Sponsor: Gilead Sciences, Inc.

TPS9143 **Poster Session**

ECOG-ACRIN LUNG-MAP S1900E substudy: A phase II study of sotorasib in participants (Pts) with previously treated stage IV or recurrent *KRAS* G12C mutant non-squamous (Non-sq) non-small cell lung cancer (NSCLC).

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Background: *KRAS* mutant NSCLC is further defined molecularly by specific mutation subtypes and co-mutations in tumor suppressor genes. Two targeted therapeutics, sotorasib and adagrasib, are currently approved for the treatment of previously treated advanced *KRAS* G12C mutant NSCLC. Sotorasib has also demonstrated superiority to docetaxel in the randomized phase III CodeBreaK 200 study (*de Langen et al Lancet. 2023 Feb 7 Epub*). The impact of co-mutations in tumor suppressors, including *TP53* and *STK11,* on the efficacy of first generation KRAS G12C inhibitors has been inconclusive. The S1900E substudy aims to prospectively understand, using rigorous biomarker testing/definitions, the impact of co-mutations on the clinical activity of sotorasib in pts with *KRAS* G12C mutant NSCLC. **Methods:** S1900E is a phase 2 open-label study of sotorasib in biomarker-defined cohorts for pts who have *KRAS* G12C stage IV/recurrent non-sq NSCLC, received at least one line of systemic treatment, and are naïve to KRAS G12C inhibitors. Pts are assigned to S1900E under the Lung-MAP screening protocol (NCT03851445) using FoundationOne F1CDx next generation sequencing assay on tissue (Foundation Medicine, Cambridge, MA). S1900E cohorts include: #1) Presence of *TP53* co-mutation AND Wild Type *STK11, KEAP1, NFE2L2, CUL3*; #2) Presence of *STK11* co-mutation AND Wild Type *TP53, KEAP1, NFE2L2, CUL3*; 3) All pts not eligible for Cohorts 1 and 2 (e.g. dual co-mutations in *STK11* and *TP53*; co-mutations in *KEAP1, NFE2L2, CUL3*, or others; or lack of any co-mutations). Pts with treated, clinically controlled, and asymptomatic brain metastases are eligible and with amendment 3 (Mar 20 2022), eligibility expanded to pts with asymptomatic untreated brain metastases. Sotorasib is dosed 960 mg oral daily. The primary objective is to evaluate the RECIST 1.1 response rate (ORR) per cohort. For cohorts 1 and 3, the target sample size is 40 eligible pts based on a design with 92% exact power to rule out a 14% ORR at the 1-sided 5% level, if the true ORR were 34%; $\geq$10 responses would rule out a 14% ORR. Cohort 2 has a target sample size of 25 eligible pts with 93% exact power to rule out a 14% ORR at the 1-sided 5% level, if the true ORR were 40%; $\geq$7 responses would rule out a 14% ORR. Secondary endpoints include PFS, OS, duration of response, and toxicity. Circulating tumor DNA is being collected at day 1 of cycle 1, 2, and 3 and at progression. Enrollment started April 2 2021 with conservative accrual targets met, currently with 72% enrolled (84/116) as of Feb 14 2023, including 37, 16, and 31 pts, in cohorts 1, 2, and 3, respectively. Clinical trial information: NCT04625647. Research Sponsor: Multiple Sources: NIH/NCI grants U10CA180888, U10CA180819, U10CA180821, U10CA180820, U10CA180868; and in part by Foundation for the National Institutes of Health; and Amgen, Inc.

TPS9144 **Poster Session**

KontRASt-02: A phase III trial investigating the efficacy and safety of the $KRAS^{G12C}$ inhibitor JDQ443 vs docetaxel in patients with previously treated, locally advanced or metastatic, *KRAS G12C*-mutated NSCLC.

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Background: Kirsten rat sarcoma viral oncogene homolog (*KRAS*) is the most frequent mutated oncogene in non-small cell lung cancer (NSCLC). *KRAS G12C* is the most common *KRAS* variant, present in ~13% of patients (pts) with non-squamous NSCLC. *KRAS G12C* mutations cause the accumulation of active, GTP-bound KRAS, which leads to activation of downstream pathways involved in cell proliferation and invasiveness. JDQ443 is a potent, structurally novel, selective $KRAS^{G12C}$ inhibitor that irreversibly traps $KRAS^{G12C}$ in its inactive, GDP-bound form. Data from the JDQ443 monotherapy arm of the first-in-human KontRASt-01 study demonstrated encouraging anti-tumor activity and an acceptable safety profile of JDQ443 in pts with previously treated, *KRAS G12C*-mutated, advanced NSCLC. For pts with advanced NSCLC who progress following first-line immunotherapy or doublet platinum-based chemotherapy, single agent docetaxel remains a standard option, although it presents modest activity and is generally poorly tolerated. In this context, alternative treatment options are needed to improve pt outcomes. **Methods:** KontRASt-02 (NCT05132075) is a global, Phase III, open-label, randomized, multicenter study evaluating JDQ443 as a monotherapy in comparison to docetaxel in pts with *KRAS G12C*-mutated, advanced NSCLC previously treated with PD-(L)1 inhibitors and platinum-based chemotherapy (either in combination or as sequential treatments). Approximately 360 pts stratified by ECOG performance status (0 vs 1 and 2) and prior therapy (platinum-based chemotherapy and immunotherapy combined vs sequential) will be randomized at 1:1 to receive 200 mg oral JDQ443 twice daily continuously or 75 mg/m^2 intravenous docetaxel once every 21 days. The primary endpoint of this study is progression-free survival (PFS) per Blinded Independent Review Committee (BIRC) according to RECIST version 1.1. The key secondary endpoint is overall survival (OS); other secondary endpoints include objective response rate, disease control rate, time to response, duration of response, PFS on subsequent therapy, safety of JDQ443 monotherapy, pt-reported outcomes, pharmacokinetics, time to deterioration of ECOG performance status, and safety in pts who crossover from docetaxel to JDQ443. Exploratory objectives include biomarker analyses aimed at investigating predictors of responsiveness to JDQ443. Pts randomized to docetaxel will be allowed to crossover to JDQ443 following confirmed disease progression per BIRC. To allow more pts to be treated with JDQ443, crossover will also be offered to all patients on docetaxel if the primary endpoint (PFS) is met. Treatment beyond progression will be allowed for pts receiving JDQ443 according to investigator judgement. The KontRASt-02 study is currently enrolling pts. Clinical trial information: NCT05132075. Research Sponsor: Novartis Pharmaceuticals Corporation.

TPS9145 **Poster Session**

REFINE-Lung: A multicentre phase III study to determine the optimal frequency of pembrolizumab in non-small cell lung cancer utilising a novel multi-arm design.

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Background: Pharmacological and clinical data suggest standard regimens for anti-PD1 agents nivo and pembro result in overtreatment. These agents have high target affinity, saturate PD1 at very low concentrations and maintain receptor occupancy for up to 30 wks following discontinuation. Clinical studies suggest no dose-response relationship in the wide range tested (0.1 – 10 mg/kg) and retrospective data suggest the efficacy of lower doses or longer administration frequency. Given their high costs and important implications for pt quality of life and toxicity, new approaches to optimise treatment regimens are required. However, conventional 2-arm non-inferiority designs require large numbers of patients, explore a single alternative to the standard of care and potentially require multiple trials to establish optimal parameters such as dose or frequency. Here we present a new multi-arm trial design to tackle this problem, implemented in the UK multicentre phase III REFINE-Lung study that aims to determine the optimal treatment frequency of pembro in NSCLC. Pts who are progression free after 6 months of standard therapy are randomised to 5 pembro frequency reduced arms (q6w, q9w, q12w, q15w and q18w). By evaluation of the frequency-response relationship, we will determine the longest frequency that is equivalent to standard of care within a pre-defined margin. **Methods:** The REFINE-Lung trial (NCT05085028) is a multicentre, randomised open-label, phase III trial in advanced NSCLC. REFINE-Lung utilises a novel Multi-Arm Multi-Stage Response Over Continuous Interventions (MAMS-ROCI) design to determine the optimal dose frequency of pembro. 1750 pts aged $\geq$18 and progression free at six months into 1st line pembro and planning to continue, will be enrolled from up to UK 35 hospital groups. Pts will be randomised across 5 arms to determine the optimal dose frequency. To assess safety, pts will initially be randomised 1:1 into q6w (control) and q12w arms. Interim analysis will be conducted once 37 progression free events are observed in the control arm. If PFS in the q12w arm is not significantly reduced, the remaining q9w, q15w and q18w arms will be opened. Pts who progress on a frequency reduced arm may re-escalate to q6w therapy. The primary objective is to determine the optimal continuing dose frequency of pembro, defined as the longest dose interval non-inferior to standard therapy using 2-year survival as the primary outcome. Secondary endpoints include OS, PFS, ORR, duration of response, adverse events, quality of life and cost effectiveness. An exploratory sub-study will explore fundamental aspects of cancer immunotherapy and develop novel biomarkers of response, resistance, toxicity and patient suitability for dose frequency de-escalation. Recruitment is ongoing and the trial is open at 16 centres at time of submission. Clinical trial information: NCT05085028. Research Sponsor: National Institute for Health Research; Lung Cancer Research Charity and North West London Pathology Consortium.

TPS9146 **Poster Session**

PRESERVE-003: Phase 3, two-stage, randomized study of ONC-392 versus docetaxel in metastatic non-small cell lung cancers that progressed on PD-1/PD-L1 inhibitors.

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Background: For NSCLC without driver mutation, the PD-1/PD-L1 inhibitor as the first-line (monotherapy or in combination with platinum-based doublet agents) or second-line therapy after chemotherapy significantly improved overall survival. However, there remain a significant number of patients who do not have response or have an initial response followed by disease progression to PD-1/PD-L1 inhibitor therapy. CTLA-4 is a proven immunotherapy target in solid tumor, unfortunately no monotherapeutic efficacy has been shown in NSCLC by marketed anti-CTLA-4 antibodies, including ipilimumab and tremelimumab. These anti-CTLA4 mAbs cause severe toxicity that prevents adequate dosing in cancer patients. In contrast, ONC-392 keeps high-level CTLA-4 on Treg cells through a recycling mechanism and makes Treg cells a better target for antibody-dependent cellular cytotoxicity, particularly in the tumor microenvironment where macrophages are more abundant. The selective elimination of Treg cells in the tumor microenvironment and maintenance of CTLA-4 expression in Treg cells in the peripheral tissues by ONC-392 form the cellular and molecular basis for more potent tumor rejection and low toxicity in animal studies. Our first in human studies have demonstrate safety and clinical activities of ONC-392 in patients with NSCLC and other solid tumors. **Methods:** This is a seamless 2-stage, randomized, open-label, active-controlled, Phase 3 study of ONC-392 for treatment of NSCLC patients who progressed on PD-1/PD-L1 inhibitor (NCT05671510). Approximately 600 patients will be enrolled. Stage I, the dose-confirmation stage, will assess the efficacy and safety of two ONC-392 dosing regimens (3 mg/kg Q3W and 6 mg/kg Q3W with 2 loading doses of 10 mg/kg Q3W) in comparison to docetaxel 75 mg/m2 Q3W. A total of 120 patients will be randomized 1:1:1 in Stage I into one of two ONC-392 dose cohorts or docetaxel cohort. An interim analysis will be conducted at the end of Stage I when 120 patients are enrolled. Stage 2 will start when ONC-392 dose is determined and approximately 480 patients will be randomized 1:1 to receive ONC-392 or docetaxel treatment. All enrolled patients who are randomized to the ONC-392 arms will receive ONC-392 at the randomized dose for up to 17 cycles in approximately 1 year or until discontinuation criteria are met. Patients who are randomized to the docetaxel arm will receive docetaxel 75 mg/m^2 Q3W until disease progression per RECIST 1.1. The primary endpoint is overall survival. The treatment effect will be estimated using a Cox Proportional Hazard model stratified by the randomization stratification factors to calculate the estimated hazard ratio and its 95% CIs. Kaplan-Meier (i.e., product-limit) estimates of median OS time will be presented by treatment arm with two-sided 95% CIs. The analyses will be based on the ITT Population. Clinical trial information: NCT05671510. Research Sponsor: OncoC4, Inc.

TPS9147 **Poster Session**

Phase 1 multicenter dose escalation and dose expansion study of antibody-drug conjugate (ADC) MYTX-011 in subjects with non-small cell lung cancer.

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Background: cMET is a receptor tyrosine kinase and proto-oncogene whose activity is upregulated across a wide range of cancers. In NSCLC, expression of cMET is upregulated by DNA amplification (2% to 5%), exon 14 skipping mutations (2% to 4%), and overexpression (30% to 60%). In NSCLC, cMET upregulation has also been demonstrated to be a resistance mechanism for several approved EGFR-targeted kinase inhibitors, and this may limit their effectiveness. Despite the approval of MET tyrosine kinase inhibitors, almost half of patients do not respond to these inhibitors and resistance is inevitable. MYTX-011 is an ADC incorporating the clinically validated vcMMAE linker-payload conjugated to a novel, pH-dependent anti-cMET antibody. In preclinical studies, MYTX-011, compared to a surrogate of an advanced clinical stage cMET ADC, showed markedly higher ($>$ 3 fold) internalization and increased cytotoxicity in cMET+ tumor cells *in vitro*, which translates to greater ($\geq$3 fold) efficacy in high or moderate c-Met+ xenograft models *in vivo*. PK and toxicity studies revealed that MYTX-011 exhibited favorable PK characteristics, and a toxicity profile similar to previously described MMAE-based ADCs. **Methods:** MYTX-011-01 (ClinicalTrials.gov Identifier: NCT05652868) is a first-in-human Phase 1 dose escalation and dose expansion study. MYTX-011 will be administered intravenously every 21 days for a maximum of 2 years. Part 1 (dose escalation) will assess the safety and tolerability of MYTX-011 in patients with advanced NSCLC and identify the recommended Phase 2 dose (RP2D). Part 2 (dose expansion) will include subjects with NSCLC with cMET overexpression or *MET* amplification/exon 14 skipping mutations. In Part 1, subjects will be enrolled to evaluate the safety of escalating doses of MYTX-011 as a single-agent and to establish the RP2D and/or MTD. The dose escalation scheme is based on a 3-subject cohort minimum Bayesian Optimal Interval (BOIN) design. The RP2D will be selected as a biologically active dose at or below the MTD (or the highest dose tested if an MTD is not identified during the study) and will be informed by safety, tolerability, pharmacokinetic data, and preliminary anti-tumor activity of MYTX-011 based on RECIST 1.1. Part 2 of the study will be initiated once the RP2D has been determined and will enroll subjects into different cohorts based on cMET IHC positivity cutoff and/or presence of *MET* genetic alterations (*MET* amplification or exon 14 skipping). All cohorts are defined to explore preliminary antitumor activity in populations with different thresholds of cMET positivity that were selected based on data for cMET expression and efficacy observed with MYTX-011 in preclinical models, published data for responses to cMET targeting agents, and on the prevalence of subject tumors with different expression levels. Enrollment in the MYTX-011-01 study is ongoing. Clinical trial information: NCT05652868. Research Sponsor: Mythic Therapeutics.

TPS9148 **Poster Session**

ARC-10: A phase 3 study to evaluate zimberelimab + domvanalimab versus pembrolizumab in front-line, PD-L1-high, locally advanced or metastatic non–small-cell lung cancer.

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Background: Despite improvements in the management of locally advanced or metastatic non–small cell lung cancer (NSCLC) from programmed cell death/ligand protein 1 (PD-[L]1) inhibition, there remains an unmet need for improved treatment options. PD-L1 expression is a known biomarker of response to anti–PD-L1 therapies in metastatic NSCLC. The combination of PD-1 inhibition with inhibition of the immunosuppressive T cell Immunoglobulin and ITIM domain (TIGIT) pathway is associated with improved response and prolonged progression-free survival in patients with advanced NSCLC. Domvanalimab (dom) is an Fc-silent humanized IgG1 monoclonal antibody (mAb) that blocks TIGIT, thereby reducing immunosuppression of T/natural killer (NK) cells and promoting antitumor activity. Zimberelimab (zim) is an mAb that binds to PD-1 on T/NK cells, preventing PD-L1-mediated immunosuppressive effects and resulting in tumor cell death. This phase 3 study will investigate the efficacy and safety of combination therapy with dom + zim compared with pembrolizumab monotherapy in patients with PD-L1-high NSCLC. **Methods:** ARC-10 (NCT04736173) is a global, phase 3, randomized, multicenter, open-label study. Eligible patients are adults with histologically confirmed, treatment-naive, locally advanced or metastatic, squamous or non-squamous NSCLC with ≥1 measurable lesion(s) per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, high expression of PD-L1 (tumor cells [TC] ≥50%), and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Patients must not have genomic tumor aberrations for which targeted therapies are approved and available (eg, *EGFR*, *ALK*, *ROS*, *BRAF*, *NTRK*). Approximately 600 patients will be randomized 1:1 to receive combination therapy with dom + zim (dom 1200 mg intravenous [IV] once every 3 weeks [Q3W] + zim 360 mg IV Q3W) or pembrolizumab monotherapy (200 mg IV Q3W) for 21-day cycles until disease progression, intolerance, or a maximum of 35 cycles. Randomization will be stratified by ECOG performance status (0 vs 1), geographical region (Asia vs non-Asia), and histology (squamous vs non-squamous). The primary efficacy endpoint is overall survival. Secondary efficacy endpoints include blinded independent central review of progression-free survival and confirmed overall response rate according to RECIST v1.1. Safety endpoints include the presence of treatment-emergent adverse events and laboratory parameters. Health-related quality of life will be assessed by measuring the time to first symptom deterioration in the NSCLC-Symptom Assessment Questionnaire total score. Study recruitment is planned in Asia, North and South America, Africa, and Europe. Clinical trial information: NCT04736173. Research Sponsor: Arcus Biosciences.

TPS9149 **Poster Session**

Phase 2 study of telisotuzumab vedotin (Teliso-V) monotherapy in patients with previously untreated *MET*-amplified locally advanced/metastatic non-squamous non-small cell lung cancer (NSQ NSCLC).

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Background: Teliso-V is a first-in-class anti–c-Met antibody-drug conjugate composed of the monoclonal antibody telisotuzumab (ABT-700), a cleavable valine-citrulline (dipeptide) linker, and cytotoxic monomethylauristatin E (MMAE; potent microtubule polymerization inhibitor). Direct MMAE payload delivery to c-Met protein overexpressing (OE) cells enables Teliso-V to work independently of c-Met signaling. In NSCLC, while c-Met OE is more common than *MET* gene amplification (Amp), about 90% of *MET* Amp tumors will also be c-Met OE. In an ongoing phase 2 trial, Teliso-V showed encouraging efficacy and acceptable safety in previously treated c-Met OE NSQ NSCLC population (Camidge et al. JCO.2022.40.16_suppl.9016). From this study, a retrospective analysis of 10 patients with *MET* Amp (≥1.8 *MET* gene to chromosome 7 copy number ratio by fluorescence in situ hybridization [FISH]) demonstrated an objective response rate (ORR) of 80%. Described here is an ongoing phase 2 study evaluating efficacy and safety of Teliso-V monotherapy in patients with previously untreated *MET* Amp locally advanced/metastatic NSQ NSCLC. **Methods:** This is a phase 2, single-arm, open-label, global study (NCT05513703). Eligible patients (≥18 years) have histologically documented advanced/metastatic NSQ NSCLC, measurable disease by RECIST v1.1, confirmed *MET* Amp determined centrally by FISH or locally by FISH, tissue next-generation sequencing (NGS), or plasma NGS using sponsor-approved assays. Additional eligibility criteria include Eastern Cooperative Oncology Group performance status 0 or 1, no alterations in *EGFR*, *ALK*, *ROS1*, or *BRAF* that predict sensitivity to targeted therapy, no prior systemic therapy for locally advanced or metastatic NSCLC, no prior c-Met–targeted antibody therapy. Teliso-V is administered intravenously at 1.9 mg/kg every 2 weeks until disease progression, intolerable toxicity, or other study drug discontinuation criteria are met. Primary endpoint is ORR assessed by independent central review (ICR). Secondary endpoints include duration of response and disease control rate, progression-free survival per ICR, overall survival, patient-reported outcomes (PROs). Tumor assessments (per RECIST v1.1) are performed at baseline and approx. every 6 (year 1), 8 (year 2), and 12 weeks (year 3 and beyond). PROs are assessed through validated questionnaires (EORTC QLQ-LC13, EORTC QLQ-C30, EQ-5D-5L). Safety and tolerability are evaluated by adverse events, physical examinations, laboratory data, and vital signs. Pharmacokinetic and biomarker evaluations may be used for exploratory analyses. The trial intends to enroll approx. 70 efficacy-evaluable patients, with interim analyses planned after 20 and 50 patients are able to be followed for ≥6 months. The study was open to enrollment as of Nov 2022. Clinical trial information: NCT05513703. Research Sponsor: AbbVie Inc.

TPS9150 **Poster Session**

Circulating tumor DNA to guide furmonertinib monotherapy or combination therapy in advanced EGFR mutant non-small cell lung cancer (NSCLC): A randomized, open-label, multicenter study (FOCUS-C).

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Background: Detection of EGFR ctDNA after several weeks EGFR-TKIs treatment was an effective method to identify prognosis of advanced EGFR mutant NSCLC patients. Patients with uncleared EGFR ctDNA had shorter progression-free survival (PFS) (*Mack PC et al; CCR 2022*). However, whether they can benefit from EGFR-TKI combination therapy has not been reported. Furmonertinib (AST2818), a potent, orally bioavailable, highly brain penetrant, third generation EGFR-TKI with unique chemical structure designed to improve potency and specificity, showed superior efficacy compared with gefitinib as first-line therapy in EGFR mutant NSCLC along with an acceptable safety profile without new signals (*Shi, YK et al.; Lancet Respir Med 2022*). We hypothesized that monitoring clearance of EGFR ctDNA in blood could rationally guide subsequent monotherapy or combination therapy with furmonertinib and will improve outcomes in patients with uncleared EGFR ctDNA. **Methods:** The FOCUS-C study is a multicenter, open-label, randomized study. Patients who are aged 18 years or older and have histologically confirmed, locally advanced or metastatic, stage IIIB, IIIC, or IV unresectable NSCLC with EGFR exon 19 deletions (19Del) or exon 21 Leu858Arg mutation (L858R) on tissue biopsy and plasma will be treated with furmonertinib. Eligible patients with uncleared EGFR 19Del or L858R ctDNA after 3 weeks furmonertinib treatment will be stratified according to EGFR mutation (19Del or L858R), central nervous system metastases (with or without) and detectable accompanying gene aberrances in plasma (with or without) and randomly assigned (2: 2: 1) to receive furmonertinib or furmonertinib plus chemotherapy (pemetrexed and carboplatin for 4 cycles followed by maintenance pemetrexed) or furmonertinib plus chemotherapy plus bevacizumab (pemetrexed, carboplatin and bevacizumab for 4 cycles followed by maintenance pemetrexed and bevacizumab) in 21-day cycles until disease progression, the occurrence of intolerable toxicities, withdrawal of consent, or other discontinuation reasons judged by the investigators. The primary endpoint is PFS between furmonertinib plus chemotherapy versus furmonertinib alone. Secondary endpoints include PFS, objective response rate, duration of response, disease control rate, overall survival and safety. Several exploratory endpoints will also be evaluated based on ctDNA detection by next-generation sequencing (Genecast, Wuxi, China). The study is enrolling. 34 patients had been enrolled till 2nd Feb 2023. Clinical trial information: NCT05334277. Research Sponsor: Y-2021AST/zd-0053/Beijing Xisike Clinical Oncology Research Foundation, CSCO-Leading Oncology Research Fund.; Shanghai Allist Pharmaceuticals Co., Ltd, Shanghai, China. Genecast Biotechnology Co., Ltd, Wuxi, China. Qilu Pharmaceutical Co., Ltd, Jinan, China.

TPS9151 **Poster Session**

LUNG-IST-127: A pilot phase II study of maintenance cabozantinib plus pembrolizumab for patients with metastatic squamous non-small cell lung cancer (sqNSCLC) with disease control following induction therapy.

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Background: First-line combination chemotherapy with pembrolizumab followed by maintenance pembrolizumab is the standard of care treatment for patients with metastatic sqNSCLC. This was established by the phase III KEYNOTE-407 trial, which demonstrated a median progression-free survival (PFS) of 6.4 months in the experimental arm. Despite these advances, there remains a need to continue to improve upon survival outcomes for these patients. Cabozantinib is a small-molecule inhibitor of multiple tyrosine kinsases including MET, VEGFRs, AXL, RET, and ROS, which are receptors involved in tumor cell-proliferation, angiogenesis, and immune cell regulation. Preclinical studies have demonstrated the ability of cabozantinib to modulate both adaptive and innate immune cells and to exhibit synergistic activity when used in combination with immune checkpoint inhibitors. We hypothesize that cabozantinib in combination with pembrolizumab in the maintenance phase of first-line treatment of metastatic sqNSCLC will prolong median PFS with a tolerable toxicity profile.
Methods: LUNG-IST 127 is a pilot phase II, single-arm clinical trial of maintenance cabozantinib in combination with pembrolizumab for patients with metastatic sqNSCLC who achieved disease control following standard 1L induction therapy with chemotherapy and pembrolizumab. Thirty-six patients will be enrolled at 2 US sites to receive first-line induction therapy with carboplatin, nab-paclitaxel or paclitaxel, and pembrolizumab for four cycles. After induction therapy, those who have achieved disease control based on re-staging imaging will continue onto maintenance therapy with cabozantinib 40mg PO daily in combination with pembrolizumab 200mg IV every 3 weeks. The primary endpoint is PFS estimated by Kaplan-Meier methods with associated 95% confidence intervals. Based on an exploratory power analysis using an elevated one-sided alpha level of 0.40, we hypothesize that the proposed therapy will prolong median PFS from 6.4 to 9 months. Key secondary endpoints include overall survival (OS), overall response rate (ORR), and characterizing the safety and tolerability of cabozantinib in combination with pembrolizumab. Quality of life will also be measured with the EORTC QLQ-C30. Correlative endpoints include characterizing cfDNA from biofluids and assessing the change in circulating immune cells in different phases of treatment in association with PFS and OS. This trial would be the first to address whether there is clinical benefit in utilizing combination cabozantinib and pembrolizumab in the maintenance phase of treatment in metastatic sqNSCLC. Clinical trial information: NCT05613413. Research Sponsor: Exelixis.

TPS9152 **Poster Session**

A phase II multi-cohort single-arm study of tiragolumab with atezolizumab plus bevacizumab in previously treated advanced non-squamous non–small-cell lung cancer.

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Background: Checkpoint inhibitor immunotherapy (CPI) offers durable, immune-mediated, anti-tumor responses to a subset of patients (pts) with advanced non-small cell lung cancer (NSCLC), but not all derive meaningful benefit. Two clinical unmet needs where CPI has fallen short include *EGFR*-mutated NSCLC, where CPI is minimally effective, and NSCLC with intrinsic or acquired resistance to currently available CPI. Novel combination strategies have shown promise. Two agents that have demonstrated synergy with the anti-PD-L1 CPI atezolizumab in NSCLC are bevacizumab, a vascular endothelial growth factor (VEGF)-blocking antibody, and tiragolumab, a T-cell immunoglobulin and ITIM domain (TIGIT) immune checkpoint-blocking antibody. This multi-cohort phase II trial seeks to evaluate the efficacy of tiragolumab with atezolizumab plus bevacizumab in 2 CPI-resistant cohorts - *EGFR*-wild type, CPI-refractory advanced NSCLC (cohort A) and *EGFR*-mutated, CPI-naïve advanced NSCLC (cohort B) - incorporating novel genomic and immunologic analyses to deliver mechanistic insight into the biology of CPI-resistance in NSCLC. **Methods:** This open-label, phase II study has two cohorts. Cohort A includes pts with advanced PD-L1+ (TPS $\geq$ 1%), *EGFR/ALK/ROS1* wild type NSCLC with progression on prior anti-PD(L)1-based CPI therapy. Cohort B includes pts with targeted therapy-refractory *EGFR*-mutated NSCLC who are CPI-naïve. Pts must have measurable disease and those with symptomatic and/or untreated brain metastases are excluded. Pts in both arms will receive tiragolumab 600mg IV with atezolizumab 1200mg IV and bevacizumab 15mg/kg IV every 3 weeks until progressive disease or unacceptable toxicity. The primary efficacy endpoint will be assessed separately in each cohort by investigator-assessed objective response rate (ORR) according to RECIST v1.1. Each cohort utilizes a Simon 2-stage design in which a null ORR of 4% is tested against a one-sided alternative of 20%. A sample size of 21 pts/cohort provides 80% power with a one-sided type 1 error rate of 5% to determine a true ORR of 20%. Secondary efficacy endpoints include: duration of response, progression-free survival (PFS), 6-month PFS, overall survival. Blood and tumor specimens will be acquired pre- and on-treatment. Correlative analyses to illuminate the biology of CPI resistance will include multiplex imaging mass cytometry of tumor tissue. In addition, whole exome sequencing, T-cell receptor sequencing, and MANAFEST neoantigen prediction will be used to identify neoantigen-specific T-cells and track these temporally (during/post treatment) and spatially (across biologic compartments). The study is activated and both cohorts are accruing simultaneously with enrollment ongoing. Clinical trial information: NCT04958811. Research Sponsor: Georgetown Lombardi Comprehensive Cancer Center; LUNGevity Foundation; MedStar Health Research Institute; Genentech/Roche.

TPS9153 **Poster Session**

Aumolertinib with chemotherapy or alone compared with osimertinib in patients with EGFR-mutant non–small-cell lung cancer (TREBLE).

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Background: Aumolertinib is a novel third-generation (3G) epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI). Safety and efficacy of aumolertinib have been demonstrated in patients with *EGFR*-mutated locally advanced or metastatic (LA/m) NSCLC. (Lu, 2021; Lu, 2022) A phase 3 study in these patients in the first-line setting showed a significant improvement in progression-free survival (PFS) for aumolertinib vs gefitinib (median 19.3 months versus 9.9 months; $P < 0.0001$). Aumolertinib was generally well-tolerated. (Lu, 2022) Aumolertinib is approved in China for patients with LA/m NSCLC who have an *EGFR* T790M resistance mutation upon disease progression and for treatment naïve patients with *EGFR*-mutated NSCLC. Studies evaluating first-generation EGFR-TKI + chemotherapy (chemo) showed improved PFS in select patient populations. (Hosomi, 2019) It is unclear if the addition of chemo to a 3G EGFR-TKI will improve PFS in patients with *EGFR*-mutated LA/m NSCLC. As the addition of chemo to a 3G EGFR-TKI may prove warranted, there is a need to understand the relative efficacy and safety in the diversity of patients encountered in routine clinical practice. (Tanaka, 2021). **Methods:** This is a randomized, multi-regional, phase 3 clinical trial comparing aumolertinib + chemo or aumolertinib monotherapy with osimertinib monotherapy. Patients are eligible if they have stage IIIB, IVA, or IVB NSCLC; harbor ex19del or L858R *EGFR* mutations alone or with other *EGFR* mutations; and have an ECOG PS of $\leq$2. Patients are ineligible if they received prior systemic therapy for mNSCLC or are a candidate for curative intent therapy. Eligible patients will be randomized 2:2:1 and stratified by mutation status (ex19del or L858R), ECOG PS (0 vs 1/2), and race (White vs Asian vs other races combined). Anticipated enrollment is 500 patients; 200 to receive aumolertinib + chemo (110 mg PO QD aumolertinib + investigator's choice chemo), 200 to receive osimertinib (80 mg PO QD), and 100 to receive aumolertinib (110 mg PO QD). The primary endpoint is PFS, by blinded independent review committee (BICR) per RECIST 1.1, for aumolertinib + chemo vs osimertinib. Overall survival (OS) is a key secondary endpoint for aumolertinib + chemo vs osimertinib. Additional efficacy endpoints will be assessed for aumolertinib + chemo vs osimertinib and aumolertinib vs osimertinib, as well as safety and patient reported outcomes. Exploratory endpoints include characterizing mechanisms of acquired resistance across all arms, CNS efficacy, and exposure-response relationship. Enrollment began in July 2022. The study is currently recruiting and will include approximately 200 sites globally. The study design will provide a power of 80% at a 2-sided Type I error of 0.05 for the primary endpoint. If the primary endpoint is statistically significant, a sequential test method will be used to evaluate OS. Clinical trial information: NCT05493501. Research Sponsor: EQRx.

TPS9154 **Poster Session**

Phase 1b/2a safety and tolerability study of bemcentinib (BEM) with pembrolizumab/carboplatin/pemetrexed in first line (1L) advanced or metastatic non-squamous non-small cell lung cancer (NSCLC) without/with a STK11 mutation.

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Background: The combination of platinum, pemetrexed, and pembrolizumab (CIT) has become the standard of care in 1L non–oncogene addicted NSCLC. Despite an initial improvement in response rate and survival, the 5-year survival of NSCLC remains approximately 20-30%, due to the emergence of primary and acquired resistance. Additionally, the presence of brain metastases occurs in ~30-50% of NSCLC patients and confers a poor prognosis. Among the currently non-actionable mutations, STK11/LKB1 mutations (STK11m) are common (~20%) in NSCLC. Recent evidence suggests that STK11m NSCLC patients have a minimal response to checkpoint inhibitors and to chemo-immunotherapy in the first line setting. STK11m tumors are characterized by an immune-suppressed phenotype which is highly associated with AXL signalling. BEM, a first-in-class, oral, selective AXL inhibitor, has demonstrated the ability to prevent chemoresistance, re-sensitize STK11m NSCLC tumors to pembrolizumab, and enhance efficacy of CIT in preclinical lung models. Moreover, following oral administration, BEM readily distributes in brain tumour tissue in recurrent glioblastoma patients, with a 25.9 mean ratio of drug concentration in brain tissue to plasma. Therefore, the addition of BEM to CIT has the potential to improve 1L treatment outcomes in NSCLC overall and particularly in STK11m tumors. **Methods:** This is an open-label, multi-center, phase 1b/2a study to assess the safety, tolerability, and preliminary anti-tumor activity of BEM + CIT as 1L treatment in patients with advanced (Stage IIIb/IIIc) or metastatic (Stage IV) non-squamous NSCLC without actionable mutations. Patients with stable brain metastases are eligible to participate. Phase 1b follows a 3+3 design and will explore CIT in combination with one of 3 BEM dose levels: Cohort 1 = 75mg; Cohort 2 = 100 mg; or Cohort 3 = 150 mg. BEM is administered orally once/day on Day 1 of each 21-day treatment cycle. After 4 cycles of CIT + BEM, maintenance with BEM + pemetrexed + pembrolizumab is administered for up to 2 years. An independent data safety monitoring board will assess the safety data at the end of the dose-limiting toxicity period (the first 21 days of treatment for each patient, i.e. cycle 1) of each cohort and will recommend the BEM dose for the phase 2a expansion. In the phase 2a, up to 40 patients harboring a STK11m (regardless of their co-mutational status), in the absence of driver mutations will be enrolled. The study will include extensive co-mutational analyses via next-generation sequencing to identify potential sub-groups of patients deriving particular benefit. The trial is open to patient enrolment in phase1b in the US; recruitment for phase 2a is planned to open in Q2 2023 in Europe and US. *EudraCT 2019-003806-28/NA/124645*. Clinical trial information: NCT05469178. Research Sponsor: BerGenBio ASA.

TPS9155 **Poster Session**

VELOCITY-Lung: A phase (Ph) 2 study evaluating safety and efficacy of domvanalimab (dom) + zimberelimab (zim) + sacituzumab govitecan (SG), or etrumadenant (etruma) + dom + zim, or etruma + zim in patients (pts) with treatment-naïve metastatic non-small cell lung cancer (mNSCLC).

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Background: Current standard of care (SOC) for pts with mNSCLC lacking an actionable mutation includes checkpoint inhibitor (CPI), platinum (PT)-based therapy, or a combination of the two, but is associated with poor outcomes. SG is a Trop-2–directed antibody-drug conjugate. SG monotherapy resulted in a 17% objective response rate (ORR), with a manageable safety profile in pts with mNSCLC who had multiple prior therapies (Heist RS, et al. *J Clin Oncol*. 2017), and a Ph 2 study is currently ongoing assessing SG+CPI±PT-based therapy (NCT05186974) in treatment-naïve mNSCLC. Etruma (dual adenosine receptor antagonist), dom (anti-TIGIT), and zim (anti–PD-1) are under clinical investigation for antitumor activity. Substudy-01 is part of the VELOCITY-Lung Ph 2 platform study evaluating novel treatment combinations in pts with treatment-naïve mNSCLC. **Methods:** VELOCITY-Lung (NCT05633667) is an open-label, multicenter, randomized, Ph 2 platform study. Key eligibility criteria for substudy-01 include age ≥18 y; pathologically documented stage IV NSCLC at time of study entry without *EGFR*, *ALK*, or other actionable genomic alterations; no prior systemic treatment for mNSCLC; ECOG PS 0-1; any PD-L1 status. Pts previously treated in the (neo)adjuvant setting may be included if therapy was completed ≥12 mo before study drug initiation. Current treatment arms in the preliminary stage are Arm A: dom+zim+SG; Arm B: etruma+dom+zim; Arm C: etruma+zim. Dosing will be as follows: etruma 150 mg po once daily, dom 1200 mg IV q3wk, zim 360 mg IV q3wk, SG 10 mg/kg IV on D1 and D8 of a 21-D cycle. Randomization will be stratified by histology and baseline PD-L1 status (central testing; ≥50% vs < 50%). Pts are randomized equally between treatment arms (arms can be added to evaluate additional novel combinations) in the preliminary stage. Once the expansion stage opens, pts will be randomized based on the number of experimental arms in the expansion stage, the comparator arm, and any newly added preliminary stage treatment arms. Pts will continue to receive treatment until progressive disease, death, unacceptable toxicity, or initiation of a subsequent anticancer therapy. The primary endpoint is ORR assessed by investigator per RECIST v1.1. Secondary endpoints include progression-free survival, duration of response, overall survival, and safety. During the preliminary stage, efficacy will be compared with historical SOC; during the expansion stage, efficacy will be compared with an active comparator arm within the study. Depending on the number of arms being tested in the expansion stage, this study plans to enroll ~69 to 289 patients globally and is open for recruitment. Clinical trial information: NCT05633667. Research Sponsor: Gilead Sciences, Inc.

TPS9156 **Poster Session**

A phase 1 study to assess BDTX-1535, an oral EGFR inhibitor, in patients with glioblastoma or non–small-cell lung cancer.

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Background: The epidermal growth factor receptor (EGFR) is a potent oncogene commonly altered in many cancers, including glioblastoma (GBM) and non-small cell lung cancer (NSCLC). EGFR tyrosine kinase activity driven by common EGFR mutations can be inhibited by small molecules, however, resistance to available agents may be driven by mutations in the EGFR active kinase site or other regions. BDTX-1535 is an orally available, highly potent, selective, irreversible inhibitor of EGFR mutations, including extracellular variants and amplifications commonly expressed in GBM and inhibits the common and uncommon EGFR mutations found in NSCLC, including the C797S mutation acquired following 3rd generation EGFR inhibitor therapy. Preclinical data demonstrated the ability of BDTX-1535 to cross the blood-brain barrier and produce sustained inhibition of EGFR signaling. Preclinical studies suggest that BDTX-1535 has the potential to be clinically active in suppressing tumor growth in patients with GBM and NSCLC with or without CNS metastases, including a potential survival benefit. **Methods:** BDTX-1535-101 (NCT05256290) is Phase 1, open-label, multicenter study to assess the safety, tolerability, PK, CNS activity, and preliminary antitumor activity of BDTX-1535 in recurrent GBM (rGBM) or locally advanced or metastatic NSCLC with or without CNS disease. The Monotherapy Dose Escalation portion will evaluate BDTX-1535 in patients with either rGBM expressing EGFR alterations or locally advanced/metastatic NSCLC harboring sensitizing EGFR mutations with or without CNS disease. Patients with rGBM must have previously received available standard therapy of surgical resection followed by chemoradiotherapy and/or temozolomide (TMZ). Eligible NSCLC patients must have EGFR mutated NSCLC that has progressed following standard of care EGFR inhibitor therapy. Once a provisional recommended Phase 2 dose (RP2D) has been established, BDTX-1535 monotherapy will be explored in the following Dose Expansion cohorts to further evaluate safety, PK, and preliminary assessment of efficacy: 1) rGBM with confirmed EGFR alterations, 2) NSCLC with uncommon EGFR mutations following EGFR inhibitor therapy; 3) NSCLC with acquired EGFR resistance mutation following a 3rd generation EGFR inhibitor in 1L setting. NSCLC patients may enroll with or without CNS metastases and must not be known to express excluded resistance mutations such as EGFR T790M or MET. BDTX-1535 will also be studied in combination with TMZ to assess safety, tolerability, and a recommended combination dose for the treatment of patients with rGBM harboring EGFR mutations or variants. Enrollment was initiated in 2022 and dose escalation is ongoing. Dose Expansion cohorts are expected to open in 2023. For additional information, please contact BDTX_1535_101_Study@bdtx.com. Clinical trial information: NCT05256290. Research Sponsor: Black Diamond Therapeutics.

TPS9158 **Poster Session**

A phase II trial of JDQ443 in *KRAS G12C*-mutated NSCLC with PD-L1 expression <1% or PD-L1 expression ≥1% and an *STK11* co-mutation.

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Background: Kirsten rat sarcoma viral oncogene homolog (*KRAS*) is the most frequently mutated oncogene in non-small cell lung cancer (NSCLC). *KRAS G12C*, the most frequent *KRAS* variant, is found in ~13% of patients (pts) with NSCLC. KRAS is a GTPase that regulates cell signaling pathways necessary for proliferation, differentiation, and survival. *KRAS* mutation reduces the intrinsic GTPase activity of the enzyme, allowing for the accumulation of active, GTP-bound KRAS and hyperactivation of downstream signaling, driving tumorigenesis. JDQ443 is a potent, selective $KRAS^{G12C}$ inhibitor that irreversibly traps $KRAS^{G12C}$ in its inactive, GDP bound state and blocks downstream signaling. In preliminary data from the Phase Ib part of the KontRASt-01 study (NCT04699188), JDQ443 showed promising antitumor activity and an acceptable safety profile in previously treated pts with *KRAS G12C*-mutated advanced NSCLC. Pts with *KRAS G12C*-mutated NSCLC currently receive the same first-line (1L) treatment as those without driver mutations, consisting of immunotherapy alone or combined with chemotherapy; however, ~30% of pts with NSCLC present with programmed death-ligand 1 (PD-L1) expression <1%, and ~10–20% of pts harbor an *STK11* mutation, both indicators of poor response to immunotherapy. Therefore, alternative 1L treatment options are needed for these pts. Of note, PD-L1 expression and *STK11* mutation do not affect responsiveness to $KRAS^{G12C}$ inhibitors, raising interest in the evaluation of these targeted therapies as 1L alternatives to immunotherapy for pts with *KRAS G12C*-mutated NSCLC. **Methods:** KontRASt-06 (NCT05445843) is an open-label, Phase II, single-arm, multicenter study evaluating JDQ443 monotherapy (200 mg JDQ443 twice daily in 21-day cycles) as a 1L treatment for 2 cohorts of adult pts with locally advanced or metastatic, *KRAS G12C*-mutated NSCLC. Cohort A (n=90) includes pts whose tumors have PD-L1 expression <1%, regardless of *STK11* mutation status, while Cohort B (n=30) includes pts whose tumors have PD-L1 expression ≥1% and an *STK11* co-mutation. Local testing for PD-L1 status and *KRAS* and *STK11* mutations is accepted; *KRAS* and *STK11* mutations may be assessed in blood samples. A tissue sample is required for retrospective biomarker status confirmation and exploratory study. The study is currently enrolling pts into both cohorts. The primary endpoint is the overall response rate (ORR) per RECIST version 1.1, assessed by a blinded independent review committee, in Cohort A. Key secondary endpoints are ORR in Cohort B and duration of response in both cohorts. Other secondary endpoints include progression-free survival, overall survival, safety, pharmacokinetics, and pt-reported outcomes. A comprehensive biomarker strategy aims to investigate predictors of treatment response and resistance in the study population. © 2023 American Association for Cancer Research®. Reused with permission. Clinical trial information: NCT05445843. Research Sponsor: Novartis Pharmaceuticals Corporation.

TPS9159 **Poster Session**

A first-in-human, open-label, dose escalation and expansion study of orally administered NX-019 in patients with advanced EGFR mutant cancer.

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Background: CNS involvement, brain metastases and/or leptomeningeal disease, is common in patients with EGFR mutant NSCLC and occurs in 25-50% of patient's journeys. Despite the activity and increased CNS penetration of later generation EGFR inhibitors, management of CNS disease remains a clinical challenge. NX-019 is a broad-spectrum EGFR inhibitor targeting both common and rare mutations including EGFR ex20ins, G719S, and L861Q. NX-019 exhibits selective activity towards mutant vs. wt. EGFR in preclinical studies. Substantial CNS exposure has been demonstrated in animal models, as well as potent anti-tumor activity toward intracranial xenografts with prolonged inhibition of EGFR signaling. Similar drug levels compared to plasma were measured in the brains of rats and mice. NX-019 was readily detectable in the CSF of cynomolgus monkeys, dogs and rats at concentrations similar to the estimated plasma free fraction. **Methods:** NT019-101 is a first-in-human, international, open-label study designed to evaluate single-agent NX-019 in patients with EGFR-mutant, locally advanced or metastatic NSCLC that has progressed following prior treatment. Patients with ECOG performance status 0–2 and EGFR mutant cancers including stable, asymptomatic brain metastases are eligible for Dose Escalation. Patients with known *EGFR* C797S mutations and secondary drivers, e.g., MET amplification and RET fusions, are excluded. Primary endpoints are to determine recommended phase 2 dose (RP2D), maximum tolerated dose (MTD), safety and tolerability (part 1), and to evaluate antitumor activity at the RP2D by RECIST v1.1 and RANO-BM (part 2). Secondary endpoints are to evaluate pharmacokinetics (PK) and antitumor activity by RECIST v1.1 (part 1) and PK, safety, tolerability, and CNS antitumor activity (part 2). Dose escalation will utilize a 3+3 design with up to 6 patients per cohort in part 1. Part 2 will enroll patients in 5 cohorts (n = 10 or 29 each), including patients with NSCLC who have (1) new or progressing CNS metastases including leptomeningeal disease after treatment with osimertinib, (2) active CNS disease and ex20ins mutations, (3) ex20ins mutations without CNS disease and (4) other rare mutations, based on a Simon 2-stage design. First patient was treated in October 2022 and enrollment is ongoing. The study is planned for approximately 35 centers in North America and Asia-Pacific region. Clinical trial information: NCT05514496. Research Sponsor: Nalo Therapeutics Inc.

TPS9160 **Poster Session**

Osimertinib then chemotherapy in EGFR-mutated lung cancer with osimertinib third-line rechallenge (OCELOT).

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Background: The results of the FLAURA study established osimertinib as the new first-line standard of care for patients with the two 'common' types of epidermal growth factor receptor mutation-positive (EGFR+) advanced non-small-cell lung cancer (aNSCLC). Second-line (2L) treatment is typically platinum pemetrexed chemotherapy and the standard third-line (3L) treatment is docetaxel throughout much of the globe, which has a modest response rate of 7 – 15%. Previously, when first generation (1G) EGFR tyrosine kinase inhibitor (TKIs) were standard of care in the first-line setting, a number of prospective and retrospective studies examined 3L rechallenge with the same 1G EGFR TKI following 2L chemotherapy, with varying levels of success. Osimertinib is a well-tolerated EGFR TKI which is active against the T790M resistance mutation, which would have limited the efficacy of rechallenge with 1G EGFR TKIs. **Methods:** This is a multicentered international phase II investigator-initiated study of osimertinib in the 3L rechallenge of patients with EGFR+ aNSCLC, following 1L treatment with osimertinib and 2L therapy with platinum pemetrexed chemotherapy. A maximum of 255 patients will be enrolled. Patients with 'common' EGFR exon 19 deletions or L858R mutations will enroll at the start of 2L chemotherapy or 3L osimertinib rechallenge. The primary objective is 3L objective response rate (ORR) in the first 100 evaluable patients, according to RECIST 1.1. Secondary objectives include disease control rate (DCR), progression free survival (PFS), time to treatment failure, overall survival and toxicity for 3L osimertinib rechallenge. Exploratory objectives include assessment of osimertinib resistance based on serial ctDNA samples collected from all participants. The OCELOT study, NCT04335292, is actively enrolling participants. Clinical trial information: NCT04335292. Research Sponsor: AstraZeneca.

TPS9161 **Poster Session**

LATIFY: Phase 3 study of ceralasertib + durvalumab vs docetaxel in patients with locally advanced or metastatic non-small-cell lung cancer that progressed on or after anti-PD-(L)1 and platinum-based therapy.

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Background: Following progression on first- or second-line immunotherapy ± platinum-based chemotherapy (CT), the prognosis for patients (pts) with metastatic non-small-cell lung cancer (NSCLC) is poor with limited alternative options to docetaxel. Ceralasertib is a selective inhibitor of Ataxia Telangiectasia and Rad3-related (ATR) protein kinase, which is activated in response to DNA damage. Clinical data suggest that ceralasertib may sensitize tumors to immunotherapy by biasing T cells to an immune-effective phenotype. Durvalumab is a selective, high-affinity human IgG1 monoclonal antibody that binds programmed cell death ligand-1 (PD-L1) and inhibits PD-L1-mediated suppression of T-cell activation. Combining ceralasertib with durvalumab may amplify the antitumor immune response, and potentially lead to durable tumor control. In the ongoing phase 2 HUDSON study in pts with locally advanced or metastatic NSCLC who progressed on anti-PD-(L)1 therapy and platinum-doublet regimen, ceralasertib + durvalumab showed promising efficacy with median progression-free survival (PFS) of 6.0 mos (80% CI, 4.6–7.5) and median overall survival (OS) of 15.9 mos (80% CI, 14.1–20.3). **Methods:** LATIFY is a phase 3, open-label, randomized, multicenter study in pts with NSCLC (NCT05450692). Key inclusion criteria are age ≥18 years; ECOG performance status 0–1; documented *EGFR* and *ALK* wild-type, and tumor cell PD-L1 status; and adequate organ and bone marrow function. Stable brain metastases are allowed. Pts should be eligible for second- or third-line therapy, and must have received an anti-PD-(L)1 therapy and a platinum-containing doublet regimen for locally advanced or metastatic NSCLC either separately or in combination, but no other prior therapies. Key exclusion criteria include mixed small-cell lung and NSCLC histology, unresolved toxicities of Grade ≥2 (NCI CTCAE v5.0) from prior therapy, active or prior autoimmune or inflammatory disorders, > 1 line of prior anti-PD-(L)1 therapy (alone or in combination), and > 1 line of platinum-based CT in a metastatic setting. Pts are randomized 1:1 to receive either oral ceralasertib 240 mg twice daily on Days (D) 1–7 with IV durvalumab 1500 mg on D8 (28-day cycle) or IV docetaxel 75 mg/m^2 (D1, 21-day cycle). The primary objective is to assess efficacy by OS. Secondary objectives include evaluating efficacy by PFS, objective response rate and disease control rate by RECIST v1.1; duration of, and time to, response; time to second progression or death; OS at 12 mos; time to deterioration of health-related quality of life and physical function; determining the pharmacokinetics of ceralasertib; and assessing safety. Approximately 580 pts will be recruited from around 21 countries in the Americas, Europe, and Asia Pacific. Clinical trial information: NCT05450692. Research Sponsor: AstraZeneca PLC.

TPS9162 **Poster Session**

CAN-2409 plus prodrug with standard of care immune checkpoint inhibitor for patients with stage III/IV NSCLC.

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Background: Immune checkpoint inhibitors (ICI) are a standard of care (SOC) treatment that have improved outcomes for patients (pts) with non-small cell lung cancer (NSCLC). However, most pts progress, signaling a need for combination approaches to further improve outcomes. CAN-2409 is a replication-defective adenoviral construct encoding the herpes simplex virus thymidine kinase (HSV-tk) gene that is injected intratumorally followed by 2 weeks of prodrug (valacyclovir or acyclovir). HSV-tk converts the prodrug in the tumor microenvironment into a toxic metabolite, resulting in immunogenic cell death, while the adenoviral proteins provide a strong pro-inflammatory signal. Together, this leads to *in situ* vaccination against the patient's own tumor. As a result, CD8+ cytotoxic T cells are educated on how to recognize and kill tumor cells in both the injected tumor and the uninjected metastases. A completed neoadjuvant phase I trial in resectable NSCLC demonstrated safety and immune stimulation (Predina et al 2021), warranting further investigation of CAN-2409 + prodrug as a therapy that can lead to improved long-term outcomes for pts with NSCLC who have a suboptimal response to ICI. **Methods:** LuTK02 (NCT04495153) is an open-label, multi-arm, phase II clinical trial to evaluate CAN-2409 + prodrug added to SOC ICI (anti-PD-(L)1) therapy in pts with stage III/IV NSCLC presenting with inadequate response (as defined below) to ICI. Cohort 1 includes pts with nonresponding but stable disease $\geq$18 weeks after starting ICI; cohort 2 includes pts with progressive disease $\geq$18 weeks after starting ICI. Key eligibility criteria include RECIST-evaluable disease; an injectable lesion (via bronchoscopy or US/IR guidance); ability to continue ICI for the treatment period; no change of ICI or prior interruptions of $>$ 4 weeks within 6 months of enrollment; and no focal therapy at $>$ 3 sites of disease within 12 months prior to enrollment. Key exclusion criteria include a history of ICI immune-related adverse events and known alterations in *EGFR*, *ALK*, or *ROS*1. Eligible patients receive 2 injections of CAN-2409 approximately 6 weeks apart followed by prodrug for 14 days. After treatment of ~40 evaluable pts in cohort 2 with two injections of CAN-2409, the protocol has been amended to include a new cohort (n~20) of pts treated with three injections of CAN-2409 approximately 4 weeks apart, each followed by prodrug for 14 days, to further define the optimal therapeutic regimen. Primary endpoints are overall response and/or disease control rate per RECIST 1.1 criteria and safety of CAN-2409 + prodrug. Secondary endpoints include duration of response, PFS, OS, and biomarker studies. Exploratory endpoints include evaluation of effects in non-injected lesions, changes in non-target (per RECIST) lesions, tumor growth trajectory, and viral shedding. Clinical trial information: NCT04495153. Research Sponsor: Candel Therapeutics.