9500 Oral Abstract Session, Fri, 8:00 AM-11:00 AM

Nivolumab + ipilimumab versus platinum-doublet chemotherapy as first-line treatment for advanced non-small cell lung cancer: Three-year update from CheckMate 227 Part 1. *First Author: Suresh S. Ramalingam, Winship Cancer Institute, Emory University, Atlanta, GA*

Background: In the phase 3 CheckMate 227 Part 1 (NCT02477826; minimum follow-up, 29.3 mo), 1L NIVO + IPI significantly improved overall survival (OS) vs chemo in treatment-naive patients (pts) with aNSCLC and tumor PD-L1 expression ≥ 1% (primary analysis) or < 1% (pre-specified descriptive analysis). Here we report data with 3-y minimum follow-up. **Methods:** Pts with stage IV / recurrent NSCLC and PD-L1 ≥ 1% (n = 1189) were randomized 1:1:1 to NIVO (3 mg/kg Q2W) + IPI (1 mg/kg Q6W), NIVO (240 mg Q2W) alone, or chemo. Pts with PD-L1 < 1% (n = 550) were randomized to NIVO + IPI, NIVO (360 mg Q3W) + chemo, or chemo. Primary endpoint was OS with NIVO + IPI vs chemo in pts with PD-L1 ≥ 1%. An exploratory analysis of OS in pts by response status (CR/PR, SD, progressive disease [PD]) at 6 mo was conducted. **Results:** After a median follow-up of 43.1 mo (database lock, 28 Feb 2020), pts with PD-L1 ≥ 1% continued to derive OS benefit from NIVO + IPI vs chemo (HR: 0.79; 95% CI, 0.67–0.93); 3-y OS rates were 33% (NIVO + IPI), 29% (NIVO), and 22% (chemo). At 3 y, 18% of pts with PD-L1 ≥ 1% treated with NIVO + IPI remained progression-free vs 12% with NIVO and 4% with chemo; 38% of confirmed responders remained in response in the NIVO + IPI arm at 3 y vs 32% in the NIVO arm and 4% in the chemo arm. In pts with PD-L1 < 1%, OS HR for NIVO + IPI vs chemo was 0.64 (95% CI, 0.51–0.81); 3-y OS rates were 34% (NIVO + IPI), 20% (NIVO + chemo), and 15% (chemo); 13%, 8%, and 2% of pts remained progression-free; and 34%, 15%, and 0% of confirmed responders remained in response, respectively. Pts with PD-L1 ≥ 1% with either CR/PR at 6 mo had longer subsequent OS with NIVO + IPI vs chemo; pts with SD or PD at 6 mo had generally similar subsequent OS between treatments (Table); results in PD-L1 < 1% pts will be presented. Any-grade / grade 3–4 treatment-related AEs were observed in 77% / 33% of all pts treated with NIVO + IPI, and 82% / 36% with chemo. **Conclusions:** With 3 y minimum follow-up, NIVO + IPI continued to provide durable and long-term OS benefits vs chemo for pts in 1L aNSCLC. Pts with PD-L1 ≥ 1% who achieved CR/PR at 6 mo had marked OS benefit with NIVO + IPI vs chemo. No new safety signals were identified for NIVO + IPI. Clinical trial information: NCT02477826. Research Sponsor: Bristol-Myers Squibb and Ono Pharmaceutical.

Landmark analysis of OS by response status at 6 mo in pts with PD-L1 ≥ 1% (NIVO + IPI vs chemo).

Pts alive at 6 mo	Response status at 6 mo, %	Post-landmark 1-y OS rate, %	Post-landmark 2-y OS rate, %	Post-landmark 3-y OS rate, %
NIVO + IPI (n = 295) vs Chemo (n = 306)	CR or PR, 39 vs 25 SD, 14 vs 18 PD, 46 vs 58	90 vs 73 69 vs 54 44 vs 47	76 vs 51 45 vs 38 22 vs 25	70 vs 39 34 vs 33 19 vs 17

9501 Oral Abstract Session, Fri, 8:00 AM-11:00 AM

Nivolumab (NIVO) + ipilimumab (IPI) + 2 cycles of platinum-doublet chemotherapy (chemo) vs 4 cycles chemo as first-line (1L) treatment (tx) for stage IV/recurrent non-small cell lung cancer (NSCLC): CheckMate 9LA. *First Author: Martin Reck, Department of Thoracic Oncology, Airway Research Center North, German Center for Lung Research, LungClinic, Grosshansdorf, Germany*

Background: NIVO + IPI was shown to improve overall survival (OS) and durability of response vs chemo in 1L advanced NSCLC in CheckMate 227 Part 1, regardless of PD-L1 expression. We hypothesized that a limited course of chemo combined with NIVO + IPI could provide rapid disease control while building on the durable OS benefit seen with dual PD-1 and CTLA-4 inhibition. CheckMate 9LA (NCT03215706) is a phase 3 randomized study evaluating NIVO + IPI + 2 cycles chemo vs chemo in 1L stage IV/recurrent NSCLC. **Methods:** Adults with tx-naive, histologically confirmed stage IV/recurrent NSCLC, ECOG performance status 0–1, and no known sensitizing *EGFR/ALK* alterations were randomized 1:1 to NIVO 360 mg Q3W + IPI 1 mg/kg Q6W + chemo (2 cycles) (n = 361) or chemo (4 cycles) alone (n = 358), stratified by PD-L1 (< 1% vs ≥ 1%), sex, and histology (squamous vs non-squamous). Chemo was based on histology. Pts with non-squamous NSCLC in the chemo-only arm could receive optional pemetrexed maintenance. Pts were treated with immunotherapy until disease progression, unacceptable toxicity, or for 2 y. The primary endpoint was OS; the interim analysis using Lan–DeMets alpha spending function with O'Brien–Fleming boundary was planned at ~80% information fraction (ie, after observing ~322 total events). Secondary endpoints included progression-free survival (PFS) and objective response rate (ORR) by blinded independent central review, and efficacy by PD-L1 subgroups. Exploratory endpoints included safety/tolerability. **Results:** Baseline characteristics were balanced across arms. At a preplanned interim analysis (minimum follow-up 8.1 mo), OS was significantly prolonged with NIVO + IPI + chemo vs chemo (HR 0.69, 96.71% CI: 0.55–0.87; $P = 0.0006$); statistically significant improvements in PFS and ORR were seen. With longer follow-up (minimum 12.7 mo), NIVO + IPI + chemo vs chemo continued to provide longer OS; median 15.6 vs 10.9 mo (HR 0.66, 95% CI: 0.55–0.80); 1-y OS rates were 63 vs 47%. Clinical benefit was consistent across all efficacy measures in key subgroups including by PD-L1 and histology. Grade 3–4 tx-related adverse events were reported in 47 vs 38% of pts in the NIVO + IPI + chemo vs chemo arms, respectively. **Conclusions:** CheckMate 9LA met its primary endpoint: a statistically significant improvement in OS was observed with NIVO + NSCLC-optimized IPI + a limited course of chemo vs chemo (4 cycles) in 1L advanced NSCLC. No new safety signals were reported. Clinical trial information: NCT03215706. Research Sponsor: Bristol-Myers Squibb and Ono Pharmaceutical.

9502 Oral Abstract Session, Fri, 8:00 AM-11:00 AM

CCTG BR.34: A randomized trial of durvalumab and tremelimumab +/- platinum-based chemotherapy in patients with metastatic (Stage IV) squamous or nonsquamous non-small cell lung cancer (NSCLC). *First Author: Natasha B. Leighl, Princess Margaret Cancer Centre, Toronto, ON, Canada*

Background: First-line therapy for advanced NSCLC includes PD-1 checkpoint inhibitor (ICI) monotherapy, and in combination with chemotherapy. Combination ICI have also demonstrated better survival compared to chemotherapy (CM-227). In CCTG BR.34, we compared overall survival (OS) in patients with advanced NSCLC receiving first-line durvalumab plus tremelimumab (DT) with or without platinum doublet chemotherapy (CT). **Methods:** This international, open-label, randomized trial accrued 301 participants from Canada and Australia, with stage IV NSCLC, *EGFR/ALK* wildtype, ECOG PS 0/1. Patients were randomized to DT for 4 cycles or DT+CT (pemetrexed- or gemcitabine-platinum), with ongoing D or D + pemetrexed (non-squamous) maintenance until disease progression. Stratification factors included histology, stage IVA v. IVB and smoking status. The primary endpoint was OS; secondary endpoints included progression-free survival (PFS), objective response rate (ORR = CR + PR) and adverse events (AEs). **Results:** At a median follow up of 16.6 months, no significant difference in OS was seen between the two treatment arms, with a median OS of 16.6 months with DT+CT v. 14.1 months with DT, (estimated HR 0.88, 90% CI 0.67-1.16). PFS was significantly improved in the DT+CT arm (stratified HR 0.67, 95% CI 0.52-0.88; medians 7.7 v. 3.2 months). ORR was higher in the DT+CT arm, 28% v. 14%, (odds ratio 2.1, p=0.001). Preplanned subgroup analysis demonstrated no significant differences in treatment outcomes by plasma TMB (<20 v. ≥20 mut/Mb, Guardant OMNI), age, sex, or smoking status. There was a trend to improved OS with DT+CT in the subgroup with PD-L1 TPS≥50%, (HR 0.64, 95% CI 0.40-1.04, p=0.07). Plasma TMB<20 mut/Mb was associated with shorter survival in both treatment groups (HR 1.99, 95% 1.3-3.1). Toxicity was greater in the DT+CT arm, with grade≥3 adverse events in 82% v. 70%, (p=0.02), most commonly dyspnea, nausea and cough. The incidence of immune-related adverse events was similar between arms (colitis 11%, pneumonitis 6%, endocrinopathy 21%). Grade 5 events occurred in 2.7%, (5 with DT+CT, 3 with DT). **Conclusions:** The addition of CT to first-line DT did not improve OS in advanced NSCLC. CT+DT improved ORR and PFS, and was associated with greater toxicity. No differential effects were seen by PD-L1 TPS nor bTMB. These data suggest that adding chemotherapy to ICI may be beneficial in those with PD-L1 TPS >=50%, and warrant further analysis in independent datasets. Clinical trial information: NCT03057106. Research Sponsor: Canadian Cancer Society Research Institute, Pharmaceutical/Biotech Company.

9503 Oral Abstract Session, Fri, 8:00 AM-11:00 AM

Primary analysis of a randomized, double-blind, phase II study of the anti-TIGIT antibody tiragolumab (tira) plus atezolizumab (atezo) versus placebo plus atezo as first-line (1L) treatment in patients with PD-L1-selected NSCLC (CITYSCAPE). *First Author: Delvys Rodriguez-Abreu, Hospital Universitario Insular de Gran Canaria, Las Palmas De Gran Canaria, Spain*

Background: The immunomodulatory receptor TIGIT is a novel inhibitory immune checkpoint present on activated T cells and NK cells in multiple cancers, including NSCLC. In a phase I study (GO30103), co-inhibition of TIGIT and PD-L1 signaling with tira plus atezo in CIT-naïve PD-L1 positive NSCLC potentially improved overall response rates (ORR) compared to historical ORR with PD-L1/PD-1 inhibitors. We conducted this phase II trial to confirm the efficacy and safety of tira plus atezo (TA) compared to placebo plus atezo (PA) in 1L NSCLC (GO40290, NCT NCT03563716). **Methods:** This prospective, randomized, double-blind, placebo-controlled trial enrolled patients (pts) with chemotherapy-naïve PD-L1+ (TPS ≥ 1% by 22C3 IHC pharmDx Dako assay) locally advanced or metastatic NSCLC with measurable disease, ECOG PS 0-1, and without *EGFR* or *ALK* alterations. Pts were randomized 1:1 to TA (tira 600 mg IV plus atezo 1200 mg IV) or PA (placebo plus atezo 1200 mg IV) on day 1 of every 3-week cycle. Stratification factors were PD-L1 status (TPS ≥ 50% vs TPS 1-49%), histology, and tobacco history. Co-primary endpoints were investigator assessed ORR and PFS, and additional endpoints were duration of response (DOR), OS, and safety. Exploratory endpoints were the effect of PD-L1 status on ORR and PFS. **Results:** 135 pts were randomized to PA (n = 68) or TA (n = 67). At primary analysis (30 Jun 2019), TA improved ORR and median PFS (mPFS) compared to PA, with median follow-up of 5.9 mo. In the safety population (68 in PA, 67 in TA), treatment-related AEs (TRAEs) occurred in 72% (PA) and 80.6% (TA); Grade ≥3 TRAEs occurred in 19.1% (PA) and 14.9% (TA). AEs leading to treatment withdrawal occurred in 10.3% (PA) and 7.5% (TA). Clinical trial information: NCT03563716. With an additional six months of follow-up since the primary analysis (2 Dec 2019, median follow-up of 10.9 mo), improvement in ORR and mPFS was maintained in ITT for TA (37.3% [25.0, 49.6] and 5.6 mo [4.2, 10.4]) vs PA (20.6% [10.2, 30.9] and 3.9 mo [2.7, 4.5]). The safety profile remained tolerable. **Conclusions:** Treatment with TA compared to PA showed clinically meaningful improvement in ORR and PFS in ITT. The safety profile of TA was similar to PA. Research Sponsor: Genentech, Inc.

	ITT	
	PA	**TA**
n	68	67
ORR % (95% CI)	16.2 (6.7, 25.7)	31.3 (19.5, 43.2)
Odds ratio (95% CI)	2.57 (1.07, 6.14)*	
mPFS, months (95% CI)	3.6 (2.7, 4.4)	5.4 (4.2, NE)
HR (95% CI)	0.57 (0.37, 0.90)*	

*stratified

9504 Oral Abstract Session, Fri, 8:00 AM-11:00 AM

Trastuzumab deruxtecan (T-DXd; DS-8201) in patients with HER2-mutated metastatic non-small cell lung cancer (NSCLC): Interim results of DESTINY-Lung01. *First Author: Egbert F. Smit, Netherlands Cancer Institute, Amsterdam, Netherlands*

Background: T-DXd is an antibody-drug conjugate composed of an anti-HER2 antibody, cleavable tetrapeptide-based linker, and topoisomerase I inhibitor payload. In a phase I trial, patients (pts) with HER2-mutated NSCLC who received T-DXd had a confirmed objective response rate (ORR) of 72.7% (8/11) (Tsurutani et al, WCLC 2018). DESTINY-Lung01 (NCT03505710) is an ongoing, multicenter, phase II study of T-DXd in pts with non-squamous NSCLC overexpressing HER2 or containing a HER2-activating mutation. We report data for the cohort with HER2 mutations after a median follow-up of 8.0 mo (range, 1.4-14.2 mo). **Methods:** Pts were treated with T-DXd 6.4 mg/kg every 3 weeks. The primary endpoint was confirmed ORR (complete response [CR] + partial response [PR]) by ICR. Additional endpoints were disease control rate (DCR; CR + PR + stable disease), duration of response (DOR), progression-free survival (PFS), and safety. **Results:** At data cutoff (25 Nov 2019), 42 pts (64.3% female) had received T-DXd. Median age was 63.0 years (range, 34-83 years; $<$ 65 y, 59.5%); 45.2% had central nervous system metastases; ECOG performance status was 0 in 23.8% of pts and 1 in 76.2%. HER2 mutations were predominantly in the kinase domain (90.5%). Most pts (90.5%) had prior platinum-based chemotherapy and 54.8% had anti–PD-1 or –PD-L1 treatment; median number of prior treatment lines was 2 (range, 1-6). Median treatment duration was 7.75 mo (range, 0.7-14.3 mo); 45.2% of pts remained on treatment. Confirmed ORR by ICR among the 42 pts was 61.9% (95% CI, 45.6%-76.4%); median DOR was not reached at data cutoff; 16 of 26 responders remained on treatment at data cutoff; DCR was 90.5% (95% CI, 77.4%-97.3%); estimated median PFS was 14.0 mo (95% CI, 6.4-14.0 mo). All pts (42/42) had treatment-emergent adverse events (TEAEs); 64.3% were grade $\geq$ 3 (52.4% drug-related), including decreased neutrophil count (26.2%) and anemia (16.7%). There were 5 cases (11.9%) of drug-related interstitial lung disease (ILD) as adjudicated by an independent committee (all grade 2, no grade $\geq$ 3) and 1 case of grade 1 ILD is pending adjudication. TEAEs led to dose interruption in 25 pts (59.5%), dose reduction in 16 pts (38.1%), and treatment discontinuation in 10 pts (23.8%). **Conclusions:** T-DXd demonstrated promising clinical activity with high ORR and durable responses in pts with HER2-mutated NSCLC. The safety profile was generally consistent with previously reported studies. Clinical trial information: NCT03505710. Research Sponsor: Daiichi Sankyo, Inc.

9505 Oral Abstract Session, Fri, 8:00 AM-11:00 AM

Efficacy and safety of the antibody-drug conjugate (ADC) SAR408701 in patients (pts) with non-squamous non-small cell lung cancer (NSQ NSCLC) expressing carcinoembryonic antigen-related cell adhesion molecule 5 (CEACAM5). *First Author: Anas Gazzah, Department of Drug Development (DITEP), Gustave Roussy, Villejuif Cedex, France*

Background: We report updated safety and efficacy of DM4-conjugated anti-CEACAM5 ADC from the expansion part of the first-in-human study (NCT02187848; Gazzah A et al. J Clin Oncol. 2019;37:15, 9072) in 92 NSQ NSCLC pts. **Methods:** CEACAM5 expression was assessed by immunohistochemistry on archived tumor samples. Two cohorts of pts have been analyzed: moderate and high expressors, with CEACAM5 expression at $\geq$2+ intensity between $\geq$1% to $<$ 50% and $\geq$50% of the tumor cell population, respectively. SAR408701 was administered at 100 mg/m^2 IV every 2 weeks. Tumor assessments were done every 4 cycles (8 weeks). Primary endpoint was overall response rate (ORR). **Results:** As of January 2020, 92 pts were treated: 28 moderate and 64 high expressors, with median age 62.5 years (31–91; 42.4% of pts $\geq$65), 51.1% male, 71.7% ECOG PS $\geq$1; median of 3 prior treatments (1–10 lines) for advanced disease, including anti-tubulin agents (60.9%) and anti-PD1/PD-L1 (75%). In the moderate expressor cohort, 2 confirmed partial responses (PR) were observed (ORR 7.1%). In the high expressor cohort, 13 pts had confirmed PRs (ORR 20.3% [95% confidence interval 12.27%–31.71%]); 27 (42.2%) had stable disease; ORR of 17.8% was observed in 45 pts who had prior anti-PD1/PD-L1. Pts had a median of 7 (1–49) cycles; median relative dose intensity was 0.98. Six pts discontinued due to treatment-emergent adverse events (TEAEs). Most frequent TEAEs (all grades) were asthenia (38.0%), keratopathy/keratitis (38.0%), peripheral neuropathy (26.1%), dyspnea (23.9%), and diarrhea (22.8%). 31 pts had dose modification due to a TEAE, including dose reduction for keratopathy/keratitis in 10 pts. Hematological toxicity included leukopenia (14.4%), neutropenia (4.4%), and thrombocytopenia (13.3%). Grade $\geq$3 TEAEs occurred in 47.8% of pts and were assessed as drug-related in 15.2%. **Conclusions:** SAR408701 shows promising antitumor activity in heavily pretreated advanced NSQ NSCLC pts with high CEACAM5 expression. SAR408701 was well tolerated, with minimal hematological toxicity compared to conventional chemotherapy; keratopathy was reversible and manageable with dose modification. These data support the activity of SAR408701 in NSQ NSCLC CEACAM5 high expressors. A phase 3 trial evaluating the activity of CEACAM5-DM4 ADC monotherapy in comparison with docetaxel in NSQ NSCLC CEACAM5 high expressors after failure of standard first line chemotherapy and anti-PD1/PD-L1 is underway. Clinical trial information: NCT02187848. Research Sponsor: Sanofi.

9506 Oral Abstract Session, Fri, 8:00 AM-11:00 AM

NEJ026: Final overall survival analysis of bevacizumab plus erlotinib treatment for NSCLC patients harboring activating EGFR-mutations. *First Author: Makoto Maemondo, Iwate Medical University, Morioka, Japan*

Background: In NEJ026, a phase III trial comparing bevacizumab plus erlotinib (BE) to erlotinib monotherapy (E) for EGFR-mutated non-small-cell lung cancer (NSCLC), we demonstrated the progression-free survival (PFS) of BE was significantly superior to E (Saito et al. Lancet Oncol. 2019 May;20(5):625-635.). However overall survival analysis were immature at the cutoff date. **Methods:** Chemotherapy-naïve pts with advanced non-squamous NSCLC harboring EGFR-mutation were randomly assigned to receive either combination with erlotinib (150 mg daily) plus bevacizumab (15 mg/kg iv q3w) or erlotinib (150 mg daily). The primary endpoint was PFS. Secondary endpoints were OS, RR, safety, and QoL. **Results:** The 226 pts were assigned to BE (n=112) and E (n=114). For the follow-up OS analysis, the data cut-off date was 30 November 2019. Median follow up time was 39.2 months. Median OS was 50.7 months (95% CI, 37.3 months to not reached) with BE and 46.2 months (95% CI, 38.2 months to not reached) with E (hazard ratio, 1.00; 95% CI, 0.68 to 1.48). Twenty-nine patients (25.9%) in BE and twenty-six patients (23.2%) in E were treated by osimertinib as second line treatment. The median survival time between enrollment and progressive disease of second-line treatment (median PFS2) was 28.6 months (95% CI, 22.1 months to 35.9) with BE and 24.3 months (95% CI, 20.4 months to 29.1 months) with E (hazard ratio, 0.80; 95% CI, 0.59 to 1.10). In both arms, the median OS of patients with osimertinib second-line treatment were longer than other second-line chemotherapy groups [50.7 months (95% CI, 38.0 months to 50.7 months) vs 40.1 months (95% CI, 29.5 months to not reached), (hazard ratio, 0.645; 95% CI, 0.40 to 1.03), respectively. **Conclusion:** The additional effect of bevacizumab on erlotinib monotherapy for NSCLC with EGFR mutations gradually decreased in the order of PFS2 and survival, with no significant differences. Clinical trial information: UMIN000017069. Research Sponsor: Chugai Pharmaceutical.

9507 Oral Abstract Session, Fri, 8:00 AM-11:00 AM

Concurrent osimertinib plus gefitinib for first-line treatment of EGFR-mutated non-small cell lung cancer (NSCLC). *First Author: Julia K Rotow, Dana-Farber Cancer Institute, Boston, MA*

Background: First-line treatment with an EGFR tyrosine kinase inhibitor (TKI) is standard of care for patients (pts) with *EGFR*-mutated NSCLC. The EGFR TKI osimertinib is active against the acquired gefitinib-resistant mutation *EGFR* T790M, as is gefitinib against the osimertinib-resistant *EGFR* C797S. Preclinical evidence suggests dual EGFR inhibition with gefitinib + osimertinib may delay emergence of acquired resistance. **Methods:** This ongoing phase I/II study enrolled pts with stage IV *EGFR*-mutated (L858R or del19) NSCLC, without prior therapy for metastatic disease. Treatment in dose escalation (n = 6): concurrent osimertinib 40 mg or 80 mg + gefitinib 250 mg daily. In dose expansion (n = 21): osimertinib + gefitinib at the maximum tolerated dose (MTD). Prior to protocol amendment 6 pts received alternating monthly cycles of TKI monotherapy and were excluded from this analysis. The primary endpoints in the dose escalation and expansion phases were, respectively, identification of the MTD and feasibility, defined as receipt of combination therapy for $\geq$ 6 four-week cycles. Secondary endpoints included overall response rate (ORR), survival outcomes, plasma *EGFR* mutation clearance (cell free DNA by droplet digital PCR (ddPCR)), and mechanisms of acquired resistance. **Results:** From May 2017 to July 2019 27 pts were enrolled and evaluable for the primary endpoints. The MTD was osimertinib 80 mg plus gefitinib 250 mg orally daily. In feasibility analysis, 81.5% completed $\geq$6 cycles combination therapy (1 pt discontinued for progression, 4 for toxicity). The ORR was 85.2% (95% CI 67.5%-94.1%). Best response: 85.2% partial response, 14.8% stable disease. The most common treatment-related adverse effects (TRAEs) (% any grade, % grade 3) were rash (96.3%, 3.7%), diarrhea (85.2%, 11.1%) and dry skin (70.4%, 0%). Plasma ddPCR (n = 25 pts) detected the driver *EGFR* mutation at baseline in 68% of pts. In these pts, plasma *EGFR* cleared to undetectable at 2 weeks treatment in 82.4%. At 14.8 months median follow up the median progression free survival was not yet reached. **Conclusions:** Combination therapy with osimertinib and gefitinib is tolerable for first-line treatment of *EGFR*-mutated NSCLC and resulted in rapid plasma clearance of the *EGFR* mutation. The observed ORR is consistent with previously reported first-line response rates to osimertinib. Analysis of survival outcomes and acquired resistance mechanisms are pending data maturity and will facilitate understanding of the role of first-line dual EGFR TKI therapy for this pt population. Clinical trial information: NCT03122717. Research Sponsor: AstraZeneca, U.S. National Institutes of Health.

9508 Oral Abstract Session, Fri, 8:00 AM-11:00 AM

First-line tyrosine kinase inhibitor with or without aggressive upfront local radiation therapy in patients with EGFRm oligometastatic non-small cell lung cancer: Interim results of a randomized phase III, open-label clinical trial (SINDAS) (NCT02893332). *First Author: Xiaoshan Wang, Cancer Center Hospital of University of Electronic Science and Technology of China and Sichuan Provincial People's Hospital, Chengdu, China*

Background: The effectiveness of aggressive local therapy for oligometastatic non-small-cell lung cancer (NSCLC) is unknown. This multi-institutional, randomized, open label, phase III clinical trial was performed to assess upfront stereotactic radiotherapy to all sites at diagnoses in previously untreated EGFRm oligometastatic non-small-cell lung cancer on progression-free survival and overall survival. **Methods:** The study was conducted at five centers located in different provinces of China.Eligible participants had pathologically confirmed adenocarcinoma, gene sequencing confirmed EGFRm, stage IV, five or fewer metastatic disease lesions, an ECOG performance status score of ≤ 2, systemic therapy naive, and no brain disease before randomization.Participants were randomized to receive either first-line tyrosine kinase inhibitor (TKI) treatment alone or up front stereotactic radiotherapy to all sites of disease along with TKI treatment.The primary endpoint was progression-free survival and the secondary endpoint was overall survival. **Results:** From January 2016 to January 2019, 133 participants were enrolled, including 65 (48.8%) in the TKI arm who received standard of care TKI alone and 68 (51.1%) in the stereotactic radiotherapy sites at diagnosis arm who received stereotactic radiotherapy and TKI.At a median follow-up of 19.6 months (IQR 9.4 - 41.0), the median progression-free survival for tyrosine kinase inhibitor alone was 12.5 months, and for tyrosine kinase inhibitor and stereotactic radiotherapy was 20.20months, respectively (HR 0.6188 [95% CI 0.3949-0.9697], log rank $P < .001$). The median overall survival in the TKI alone arm was 17.40 months, and for TKI and stereotactic radiotherapy arm was 25.50 months, respectively (HR 0.6824 [95% CI 0. 4654-1.001], log rank $P < .001$). Adverse events were similar between groups, with no grade 5 or deaths due to treatment. Grade 3/4 adverse events with or without radiotherapy included pneumonitis (7.3% vs. 2.9%; $P > .05$) and esophagitis (4.4%vs. 3.0% $P > .05$). **Conclusions:** Upfront stereotactic radiotherapy to sites at diagnosis along with first line TKI improved both progression-free survival and overall survival significantly compared with TKI alone. This finding suggests aggressive local therapy to sites at diagnosis should be explored further in large cohort phase III trials as a standard treatment option in this clinical scenario. Clinical trial information: NCT02893332. Research Sponsor: National scienceand technology bureau [grant numbers 3035031263], Other Foundation.

9509 Clinical Science Symposium, Fri, 8:00 AM-9:30 AM

Capmatinib in patients with high-level *MET*-amplified advanced non–small cell lung cancer (NSCLC): results from the phase 2 GEOMETRY mono-1 study. *First Author: Juergen Wolf, Center for Integrated Oncology, University Hospital Cologne, Cologne, Germany*

Background: In the ongoing, multicohort, phase 2 GEOMETRY mono-1 study, capmatinib (INC280) has shown efficacy in *METex14*–mutated NSCLC patients (pts) who were pretreated (cohort 4) or treatment (tx)-naïve (cohort 5b). Here, we report the efficacy and safety of capmatinib in pts with high-level *MET*-amplified (gene copy number [GCN] $\geq$10) advanced NSCLC who were either pretreated with 1 or 2 prior lines of systemic therapy (cohort 1a) or tx-naïve (cohort 5a). **Methods:** Adult pts ($\geq$18 years), ECOG PS 0–1 who had *ALK* and *EGFR* wt, stage IIIB/IV (any histology) *MET*-amplified NSCLC with GCN$\geq$10 received capmatinib 400 mg twice daily (fasting). Primary and key secondary endpoints were overall response rate (ORR) and duration of response (DOR), respectively, by blinded independent review committee (BIRC) assessment per RECIST v1.1. Other secondary endpoints included investigator-assessed ORR, DOR, disease control rate (DCR), progression-free survival (PFS, BIRC and investigator assessment), overall survival, and safety. **Results:** As of Jan 06, 2020, 84 pts were evaluable for efficacy (cohort 1a [2nd/3rd line], 69 pts; Cohort 5a [1st line], 15 pts). Tx was ongoing for 3 pts in cohort 1a, none in cohort 5a. Per BIRC assessment in cohorts 1a and 5a, respectively, ORR was 29% and 40%, median DOR was 8.31 months (mo, 20 responders, 95% CI: 4.17–15.44) and 7.54 mo (6 responders, 95% CI: 2.56–14.26), and median PFS was 4.07 (95% CI: 2.86–4.83) and 4.17 (95% CI: 1.45–6.87) mo. Investigator assessment was in line with BIRC assessment (Table). The most common adverse events across all cohorts ($\geq$25%, all grades, N = 364) were peripheral edema (51.1%), nausea (44.8%) and vomiting (28.0%). Data for biomarker analysis and pts with brain metastasis will be presented at the ASCO 2020 meeting. **Conclusion:** Capmatinib has demonstrated activity in the subset of pts with high-level *MET*-amplified (GCN$\geq$10) NSCLC, with a higher response rate in tx-naïve pts. Safety profile remains favorable and similar to previous reports of capmatinib. Clinical trial information: NCT02414139. Research Sponsor: Novartis Pharmaceuticals.

	Cohort 1a (2/3L) N = 69		Cohort 5a (1L) N = 15	
	BIRC	**Investigator**	**BIRC**	**Investigator**
ORR, % (95% CI)	29 (18.7–41.2)	27.5 (17.5–39.6)	40 (16.3–67.7)	40 (16.3–67.7)
DCR, % (95% CI)	71.0 (58.8–81.3)	60.9 (48.4–72.4)	66.7 (38.4–88.2)	73.3 (44.9–92.2)
Median PFS, mo (95% CI)	4.07 (2.86–4.83)	4.14 (2.79–5.52)	4.17 (1.45–6.87)	2.76 (1.45–6.87)
Median DOR, mo (95% CI)	**N = 20** 8.31 (4.17–15.44)	**N = 19** 6.80 (4.21–20.73)	**N = 6** 7.54 (2.56–14.26)	**N = 6** 9.66 (4.01–17.08)

9510 Clinical Science Symposium, Fri, 8:00 AM-9:30 AM

Safety and preliminary clinical activity of the MET antibody mixture, Sym015 in advanced non-small cell lung cancer (NSCLC) patients with MET amplification/exon 14 deletion ($MET^{Amp/Ex14\Delta}$). *First Author: D. Ross Camidge, Medical Oncology Department, University of Colorado, Aurora, CO*

Background: Sym015, a mixture of 2 humanized antibodies, triggers MET degradation by a unique mechanism with superior specificity compared to tyrosine kinase inhibitors (TKIs). The Sym015-01 phase (P)1a trial met, the primary objective of identifying the recommended P2 dose (RP2D) as 18 mg/kg on cycle 1 day 1 followed by 12 mg/kg Q2W. The P2a was expanded to enroll $MET^{Amp/Ex14\Delta}$ NSCLC patients (pts) based on preliminary efficacy findings. Here we present interim safety (n = 45) and efficacy (NSCLC cohort, n = 20) results from P2a. **Methods:** The expansion NSCLC Cohort enrolled pts with $MET^{Ex14\Delta}$ (n = 12) or MET^{Amp} (n = 8 defined as $>$ 5 *MET* copies by NGS or *MET*/CEP7 ratio $>$ 2.2 updated to $\geq$3.0 by *in situ* hybridization; including 1 with $MET^{Amp+Ex14\Delta}$). Tumor *MET* status was confirmed centrally and longitudinal ctDNA was analyzed by Guardant360. **Results:** By January 2020, 45 pts (median age 61.7 years) have been treated in P2a. Median duration of exposure (DoE) was 3.8 months (m) (n = 45; range 0.4+ to 22 m). Treatment emergent adverse events occurred in 93%, treatment related AEs (TRAE) in 42.2% and TRAE $\geq$G3 in 13.3% pts. No pts discontinued or died due to TRAE. The most common TRAE in $\geq$10% pts were fatigue (13.3%) and peripheral edema (11.1%). Of 20 NSCLC pts, 5 had confirmed PR (ORR 25%; 2/8 MET^{Amp} and 3/12 $MET^{Ex14\Delta}$); 11 had SD (DCR 80%; 6/8 MET^{Amp} and 5/12 $MET^{Ex14\Delta}$); 2 had PD (2/12 $MET^{Ex14\Delta}$); and 2 were not evaluable. 10 NSCLC pts were MET TKI naive (7 MET^{Amp} and 3 $MET^{Ex14\Delta}$) and had 50% ORR and 100% DCR (5 PR and 5 SD; DoR range 1 to 18.3 m; DoE 1.5 to 22 m); 10 NSCLC pts were prior MET TKI treated (9 $MET^{Ex14\Delta}$ and 1 $MET^{Amp+Ex14\Delta}$) with DCR 60%, (6 SD; DoE 0.4-9.6 m). Median PFS was 5.5 m overall (95% CI 3.5-9.7 m). Median PFS for MET TKI naive and MET TKI pre-treated NSCLC pts was 6.5 m (95% CI 3.4-21.9 m) and 5.4 m (95% CI 1.2-9.7 m) respectively. Median OS was not reached for overall or for prior MET TKI subgroups. 89% $MET^{Ex14\Delta}$ tumor tissue to blood concordance (8/9 NSCLC pts) was observed. **Conclusions:** Sym015 was well-tolerated at the RP2D with a response rate similar to MET TKI in MET-treatment naïve $MET^{Amp/Ex14\Delta}$ NSCLC and seems to delay disease progression in MET TKI pretreated NSCLC pts. Combination with MET TKI to delay or prevent resistance should be further explored. Clinical trial information: NCT02648724. Research Sponsor: Symphogen A/S.

9511 Clinical Science Symposium, Fri, 8:00 AM-9:30 AM

Characterization of 1,387 NSCLCs with MET exon 14 (METex14) skipping alterations (SA) and potential acquired resistance (AR) mechanisms. *First Author: Mark M. Awad, Massachusetts General Hospital, Cambridge, MA*

Background: *MET*ex14 SA are oncogenic drivers in NSCLC. Due to the numerous sites around ex14 that bind the spliceosome complex, many variations can result in deleterious alterations (alts). We present a comprehensive overview of these ex14 SA across 1,387 NSCLCs and characterized potential AR mechanisms. **Methods:** Hybrid-capture based comprehensive genomic profiling (CGP) was performed on samples from 60,495 NSCLC patients (pts). A scoring system was applied leveraging our large database of samples with METex14 SA to optimize accurate reporting of these variants. Paired samples were collected $\geq$ 60 days apart (median 462). **Results:** 1,393 *MET*ex14 SA were identified in samples (1,278 tissue, 109 circulating tumor DNA (ctDNA)) from 1,387 NSCLC pts (2.3%) spanning multiple functional sites: donor (42%), acceptor (4.7%), poly-pyrimidine tract (15%), acceptor and poly-pyrimidine tract (13%), D1010 (23%), Y1003 (2.1%), and whole exon deletions (0.3%). 6 samples (5 tissue, 1 ctDNA) harbored 2 *MET*ex14 SA, each including a mutation (mut) at the donor or acceptor site. *MDM2* and *CDK4* amplifications (amps) co-occurred in 32% and 19% of *MET*ex14 samples, respectively, but were more common with polypyrimidine tract (37% and 23%) vs donor site (32%, p = 0.07 and 18%, p = 0.07) alts. *MET* co-amp was present in 12% of cases and frequency did not significantly differ by functional site. 66 (4.8%) cases (57 tissue, 9 ctDNA) had known NSCLC co-drivers, including *KRAS* (68%) and *EGFR* (14%) mut, a subset of which may represent AR. Paired samples with a *MET*ex14 SA in the 1st sample were available for 36 pts. The *MET*ex14 SA was detected in the 2nd sample for 32 pts, excluding 3 with low ctDNA. 22/36 (61%) had reportable acquired alts detected including 9 with $\geq$1 acquired *MET* muts [D1228X (4), Y1230X (3), Y1003F (1), D1228A/E/H + L1195V (1)] and 3 with acquired *MET* amp. Other acquired alts included *ERBB2* amp and mut (1 each), *EGFR* ex19ins (1), *KRAS* amp (1), *PIK3CA* mut (1), *AKT2* amp (1) and others with unknown functional significance. Potential AR alts were present with primary *MET*ex14 SA spanning all functional sites. **Conclusions:** In a dataset of $>$ 60,000 advanced NSCLCs, *MET*ex14 SA were present in 2.3% of cases, and represented 6 major subtypes. Among paired cases, potential AR mechanisms included secondary *MET* alts (33%), and acquired alts in *EGFR*, *ERBB2*, *KRAS*, and PI3K pathways. Acquired alts were independent of the type of *MET*ex14 SA. Characterizing common co-occuring may be critical for predicting responses to MET inhibitors and informing rational combination strategies. Research Sponsor: Foundation Medicine.

9512 Poster Discussion Session; Displayed in Poster Session (Board #278), Fri, 8:00 AM-11:00 AM, Discussed in Poster Discussion Session, Fri, 8:00 AM-11:00 AM

Amivantamab (JNJ-61186372), an anti-EGFR-MET bispecific antibody, in patients with EGFR exon 20 insertion (exon20ins)-mutated non-small cell lung cancer (NSCLC). *First Author: Keunchil Park, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea*

Background: EGFR exon20ins-mutated NSCLC is generally refractory to EGFR tyrosine kinase inhibitors (TKIs) and is associated with poor prognosis. Amivantamab (JNJ-61186372) is a novel, fully human anti-EGFR-MET bispecific antibody whose mechanism of action can target both EGFR- and MET-driven disease and has shown monotherapy activity in patients (pts) with diverse EGFR mutant disease characterized by EGFR C797S, T790M, exon20ins, and MET amplification. We present preliminary results of pts with advanced NSCLC harboring exon20ins mutations from CHRYSALIS, an ongoing phase 1 study of amivantamab (NCT02609776). **Methods:** This study comprises a dose escalation phase in pts with advanced NSCLC and a dose expansion phase in pts with EGFR- and MET-mutated disease. This analysis includes all enrolled pts with exon20ins disease who received the recommended phase 2 dose (RP2D) of 1050 mg (1400 mg, pts ≥80 kg) amivantamab. Response was assessed by investigator per RECIST v1.1. **Results:** As of 30 Oct 2019, 50 pts with exon20ins mutations had received amivantamab at the RP2D. 39/50 pts were response-evaluable and had ≥2 disease assessments or had discontinued therapy prior to the assessment period; among these pts, 29 had prior platinum-based chemotherapy (PBCT). Median age for response-evaluable pts was 61 y (40–78), 51% were female, and median prior lines was 1 (0–7). In the 50 pts harboring exon20ins mutations treated at the RP2D, the most common adverse events (AEs) reported were rash (72%), infusion related reaction (60%), and paronychia (34%). Additional EGFR-related AEs included stomatitis (16%), pruritus (14%), and diarrhea (6%). Grade ≥3 AEs were reported in 36% of pts; 6% were treatment-related. One grade 3 diarrhea and no grade ≥3 rash was reported. Among the 39 response-evaluable pts, with a median follow-up of 4 months (1–26), the overall response rate (≥partial response [PR]) was 36% (95% CI, 21–53), and 41% (95% CI, 24–61) for the 29 pts who had prior PBCT. The clinical benefit rate (≥PR or stable disease ≥11 weeks) was 67% for response-evaluable pts and 72% for pts who had prior PBCT. Among all 14 responders, median duration of response was 10 months (1–16), with ongoing responses in 9 pts at data cutoff. Median progression-free survival was 8.3 months (95% CI, 3.0–14.8) for response-evaluable pts and 8.6 months (95% CI, 3.7–14.8) for pts who had prior PBCT. **Conclusions:** Amivantamab demonstrates robust and durable antitumor activity in pts with exon20ins disease, with a manageable safety profile. Clinical trial information: NCT02609776. Research Sponsor: Janssen Research & Development, LLC.

9513 Poster Discussion Session; Displayed in Poster Session (Board #279), Fri, 8:00 AM-11:00 AM, Discussed in Poster Discussion Session, Fri, 8:00 AM-11:00 AM

ECOG-ACRIN 5162: A phase II study of osimertinib 160 mg in NSCLC with EGFR exon 20 insertions. *First Author: Zofia Piotrowska, Massachusetts General Hospital Cancer Center, Boston, MA*

Background: EGFR exon 20 insertions (ins20), which comprise 4-10% of EGFR-mutant NSCLC, are generally refractory to first- and second-generation EGFR TKIs. While the clinical activity of the third-generation EGFR TKI osimertinib against EGFR ins20 is unknown, preclinical studies suggest its favorable therapeutic window may allow for inhibition of EGFR isn20 at clinically-achievable doses (Hirano, Oncotarget 2015). We report the results of EA5162, a single-arm, phase II study of osimertinib 160 mg in NSCLC pts with EGFR ins20 (NCT03191149). **Methods:** Pts with advanced NSCLC with an EGFR ins20 mutation identified by any local, CLIA-certified tissue assay were treated with osimertinib 160 mg daily until progression, intolerable toxicity or withdrawal. At least one prior line of therapy was required; stable, asymptomatic brain metastases were allowed. The primary endpoint was objective response rate (ORR). Secondary endpoints included safety, progression-free survival (PFS) and overall survival. The estimated sample size was 19 patients. **Results:** 21 pts were enrolled between 4/2018 and 7/2019 (median age 65; 15 female, 6 male; median 2 prior therapies); 1 patient did not meet eligibility criteria due to laboratory studies obtained 1 day out of window. As of 1/21/20, 6 pts remain on treatment. Among the 20 eligible pts, the best response was PR in 4 pts and CR in one pt, for a confirmed ORR of 25%; 12 (60%) pts had SD. The median PFS was 9.7 months (95% CI, 4.07, NA), median duration of response (DOR) was 5.7 months (95% CI, 4.73, NA.) Grade > 3 treatment-related adverse events (TRAE) observed in > 1 pt included anemia (n=2), fatigue (n=2), prolonged QT interval (n=2.) One pt had grade 4 respiratory failure, there were no grade 5 TRAEs. One pt discontinued study treatment due to grade 3 anemia. **Conclusions:** Osimertinib 160mg daily is well-tolerated and showed clinical activity in EGFR ins20-mutant NSCLC with a response rate of 25%, disease control rate of 85%, and mPFS of 9.7 months. The adverse events with osimertinib 160 mg QD in this cohort were consistent with other reports of this regimen; grade 3 rash and diarrhea were not observed. Clinical trial information: NCT03191149. Research Sponsor: U.S. National Institutes of Health.

9514 Poster Discussion Session; Displayed in Poster Session (Board #280), Fri, 8:00 AM-11:00 AM, Discussed in Poster Discussion Session, Fri, 8:00 AM-11:00 AM

Poziotinib shows activity and durability of responses in subgroups of previously treated EGFR exon 20 NSCLC patients. *First Author: Xiuning Le, Department of Thoracic Head and Neck Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Treatment of non-small cell lung cancer (NSCLC) with EGFR exon 20 mutations is an unmet medical need. Poziotinib is a potent tyrosine kinase inhibitor (TKI) of EGFR and HER2 exon 20 insertion mutants. We evaluated the efficacy and safety of poziotinib in previously treated NSCLC patients with EGFR exon 20 insertion mutations in an independent cohort of a multi-cohort, multi-center Phase 2 study (*ZENITH20-1*). **Methods:** *ZENITH20-1* study enrolled pts with advanced NSCLC with an EGFR exon 20 insertion identified on local tissue testing who had received at least one prior line of therapy. Poziotinib (16 mg) was administered orally QD, allowing dose reductions for AEs, with follow up for 24 months. The primary endpoint was objective response rate (ORR), evaluated centrally by RECIST v1.1. Secondary endpoints included disease control rate (DCR), duration of response (DOR), progression-free survival (PFS) and safety. Efficacy was also evaluated by specific exon 20 insertions and prior lines of therapy. **Results:** 115 patients with a median age of 61 years (33-83) were enrolled. Patients had a median of 2 prior lines of therapy (range, 1-9.) The median relative dose intensity was 72% (7-100%) with 65% having dose reductions. The ORR in the as-treated population was 14.8% (95% CI 8.9 - 22.6%), and the DCR was 68.7% (95% CI 59.4 - 77.0%) with a median DoR of 7.4 months. 65% patients had tumor size reductions and the median PFS was 4.2 months. In the evaluable population (n = 88), the ORR was 19.3% and the unconfirmed ORR was 25%. Responses were predominantly observed in insertions between residues M766 to D770 of exon 20 (8/44; 18.2%). Responses were observed in patients with 2 lines (14%); ≥3 lines of therapy (16.2%). The most common treatment-related Grade ≥3 AEs were rash (28%), diarrhea (26%), stomatitis (9%) and paronychia (6%). The incidence of treatment-related pneumonitis was 4%, however some cases may have been confounded by prior checkpoint inhibitors as first line treatment. **Conclusions:** Although the ORR primary endpoint was not met, poziotinib induced tumor reduction in the majority of patients with durable responses, including the heavily pre-treated population. Responses were more common in patients with insertions between M766 to D770 of EGFR exon 20. The safety profile was overall consistent with other 2nd generation EGFR TKIs. Evaluation of these subgroups with refined dosing and improved toxicity management to maintain continuous treatment is warranted to assess the potential of poziotinib in Exon20 related tumors. Clinical trial information: NCT03318939. Research Sponsor: Spectrum Pharmaceuticals, Inc.

9515 Poster Discussion Session; Displayed in Poster Session (Board #281), Fri, 8:00 AM-11:00 AM, Discussed in Poster Discussion Session, Fri, 8:00 AM-11:00 AM

Registrational dataset from the phase I/II ARROW trial of pralsetinib (BLU-667) in patients (pts) with advanced RET fusion+ non-small cell lung cancer (NSCLC). *First Author: Justin F. Gainor, Massachusetts General Hospital, Boston, MA*

Background: Pralsetinib is an investigational, highly potent, selective RET kinase inhibitor targeting oncogenic RET alterations. We provide the registrational dataset for pts with RET fusion+ NSCLC with and without prior treatment from the global ARROW study. **Methods:** ARROW (75 sites in 11 countries; NCT03037385) consists of a phase I dose escalation to establish recommended phase II dose (400 mg once daily [QD] orally) and phase II expansion cohorts defined by tumor type and/or RET alteration. Primary objectives were overall response rate (ORR; blinded independent central review per RECIST v1.1) and safety. Efficacy analyses are shown for response-evaluable pts (REP) with RET fusion+ NSCLC who initiated 400 mg QD pralsetinib by July 11 2019 and safety for all pts (regardless of diagnosis) treated with 400 mg QD. **Results:** As of November 18 2019, 354 pts with advanced solid tumors had received pralsetinib at starting dose of 400 mg QD with median follow-up 8.8 months. ORR, disease control rate (DCR), and % of pts with tumor size reduction are shown in the table for pts with metastatic RET fusion+ NSCLC (n=116; 72% KIF5B; 16% CCDC6; 12% other/fusion present but type unknown) and with prior platinum treatment (n=80) or without prior systemic treatment (n=26). ORR was similar regardless of RET fusion partner, prior therapies, or central nervous system involvement. Overall there were 7 (6%) complete responses, 4 (5%) in prior platinum pts and 3 (12%) in treatment naïve pts; median time to response overall was 1.8 months and median duration of response (DOR) was not reached (95% CI, 11.3–NR). In the safety population (n=354), most treatment-related adverse events (TRAEs) were grade 1-2, and included increased aspartate aminotransferase (31%), anemia (22%), increased alanine aminotransferase (21%), constipation (21%) and hypertension (20%). 4% of pts in the safety population (all tumor types) discontinued due to TRAEs. **Conclusions:** Updated, registrational, centrally reviewed data demonstrate that pralsetinib has rapid, potent, and durable clinical activity in pts with advanced RET fusion+ NSCLC regardless of RET fusion genotype or prior therapies, and QD oral dosing is well-tolerated. Clinical trial information: NCT03037385. Research Sponsor: Blueprint Medicines Inc.

	Overall (n=116[a])	Prior platinum treatment (n=80)	No prior systemic treatment (n=26)
ORR, % (95% CI)	65 (55–73)[b]	61 (50–72)[b]	73 (52–88)
DCR, % (95% CI)	93 (87–97)	95 (88–99)	88 (70–98)
Tumor size reduction, % of pts	96	95	100

[a]Including n=10 with prior non-platinum treatment
[b]Including n=2 with partial response pending confirmation

9516 Poster Discussion Session; Displayed in Poster Session (Board #282), Fri, 8:00 AM-11:00 AM, Discussed in Poster Discussion Session, Fri, 8:00 AM-11:00 AM

Intracranial activity of selpercatinib (LOXO-292) in RET fusion-positive non-small cell lung cancer (NSCLC) patients on the LIBRETTO-001 trial. *First Author: Vivek Subbiah, Department of Investigational Cancer Therapeutics, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Patients with RET fusion-positive NSCLC have an ~50% lifetime prevalence of developing central nervous system (CNS) metastases. Selpercatinib is a highly selective oral RET inhibitor with CNS penetration. Its intracranial antitumor activity was previously demonstrated in an orthotopic RET fusion-positive preclinical model. The activity of selpercatinib in RET fusion-positive NSCLC patients with CNS metastases was evaluated as a prespecified subgroup analysis in LIBRETTO-001, a registrational phase 1/2 trial (NCT03157128). **Methods:** This global (89 sites, 16 countries) trial enrolled patients with advanced RET-altered solid tumors, including patients with RET fusion-positive advanced NSCLC with baseline CNS metastases. The selpercatinib recommended phase 2 dose was 160 mg twice daily, dosed orally in 28-day cycles. CNS metastases were assessed by MRI/CT scan at baseline, then every 8 weeks for 1 year, and every 12 weeks thereafter. The primary endpoint for this analysis was intracranial objective response rate (ORR, confirmed; RECIST v1.1) as assessed by independent review committee (IRC). Secondary endpoints included intracranial duration of response (DoR) by IRC. To be included in the efficacy analysis, patients were required to have adequate follow-up time (opportunity for ≥6 months follow-up from the first dose). Analyses were based on 17Jun2019 data cutoff date. **Results:** 79 patients with RET fusion-positive NSCLC and baseline CNS metastases were enrolled. Per IRC, 22 of 79 patients had measurable (≥10 mm) CNS disease; 14 of the 22 patients had adequate follow-up time for analysis. This efficacy-evaluable population had a median age of 64 yrs (range 43-80), ECOG PS 0/1 = 21% / 79%, and all had prior systemic therapy. 5 of the 14 patients received prior intracranial radiotherapy; all radiotherapy was completed > 2 months prior to selpercatinib. The intracranial ORR in the 14 patients was 93% (n = 13; 95% CI = 66.1 – 99.8), including 2 complete responses (14%) and 11 partial responses (79%). The median intracranial DoR was 10.1 months (95% CI = 6.7 – NE), with CNS progression events (n = 5) or death (n = 1) reported in 6 of 13 responders. The remaining responders (n = 7) were ongoing and censored. Presentation will include updated IRC data as of 16Dec2019. **Conclusions:** Selpercatinib had marked intracranial anti-tumor activity in RET fusion-positive NSCLC patients with CNS metastases. Tumor responses were durable, independently-confirmed, and observed in patients with prior systemic chemotherapy. Clinical trial information: NCT03157128. Research Sponsor: Loxo Oncology, a wholly owned subsidiary of Eli Lilly and Company.

9517 Poster Discussion Session; Displayed in Poster Session (Board #283), Fri, 8:00 AM-11:00 AM, Discussed in Poster Discussion Session, Fri, 8:00 AM-11:00 AM

Correlation of baseline molecular and clinical variables with ALK inhibitor efficacy in ALTA-1L. *First Author: D. Ross Camidge, Division of Medical Oncology, University of Colorado, Anschutz Medical Campus, Aurora, CO*

Background: Efficacy of ALK TKIs in patients (pts) with *ALK*+ non-small cell lung cancer (NSCLC) varies. We evaluated the impact of *EML4-ALK* fusion variants and other baseline (BL) molecular and clinical variables on clinical efficacy of brigatinib (BRG) vs crizotinib (CRZ) as first ALK TKI therapy in pts with *ALK*+ NSCLC in the phase 3 ALTA-1L (NCT02737501) trial. **Methods:** Plasma samples were collected at screening for molecular genetic analysis of *ALK* and other genes implicated in NSCLC by next-generation sequencing. Exploratory analyses were performed to identify associations of clinical outcomes with oncogenic alterations including *ALK* fusion variants and *TP53* status. **Results:** 124 BL samples were collected from 136 BRG-treated pts and 127 from 137 CRZ-treated pts. Pts with plasma samples were representative of the intent-to-treat population. BL *ALK* fusion detection rate was 52% (65/124) and 54% (68/127) in the BRG and CRZ arms, respectively, of which 83% (54/65) and 93% (63/68) were *EML4-ALK* fusions. In pts with detectable *EML4-ALK* fusions, the three predominant *EML4-ALK* fusion variants (V1, V2, V3) were equally distributed between arms; V1 and V3 were most prevalent (BRG/CRZ: V1, 42%/47%; V3, 42%/33%) but V1 was more frequent than V3 in pts without BL brain metastasis (47% vs 36%) or prior chemotherapy (45% vs 35%). Gender and age did not impact variant type. BRG showed higher ORR and improved mPFS vs CRZ in all variant subgroups; pts with V3 had poorer PFS compared with V1 and V2 regardless of treatment (Table). In pts with V3, BRG showed significantly improved PFS (HR=0.273, 95% CI 0.125, 0.597) and higher ORR (84% vs 67%) vs CRZ. *TP53* mutation was detected in 30% (37/124) of pts in BRG arm and 26% (33/127) in CRZ arm. In pts with detectable *ALK* fusion, *TP53* mutation showed poorer PFS in both arms than nonmutant/undetected cases (Table). BRG had better ORR and PFS vs CRZ in pts regardless of *TP53* mutation status. Additional analyses of BL variables are ongoing. **Conclusions:** *EML4-ALK* fusion variant 3 and *TP53* mutation were identified as poor prognosis biomarkers in *ALK*+ NSCLC. BRG demonstrated better efficacy than CRZ as first-line therapy in pts regardless of *EML4-ALK* fusion variant and *TP53* mutation status. These findings may help define areas of greatest unmet need. Clinical trial information: NCT02737501. Research Sponsor: ARIAD Pharmaceuticals, Inc., a wholly owned subsidiary of Takeda Pharmaceutical Company Limited.

Efficacy by *EML4-ALK* variant and *TP53* status.

	BRG	CRZ
***EML4-ALK* variant**		
V1, n	25	30
ORR, %	84	73
mPFS, mo	NR	13
V2, n	6	6
ORR, %	83	50
mPFS, mo	16	11
V3, n	25	21
ORR, %	84	67
mPFS, mo	16	7
***TP53* status[a]**		
Not detected, n	43	44
ORR, %	91	68
mPFS, mo	24	11
Mutant, n	24	24
ORR, %	79	63
mPFS, mo	8	7

NR, not reached [a]*TP53* status assessed only in pts with *ALK* fusions detected.

9518 Poster Discussion Session; Displayed in Poster Session (Board #284), Fri, 8:00 AM-11:00 AM, Discussed in Poster Discussion Session, Fri, 8:00 AM-11:00 AM

Updated overall survival (OS) and safety data from the randomized, phase III ALEX study of alectinib (ALC) versus crizotinib (CRZ) in untreated advanced *ALK*+ NSCLC. *First Author: Solange Peters, Lausanne University Hospital (CHUV), Lausanne University, Lausanne, Switzerland*

Background: Final, mature PFS from the global phase III ALEX study (NCT02075840) of ALC vs CRZ in untreated, advanced/metastatic *ALK*+ NSCLC have been previously published: ALC 34.8 months (m) (95% CI 17.7–NR) vs CRZ 10.9 m (95% CI 9.1–12.9), (HR 0.43, 95% CI 0.32–0.58). We report 5-year OS and updated safety data from ALEX with a further 12 m follow-up (FU) (cutoff date: Nov 29, 2019). **Methods:** Patients (pts) with stage IIIB/IV *ALK*+ NSCLC (by central IHC), ECOG PS 0–2 and no prior systemic therapy for advanced NSCLC were randomized 1:1 to ALC 600 mg BID (n = 152) or CRZ 250 mg BID (n = 151). Asymptomatic CNS metastases (mets) at baseline (BL) were allowed. OS was a secondary endpoint, and no formal statistical testing was planned. **Results:** Median duration of FU: 48.2 m with ALC vs 23.3 m with CRZ. OS data remain immature (events: 37%; stratified HR 0.67 [95% CI 0.46–0.98]); median OS with CRZ was 57.4 m (95% CI 34.6–not estimable [NE]) vs NE with ALC. The 5-year survival rate was 62.5% (95% CI 54.3–70.8) with ALC vs 45.5% (95% CI 33.6–57.4) with CRZ (Table). In pts with CNS mets at BL the OS HR was 0.58 (95% CI 0.34–1.00) and 0.76 (95% CI 0.45–1.26) in pts without CNS mets at BL. The OS benefit of ALC vs CRZ was generally consistent across all subgroups. Considering the longer treatment duration for ALC (28.1 m) vs the previous analysis (27.7 m), the safety profile of ALC remains consistent; no new safety signals were observed. With ALC, 35% of pts remain on study treatment vs 9% of pts remaining on CRZ. In pts with ≥1 known post-progression treatment (ALC: 32.2%; CRZ: 45.7%), lorlatinib was the most common ALK TKI received after first-line ALC (7.2%), compared with ceritinib after first-line CRZ (15.2%). **Conclusions:** This is the first global randomized study of a 2nd generation ALK TKI to demonstrate a clinically meaningful improvement in OS vs CRZ in *ALK*+ NSCLC (5-year survival rate: 62.5%, ALC vs 45.5%, CRZ); longer FU is required as OS data remain immature. Clinical trial information: NCT02075840. Research Sponsor: F. Hoffman-La Roche Ltd.

	ALC (n = 152)	CRZ (n = 151)	
Survival rate, % (95% CI) [No. pts at risk]			Difference, % (95% CI)
Year 1	84.3 (78.4–90.2) [120]	82.5 (76.2–88.9) [104]	-1.8 (-10.4–6.9)
Year 2	72.5 (65.1–79.9) [94]	65.3 (57.0–73.6) [73]	-7.2 (-18.3–3.9)
Year 3	67.0 (59.1–74.8) [81]	57.0 (48.2–65.9) [60]	-9.9 (-21.8–1.9)
Year 4	65.3 (57.3–73.3) [77]	51.2 (42.1–60.3) [48]	-14.1 (-26.2– -2.0)
Year 5	62.5 (54.3–70.8) [8]	45.5 (33.6–57.4) [3]	-17.0 (-31.5– -2.5)
Safety event, n (%) [median treatment duration: 28.1 m ALC; 10.8 m CRZ]			
AEs leading to discontinuation	22 (14.5)	22 (14.6)	
AEs leading to dose reduction	31 (20.4)	30 (19.9)	

9519 Poster Discussion Session; Displayed in Poster Session (Board #285), Fri, 8:00 AM-11:00 AM, Discussed in Poster Discussion Session, Fri, 8:00 AM-11:00 AM

Phase II study of savolitinib in patients (pts) with pulmonary sarcomatoid carcinoma (PSC) and other types of non-small cell lung cancer (NSCLC) harboring MET exon 14 skipping mutations (METex14+). *First Author: Shun Lu, Shanghai Lung Cancer Center, Shanghai Chest Hospital, Shanghai Jiao Tong University, Shanghai, China*

Background: There are unmet medical needs for pts with METex14+ NSCLC. PSC is a rare type of NSCLC with high incidence of MET exon 14 mutations and poor prognosis. Savolitinib (AZD6094, HMPL-504, volitinib) is a highly selective oral MET tyrosine kinase inhibitor, and its anti-tumor activity has been shown in combination with osimertinib in pts with EGFR-mutant, MET-amplified NSCLC (Yu H, et al. 2019 AACR, Abstract CT032). **Methods:** This was a multicenter, multi-cohort, single-arm phase II study (NCT02897479) to evaluate the efficacy, safety, and pharmacokinetics of savolitinib in pts with unresectable or metastatic METex14+ PSC and other NSCLC. MET mutation was tested or retrospectively confirmed by central laboratory. Savolitinib was taken orally, once daily (QD) (600mg for weight ≥50kg or 400mg weight < 50kg) until disease progression or intolerable toxicity. Tumor was evaluated every 6 weeks during the 1st year and every 12 weeks thereafter. The primary endpoint was independent review committee (IRC) assessed objective response rate (ORR) (RECIST version 1.1). Here we report the results of one cohort of prior MET-treatment naïve patients. **Results:** As of October 31, 2019, 593 pts were pre-screened/screened, 87 identified with METex14+ and 70 treated. Among treated pts, median age was 68.7 years (range 51.7-85.0), 58.6% pts were male, 92.9% stage IV, 60.0% previously treated, 57.1% with adenocarcinoma, 35.7% with PSC and the rest with other pathological types. Sixty-one pts were efficacy evaluable by IRC assessment (N = 61) (including pts who had at least one measurable lesion at baseline and had ≥1 scheduled post-baseline tumor assessment or evidence of any post-baseline radiological disease progression): ORR was 47.5% (95% CI: 34.6%, 60.7%), disease control rate 93.4% (95% CI: 84.1%, 98.2%) and median duration of response not reached yet. The median progression-free survival was 6.8 months (95% CI 4.2, 13.8) among all treated pts. Efficacy results were consistent with investigators'assessments. The most common (≥20%) treatment-related adverse events (TRAEs) were peripheral edema, nausea, increased AST/ALT, vomiting and hypoalbuminemia. The incidence of ≥ grade 3 TRAEs was 41.4%. TRAEs leading to treatment discontinuation occurred in 14.3% pts, among which liver injury and hypersensitivity were most common (each 2.9%). **Conclusions:** Savolitinib demonstrated promising anti-tumor activity and acceptable tolerability in METex14+ NSCLC pts. Clinical trial information: NCT02897479. Research Sponsor: Hutchison MediPharma Limited.

9520 Poster Discussion Session; Displayed in Poster Session (Board #286), Fri, 8:00 AM-11:00 AM, Discussed in Poster Discussion Session, Fri, 8:00 AM-11:00 AM

Capmatinib in patients with *METex14*-mutated or high-level *MET*-amplified advanced non–small-cell lung cancer (NSCLC): results from cohort 6 of the phase 2 GEOMETRY mono-1 study. *First Author: Harry J.M. Groen, University of Groningen and University Medical Center Groningen, Groningen, Netherlands*

Background: Capmatinib (INC280) has shown promising efficacy in patients (pts) with *MET* exon 14 (*METex14*)–mutated NSCLC who were pretreated (cohort 4) or treatment (tx)-naïve (cohort 5b) in the ongoing, multicohort, phase 2 GEOMETRY mono-1 study. We report the results for pts enrolled in the expansion cohort 6 with either high-level *MET* amplification (gene copy number [GCN] ≥10) or *METex14* mutation (any *MET* GCN) whose disease progressed on 1 prior line of systemic therapy. **Methods:** Adult pts (≥18 years), ECOG PS 0–1 who had *ALK* and *EGFR* wt, stage IIIB/IV NSCLC (any histology) received capmatinib tablets 400 mg twice daily (with or without food). Key efficacy endpoints were overall response rate (ORR) and duration of response (DOR) by blinded independent review committee (BIRC) per RECIST v1.1. Other secondary endpoints included investigator-assessed ORR, DOR, disease control rate (DCR), progression-free survival (PFS; BIRC and investigator assessment) and safety. **Results:** As of Jan 6, 2020, 34 NSCLC pts with *METex14* mutation (n = 31) or high-level *MET* amplification (n = 3) were included in this analysis. Tx was ongoing for 38.2% of pts. In *METex14*-mutated NSCLC pts, per BIRC assessment: ORR was 48.4%, median DOR was 6.93 months (mo, not yet mature, 95% CI: 4.17–NE) and median PFS was 8.11 mo (not yet mature, 95% CI: 4.17–9.86). Investigator-assessed responses were similar to BIRC assessment (Table). Only 3 pts with high-level *MET* amplification were included in this cohort due to challenges in enrollment. All 3 pts had stable disease per BIRC assessment and were on treatment for 48, 85 and 97 days. Most common AEs (≥25%, all grades, N = 34) were peripheral edema (64.7%), nausea (35.3%), fatigue (29.4%), back pain (26.5%) and vomiting (26.5%). Data for pts with brain metastasis will be presented at the ASCO 2020 meeting. **Conclusions:** Capmatinib was confirmed to be efficacious in 2nd line, *METex14*-mutated NSCLC pts. This is the first cohort where capmatinib has been administered without fasting restriction and data confirm the favorable safety profile. Clinical trial information: NCT02414139. Research Sponsor: Novartis Pharmaceuticals.

	Cohort 6 (2L, *METex14*-mutated) N = 31	
	BIRC	**Investigator**
ORR, % (95% CI)	48.4 (30.2–66.9)	41.9 (24.5–60.9)
DCR, % (95% CI)	90.3 (74.2–98.0)	90.3 (74.2–98.0)
Median PFS, mo (95% CI)	8.11 (4.17–9.86)	6.9 (5.55–NE)
Median DOR, mo (95% CI)	**N = 15** 6.93 (4.17–NE)	**N = 13** 8.18 (4.17–NE)

9521 Poster Discussion Session; Displayed in Poster Session (Board #287), Fri, 8:00 AM-11:00 AM, Discussed in Poster Discussion Session, Fri, 8:00 AM-11:00 AM

Evaluation of blood TMB (bTMB) in KEYNOTE-189: Pembrolizumab (pembro) plus chemotherapy (chemo) with pemetrexed and platinum versus placebo plus chemo as first-line therapy for metastatic nonsquamous NSCLC. *First Author: Marina Chiara Garassino, Department of Medical Oncology, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy*

Background: In a previous analysis of KEYNOTE-189 (NCT02578680), we showed that tissue TMB (tTMB) assessed by whole-exome sequencing was not significantly associated with efficacy in either arm and that pembro + chemo improved outcomes vs placebo + chemo in both the tTMB ≥175 and tTMB < 175 mut/exome subgroups. Here, we explored the association of bTMB with efficacy in KEYNOTE-189. **Methods:** 616 patients (pts) were randomized 2:1 to pembro + chemo or placebo + chemo. bTMB was assessed in cfDNA using the Guardant Health Omni assay. Association of bTMB (continuous square root transformed) with outcomes in each arm was assessed using Cox proportional hazards models (OS, PFS) and logistic regression (ORR) adjusted for ECOG PS; statistical significance was determined at the 0.05 level without multiplicity adjustment. The clinical utility of bTMB on outcomes was assessed using the cutoff that most closely approximated the 175 mut/exome tTMB cutoff as determined by AUROC analysis. Data cutoff was 21 Sep 2018. **Results:** 235 (38%) treated pts had evaluable tTMB and bTMB: 160 in the pembro + chemo arm and 75 in the placebo + chemo arm. bTMB as a continuous variable was not significantly associated with OS or ORR for pembro + chemo (one-sided P = .229 and .051) or placebo + chemo (two-sided P = .641 and .069); bTMB was significantly associated with PFS in the pembro + chemo arm (one-sided P = .015) but not the placebo + chemo arm (two-sided P = .058). bTMB and tTMB scores were moderately correlated (r = .61). The bTMB cutoff that most closely approximated tTMB 175 mut/exome was 15 mut/Mb (AUROC 0.81, 95% CI 0.75-0.86). 178 (76%) pts had concordant bTMB and tTMB results—101 low and 77 high by both—whereas 57 (24%) had discordant results—21 high bTMB but low tTMB, 36 low bTMB but high tTMB. Pembro + chemo improved OS, PFS, and ORR vs placebo + chemo for bTMB ≥15 and < 15 mut/exome (Table). **Conclusions:** Similar to previous findings based on tTMB, bTMB has limited clinical utility in the setting of pembro with pemetrexed and platinum given as first-line therapy for metastatic nonsquamous NSCLC. Clinical trial information: NCT02578680. Research Sponsor: Merck & Co., Inc., Kenilworth, NJ, USA.

	bTMB ≥15 mut/Mb		bTMB < 15 mut/Mb	
	Pembro + Chemo n = 70	**Placebo + Chemo n = 28**	**Pembro + Chemo n = 90**	**Placebo + Chemo n = 47**
Median OS (95% CI), mo	20.4 (17.4-NE)	9.7 (7.6-NE)	17.7 (12.2-NE)	8.0 (6.5-18.8)
HR (95% CI), OS	0.61 (0.36-1.06)		0.64 (0.41-0.99)	
Median PFS (95% CI), mo	8.3 (4.9-14.1)	4.7 (2.8-5.5)	7.0 (6.2-9.7)	4.7 (4.0-5.3)
HR (95% CI), PFS	0.35 (0.21-0.57)		0.50 (0.34-0.73)	
ORR, % (95% CI)	49 (36-61)	11 (2-28)	40 (30-51)	19 (9-33)

9523 Poster Discussion Session; Displayed in Poster Session (Board #289), Fri, 8:00 AM-11:00 AM, Discussed in Poster Discussion Session, Fri, 8:00 AM-11:00 AM

Prevalence and association of *ARID1A* with driver alterations and immune checkpoint inhibitor (ICPi) biomarkers in cell-free circulating tumor DNA (ctDNA) from 27,000 non-small cell lung cancer (NSCLC) patients. *First Author: David R. Gandara, University of California Davis Comprehensive Cancer Center, Sacramento, CA*

Background: Recent data suggest that the tumor suppressor gene *ARID1A* is associated with high anti-tumor immunity and may have value as a predictive biomarker for response to ICPi therapy in NSCLC. We examined *ARID1A* alterations detected in ctDNA from a large cohort of advanced NSCLC patients using a commercially available liquid biopsy assay and explored associations of *ARID1A* with lung cancer driver alterations and other putative ICPi mutational biomarkers. **Methods:** Consecutive samples from stage IIIB/IV NSCLC patients tested from March 2016 - August 2019 using a 73- to 74-gene targeted next-generation sequencing ctDNA assay (Guardant360) were queried. Testing included analysis of single nucleotide variants, insertions/deletions, fusions, and amplifications (*KEAP1* not tested). Mutation frequencies were compared using Fisher's exact test, with variants of uncertain significance and synonymous variants excluded. **Results:** Of 27,776 NSCLC patients with >1 ctDNA alteration detected, 1,094 (3.9%) had >1 functional *ARID1A* (f*ARID1A*) mutation. f*ARID1A* mutations were significantly more common in patients with squamous histology compared to adenocarcinoma (5.1% vs 3.8%, p = 0.0007). There were significantly fewer *EGFR* exon 19 deletion mutations (4.9% vs 11.1%; p < 0.0001) and *EGFR* L858R mutations (4.0% vs 7.0%; p < 0.0001), and significantly more *BRAF* V600E alterations (2.2% vs 1.4%; p = 0.0338) in patients with f*ARID1A*. There was no significant difference in the frequency of *ALK* and *ROS1* fusions, nor *STK11* mutations between patients with and without f*ARID1A* (8.0% vs 6.8%; p = 0.126). Activating *KRAS* mutations were significantly more frequent in patients with f*ARID1A* (31.1% vs 19.4%; p < 0.0001), including *KRAS* G12C (10.9% vs 7.0%; p < 0.0001). **Conclusions:** These data provide a mutational landscape for f*ARID1A* mutations in NSCLC. f*ARID1A* was associated with significant differences in the frequency of multiple lung cancer driver alterations, of particular interest in the *EGFR*-mutated cohort, where ICPi efficacy is low. The frequency of *STK11* mutations, a possible negative predictor of ICPi efficacy, was not significantly different. *KRAS* mutations were significantly more frequent in patients with f*ARID1A*, notable given recent data reporting that *KRAS* mutations, particularly *KRAS* G12C, may be a positive predictor of ICPi response in NSCLC. Determination of ICPi efficacy in patients with f*ARID1A* is in-process. Research Sponsor: None.

9524 Poster Session (Board #290), Fri, 8:00 AM-11:00 AM

PREDICT1: An observational study for identifying blood biomarkers associated with clinical benefit from carboplatin and pemetrexed (CbP) treatment in patients with non-squamous (NS) non-small cell lung cancer (NSCLC) (CJLSG1201). *First Author: Tetsunari Hase, Department of Respiratory Medicine, Nagoya University Graduate School of Medicine, Nagoya, Japan*

Background: At present, platinum-doublet chemotherapy or in combination with an immune check point inhibitor are standard treatment for patients with metastatic or recurrent NSCLC which lacks somatic gene alterations. Although CbP is one of the commonly used treatment options for NS-NSCLC, its clinical utility is limited due to lack of optimal biomarkers. **Methods:** Chemotherapy-naïve patients with pathologically proven advanced or recurrent NS-NSCLC received carboplatin (area under the curve = 5-6, at investigator's discretion) plus pemetrexed (500 mg/m2) every 3 weeks followed by maintenance pemetrexed until disease progression. Blood samples were collected before treatment for proteomic analysis using mass spectrometry (MS). A classifier was constructed based on both an objective response assessed by radiologist independent of attending physicians in accordance with RECIST v1.1 and expression profiles of protein in a training cohort. The constructed classifier was then assessed with a validation cohort evaluating prediction accuracy of good responder, progression free survival (PFS) and overall survival (OS). **Results:** Of 244 patients with NS-NSCLC in a training cohort, proteomic profiles in blood from 96 patients who responded or progressed after treatment with CbP were analyzed to develop a classifier based on weighted voting. Details of the classifier will be presented at the 2020 ASCO Annual Meeting. The classifier was then applied to validation cohort (n = 94), and we successfully identified patients who benefit from the treatment (55 in good MS group) or not (39 in poor MS group). The objective response rate of the good MS group was significantly higher than that of the poor MS group (30.9% vs. 5.1%; p = 0.0018). The good MS group showed a significantly improved survival compared to the poor MS group (median PFS, 6.0 m vs. 2.3 m; hazard ratio [HR], 0.15; 95% confidence interval [CI], 0.09-0.27; p < 0.001; median OS, 25.7 m vs. 5.1 m; HR, 0.18; 95% CI, 0.1-0.34; p < 0.001). **Conclusions:** In the present study, we successfully developed and validated a predictive classifier using proteomic analyses with blood samples collected from patients before treatment with CbP, suggesting the clinical utility of the classifier in selecting NS-NSCLC patients for treatment with CbP. Clinical trial information: UMIN000008476. Research Sponsor: Japan Agency for Medical Research and Development.

9525 Poster Session (Board #291), Fri, 8:00 AM-11:00 AM

Comprehensive modeling of longitudinal circulating tumor DNA dynamics to predict clinical response to first-line immunotherapy and chemo-immunotherapy in advanced non-small cell lung cancer. *First Author: Joseph Christopher Murray, Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins School of Medicine, Baltimore, MD*

Background: First-line immunotherapy (IO) and chemo-immunotherapy (chemo-IO) are approved for PD-L1-expressing advanced non-small cell lung cancer (NSCLC), but PD-L1 expression does not reliably predict therapeutic response. Therefore, accurate on-therapy response assessment is needed to guide clinical decision-making. Conventional radiographic imaging is the gold-standard, but may not capture the nature and timing of an immune-mediated response. We investigated whether comprehensive longitudinal circulating tumor DNA (ctDNA) dynamics could enhance prediction of clinical response. **Methods:** We conducted targeted error correction sequencing (TEC-Seq) of longitudinal plasma specimens and matched white blood cells (WBCs) in patients with NSCLC treated with first-line IO or chemo-IO. Plasma ctDNA variants were identified by filtering out clonal hematopoiesis (CH) and germline (GL) variants found in matched WBCs. Clinical and pathological data, including PD-L1 tumor proportion score (TPS), and imaging response by RECIST1.1 were assessed. ctDNA dynamics were modeled to predict durable clinical benefit (at 6 months), progression-free survival (PFS), and overall survival (OS). **Results:** A total of 143 longitudinal plasma and 24 white blood cell samples underwent TEC-Seq for 31 patients with NSCLC treated with IO (n = 17) or chemo-IO (n = 14). ctDNA variants were found in 77% (n = 24) of patients after filtering out CH and GL variants, which comprised 53% (n = 196 of 373) of all variants. Molecular response, signified by elimination of ctDNA variants, was detected in 32% (n = 10) of patients and associated with improved PFS (p = 0.0004, log rank) and OS (p = 0.017, log rank). Time to molecular response was shorter than time to best RECIST response (median 3 vs. 7.71 weeks, p = 0.048, Mann-Whitney U test). A logistic regression model incorporating molecular response, recrudescence, or emergence of new variants predicted durable clinical benefit (sensitivity 84%, specificity 76%, AUC 0.88) better than PD-L1 TPS (AUC 0.67, p = 0.046, bootstrap method). **Conclusions:** Comprehensive modeling of ctDNA variant dynamics predicts clinical outcome independent of PD-L1 status in patients with advanced NSCLC treated with first-line IO or chemo-IO. Verification of bona fide ctDNA variants by matched WBC sequencing is essential. Molecular response can be identified earlier than imaging response and could enable on-therapy decision-making to alter clinical outcomes. Research Sponsor: NCI R01 CA121113, Emerson Collective, LUNGevity Foundation, The V Foundation, Swim Across America.

9526 Poster Session (Board #292), Fri, 8:00 AM-11:00 AM

Targeted DNA sequencing analysis to reveal genetic diversity and androgen-receptor alteration in advanced EGFR mutant lung adenocarcinoma. *First Author: Wei Wu, University of California, San Francisco, San Francisco, CA*

Background: Lung cancer remains the leading cause of death from cancer around the world. Several oncogenic drivers have been identified from large cancer genome projects focused mainly on profiling early-stage lung cancers. Targeted therapies have been developed for specific activated driver gene mutations and are used in advanced-stage patients. For instance, advanced EGFR mutant lung cancer is primarily treated with EGFR tyrosine receptor inhibitors (TKIs). However, resistance remains an obstacle to durable anti-tumor control. We hypothesize that concurrent genetic alterations co-exiting with EGFR driver mutations contribute to the failure of EGFR TKI therapy. **Methods:** To understand the complexity and diversity of genetic alterations present in EGFR mutant advanced lung cancers, we utilized 660 EGFR mutant advanced lung adenocarcinomas samples with targeted DNA sequencing from Foundation Medicine, 394 cases from MSK-IMPACT dataset, along with TCGA lung cancer data. We performed systematic co-mutation analysis, molecular simulation, functional annotation and pathway enrichment analysis. **Results:** We updated mutational profiling on EGFR gene with hotspots at exon 18, 19, 20 and 21. Among them, EGFR L858R, exon19 deletion, T790M and G719A are top ranking alleles among EGFR mutations. Interestingly, a subset (n = 26 cases) of EGFR T790M mutations parallel with other EGFR mutations, which could affect the TKI binding pocket as inferred by molecular simulations. Furthermore, in advanced lung cancer EGFR mutations co-occurred with known oncogenic mutations in KRAS, MET, NF-1, MAP2K1, ERBB2, and ALK/ROS-1/RET fusions. Functional annotation suggests that concurrent mutated genes and copy number alterations in advanced EGFR mutant lung cancer were enriched in signatures of epigenetic modifiers, genome instability, WNT signaling, and RNA splicing. Compared to early stage TCGA-lung adenocarcinomas, Cell cycle, DNA repair, WNT signaling and androgen receptor-mediated signaling pathways are predominantly altered in advanced EGFR mutant lung cancers. **Conclusions:** We characterized the genetic landscape of advanced EGFR-mutant lung adenocarcinomas and further dissected concurrent mutated genes with EGFR driver mutations. Our findings provide a rational for polytherapy roadmap for testing in advanced EGFR-mutant lung cancer. Research Sponsor: U.S. National Institutes of Health.

9527 Poster Session (Board #293), Fri, 8:00 AM-11:00 AM

RELAY study of erlotinib (ERL) + ramucirumab (RAM) or placebo (PL) in *EGFR*-mutated metastatic non-small cell lung cancer (NSCLC): Biomarker analysis using circulating tumor DNA (ctDNA) in Japanese patients (pts). *First Author: Kazuto Nishio, Department of Genome Biology, Kindai University Faculty of Medicine, Osaka, Japan*

Background: The phase III RELAY study (NCT02411448) showed significantly improved progression-free survival (PFS) for RAM+ERL vs PL+ERL in 449 pts with previously untreated *EGFR* mutation-positive metastatic NSCLC (median PFS 19.4 vs 12.4 mo, HR 0.591 [95% CI 0.461–0.760], p<.0001). To understand baseline genetic mutations and treatment-emergent (TE) resistance mechanisms, this exploratory liquid biopsy substudy examined biomarkers in ctDNA from participating Japanese pts by next-generation sequencing (NGS) and droplet digital PCR (ddPCR). **Methods:** Plasma samples were collected at baseline, during treatment (Cycle 4, 13, and every 6 cycles to Cycle 53) and post-study treatment discontinuation (30-day follow-up [30d FU]). Mutations were assessed at baseline and 30d FU by NGS (Ion AmpliSeq Colon and Lung Cancer panel). *EGFR* mutations and *MET* and *ERBB2* copy number (CN) were assessed at all time points by ddPCR. Baseline markers were analyzed in pts with any detectable baseline mutation (to confirm ctDNA presence; NGS N=84, ddPCR N=74). TE mutations were analyzed in pts with any detectable mutation at baseline and 30d FU (NGS N=26, ddPCR N=28). Among these pts, 81% and 57% for NGS and ddPCR, respectively, had progressed by 30d FU. **Results:** By plasma NGS, baseline *EGFR* activating mutations (exon 19 deletion or exon 21 [L858R] mutation) were detected in 83.3% of pts. Common co-occurring baseline mutations were *TP53* (42.9%), *PTEN* (7.1%) and *KRAS* (6.0%). Baseline *TP53* mutation rate was higher in men vs women (p=.02). No difference in PFS was detected by baseline *TP53* status (interaction predictive p=.45, prognostic p=.33). TE mutations were detected in *EGFR* (including T790M), *FGFR3*, *KRAS* and *TP53*. Slightly higher rates of TE *KRAS* (p=.03) and *TP53* (p=.07) mutations were detected in RAM+ERL than in PL+ERL. TE total *EGFR* mutations (p=.65) or TE T790M (p=.69) did not differ by arm. By ddPCR, baseline *EGFR* activating mutations were detected in all pts. T790M was detected at baseline in 2/37 pts/arm (5.4%) and was TE in 6/11 (55%) RAM+ERL pts and 7/17 (41%) PL+ERL pts. There was a trend (p=.054) for greater *ERBB2* CN in RAM+ERL vs PL+ERL at Cycle 4. *MET* CN decreased slightly at Cycle 4 in both arms (significant in PL+ERL, p=.003). Biomarker levels by ddPCR across all time points will be presented. **Conclusions:** Though limited by sample size and likely inconsistent tumor shedding, this exploratory study identified potential differences in *TP53*, *KRAS*, *ERBB2* and *MET* by demographics, treatment and/or time. Clinical trial information: NCT02411448. Research Sponsor: Eli Lilly and Company.

9528 Poster Session (Board #294), Fri, 8:00 AM-11:00 AM

Exon-16-skipping *ERBB2* (*ERBB2*ΔEx16) as a novel resistance mechanism against EGFR tyrosine kinase inhibitors in non-small cell lung cancer (NSCLC). *First Author: Xin Zhao, Department of Respiratory and Critical Care Medicine, Jiangsu Province Hospital, The First Affiliated Hospital of Nanjing Medical University, Nanjing, China*

Background: In addition to *ERBB2* amplification/protein overexpression, activating *ERBB2* alterations have been increasingly discovered in diverse human cancers with varying incidence. *ERBB2*ΔEx16 is an alternatively spliced isoform of *ERBB2*, lacking the entire exon 16 which encodes a small extracellular domain. *ERBB2*ΔEx16 was recently reported to lead to oncogenic activation of ERBB2 and osimertinib resistance in *EGFR* T790M+ non-small cell lung cancer (NSCLC). **Methods:** A total of 38,680 Chinese cancer patients whose tumor specimen or circulating cell-free DNA underwent genomic profiling by targeted next-generation sequencing of cancer-related genes were retrospectively reviewed. Clinicopathological features and treatment history of *ERBB2*ΔEx16+ patients were evaluated. RNA sequencing was performed to validate the presence of exon-16-skipping *ERBB2* at the transcriptional level. **Results:** A total of eighteen *ERBB2*ΔEx16+ patients (11 NSCLC, 2 colorectal cancer, 2 gastric cancer, and 3 others) were identified (0.047%, 18/38,680). *ERBB2* exon 16 skipping may result from large fragment deletion spanning the whole or partial region of exon 16 (72.2%, 13/18), base substitution at the splice acceptor site (16.7%, 3/18) and deletion of the splice donor site (11.1%, 2/18). *ERBB2* exon 16 skipping, including large fragment deletion and splice site deletion, was validated at the RNA level by RNA sequencing in 3 patients with available samples. Co-occurrence of *ERBB2* amplification and *ERBB2* mutations were found in 83.3% (15/18) and 50% (9/18) of cases, respectively. Concurrent copy number variations were prevalent in *CDK12* (55.6%, 10/18), *CDKN2B* (44.4%, 8/18), *NKX2.1* (38.9%, 7/18) and *PTPRD* (33.3%, 6/18). Among the 11 cases of *ERBB2*ΔEx16+ NSCLC, 9 had coexisting activating *EGFR* mutations (exon 19 deletions, exon 21 L858R) and received prior treatment with EGFR tyrosine kinase inhibitors (TKIs), with 2 harboring acquired *EGFR* T790M mutation and 1 *EGFR* copy number gain. Further analysis of the matched pretreatment samples in 3 *EGFR*-mutated NSCLC patients confirmed that *ERBB2*ΔEx16 was acquired during EGFR TKI therapy. In the 7 cases of other cancers, 4 to 31 non-*ERBB2* mutations were identified in each sample, with *TP53* being the most frequently mutated gene. **Conclusions:** Our data suggest that *ERBB2*ΔEx16 may be a general mechanism of EGFR TKI resistance in a subset of *EGFR*-mutated NSCLC patients, in addition to being an oncogenic driver as reported in some solid malignancies including colorectal, gastric and ovarian cancers. Research Sponsor: None.

9529 Poster Session (Board #295), Fri, 8:00 AM-11:00 AM

A model comparing the value of broad next-gen sequencing (NGS)-based testing to single gene testing (SGT) in patients with nonsquamous non-small cell lung cancer (NSCLC) in the United States. *First Author: Nathan A. Pennell, Cleveland Clinic Foundation, Cleveland, OH*

Background: Patients (pts) with nonsquamous (ns) NSCLC should be tested for actionable driver oncogenes (ADOs), and highly effective treatments (tx) may be available for these pts. Although EGFR and ALK single gene testing (SGT) is relatively common (>80%) in the US, testing for less common ADOs is rare. Unidentified pts with ADOs have survival comparable to pts without alterations. We interrogate plausible testing configurations and discuss their implications for the US population. **Methods:** Simulation was used to evaluate various levels of testing with SGT or NGS on the basis of life years gained (LYG) as well as cost per LYG. Expected prevalence of ADOs among nsNSCLC pts as well as the survival distribution of pts in the presence versus absence of an ADO tx strategy were calibrated based on current literature. Survival duration for each simulated pt was generated from Weibull distributions fit to statistical estimates of median and 5-year survival. With appropriate match between ADO and targeted tx, the Weibull distribution offered a median additional 2 years of life. ADOs included in NGS: EGFR, ALK, ROS1, BRAF, RET, MET, NTRK. SGT: EGFR and ALK. **Results:** Each incremental 10% increase in NGS instead of SGT produces 2630 additional LYG and a cost savings per LYG between -$49 to -$109. At the current 80% testing rate, replacing SGT with NGS would result in an additional 21,019 LYG with reduced cost per LYG of -$599. Increasing testing from 80% to 100% of eligible pts would increase LYG by 15,017 over the current state. If 100% of eligible pts were tested with NGS and every identified pt received tx, the cost per LYG of this strategy would be $16,641.57. **Conclusions:** In a hypothetical model where highly effective tx is available to all identified pts with ADOs, broad NGS testing compared to SGT for EGFR/ALK leads to large gains in life years at reduced cost per LYG compared to SGT, supporting universal NGS testing of all advanced nsNSCLC pts. Conversely, lower levels of testing or only testing for common ADOs (as is the current state) result in large numbers of pts being unidentified and not experiencing these benefits. Research Sponsor: None.

Eligible nsNSCLC pts for testing in US annually.	89,000
Estimated pts with ADOs (EGFR/ALK/ROS1/BRAF/RET/MET/NTRK)	26,300
CMS reimbursement for NGS	$627.50
CMS reimbursement for SGTs (EGFR+ALK)	$732.30
Cost of treatment for 2 years	$10K/year = $20,000
Estimated median and 5-year survival of pt with ADO with highly-effective tx	39 months and 25%
Estimated median and 5-year survival of pt with ADO who goes unidentified	14 months and 5%

9530 Poster Session (Board #296), Fri, 8:00 AM-11:00 AM

Impact of SWI/SNF complex mutations in patients with non-small cell lung cancer (NSCLC) treated with immune checkpoint inhibitors: Immuno-oncology biomarker study in LC-SCRUM-Japan (LC-SCRUM-IBIS). *First Author: Kiyotaka Yoh, National Cancer Center Hospital East, Kashiwa, Japan*

Background: The SWI/SNF chromatin remodeling complex is reported to be involved in sensitivity and resistance to immune checkpoint inhibitor (ICI). However, their role in non-small cell lung cancer (NSCLC) remains unclear. We examined the relationship between SWI/SNF complex mutations and clinical outcomes of ICI in patients with NSCLC. **Methods:** Of 1017 lung cancer patients enrolled in LC-SCRUM-IBIS, 350 patients were analyzable for whole-exome sequencing (WES). WES data were used to analyze the presence of mutations in 29 major subunits of the SWI/SNF complexes. ARID1A and SMARCA4 mutations were also evaluated in a targeted NGS panel (Oncomine comprehensive assay, OCA). PD-L1 expression by 22C3, tissue tumor mutational burden (tTMB) by WES, STK11 and KEAP1 mutations by WES or OCA were also assessed. Durable clinical benefit (DCB) including CR, PR and SD > 6 mos to ICI, progression-free survival (PFS) and overall survival (OS) were compared in status of each of SWI/SNF complex mutations and other factors. **Results:** At least one mutation in any subunits of the SWI/SNF complex was present in 28% of NSCLC patients. The most common mutated subcomplexes were SMARCA4 (12%), BAF (7%: ARID1A, 4%), non-canonical BAF (3%), PBAF (3%), and SMARCA2 (2%). Of 101 NSCLC patients treated with PD-1/PD-L1 inhibitors, SMARCA4 mutations tended to be associated with lower DCB (16 vs 31%) and shorter median PFS (1.9 vs 3.6 m) and OS (7.4 vs 18.1m). Patients with ARID1A mutations tended to have better clinical outcomes (DCB, 40 vs 28%) compared to those without mutations. No significant associations were found between PD-L1 expression and SMARCA4 or ARID1A mutations. Patients with STK11/KEAP1 mutations had lower rate of PD-L1 expression (TPS > 50%) (18% vs 48%, $P = 0.03$) and worse clinical outcomes (DCB, 6 vs 33%) compared to those without mutations. There was no significant association between a tTMB status and clinical outcome. **Conclusions:** SMARCA4 and ARID1A mutations appear to affect clinical outcomes of ICI in NSCLC patients. These findings indicate that SWI/SNF complex mutations may serve as a predictive biomarker for ICI in NSCLC patients. Research Sponsor: AstraZeneca, Bristol-Myers Squibb, Chugai, Ono.

9531 Poster Session (Board #297), Fri, 8:00 AM-11:00 AM

Identification and in silico structural insights of rare recurrent *EGFR* mutations as resistance mechanisms to osimertinib in *EGFR*-mutated lung cancer. *First Author: N/a Zhoutong, Department of Medical Oncology, Changzhou Cancer Hospital of Soochow University, Changzhou, China*

Background: Inevitable progression on 3rd-generation EGFR-tyrosine kinase inhibitor (TKI) osimertinib of *EGFR*-mutated lung cancer patients represents a great challenge in clinic. Previous studies have revealed that one-third of the resistant mechanisms are due to acquired *EGFR* secondary mutations, mainly on C797, L718 and L792 residues. Our study aims to gain insights into novel mechanisms of acquired resistance to osimertinib. **Methods:** We performed genomic profiling on a total of 1,058 *EGFR*-mutated lung cancer patients with progressed disease on osimertinib, and a cohort of 1,803 patients who received only 1st-generation EGFR TKIs upon progression. Recurrent *EGFR* mutations with a significant enrichment in the osimertinib group were identified. We further established and applied molecular dynamic simulation-based computational model of the mutant EGFR protein to predict its sensitivity to osimertinib. **Results:** As expected, compared with 1st-TKIs alone group, *EGFR* mutations, including C797S/G (22.1% vs. 0.5%), L718Q/V (6.2% vs. 0.3%), L792F/H (4.4% vs. 0.3%), were significantly more enriched in the osimertinib cohort. Our computational model has also successfully predicted their sensitivities to osimertinib: WT (-35.19 kcal/mol) > L792F (-34.10 kcal/mol) > L718Q (-30.33kcal/mol) > C797S (-28.02 kcal/mol), which are consistent with our previous *in vitro* validations. Importantly, a total of 14 low-frequency *EGFR* mutations were exclusively observed in the osimertinib group, seven of which, including *EGFR* G796S(n = 6), V802F(n = 3), T725M(n = 2), Q791L/H(n = 2), P794S/R(n = 2), were predicted to dramatically reduce the binding affinity of osimertinib to EGFR. Of note, analysis of the pretreatment samples of two patients supported that *EGFR* V802F and Q791L/H were acquired during osimertinib treatment. Interestingly, *EGFR* G796S was predicted to be sensitive to gefitinib, suggesting the possibility of administration of gefitinib in patients with acquired *EGFR* G796S to first-line osimertinib treatment. Further *in vitro* functional validations are currently ongoing. **Conclusions:** Our study represents the largest *EGFR*-mutated lung cancer cohort so far to investigate osimertinib resistance in a real-world setting, and has uncovered a list of recurrent low-frequency *EGFR* mutations that may confer acquired resistance to osimertinib. Our *in silico* structural model was proved to be powerful and robust in the prediction of osimertinib sensitivity of EGFR mutants. Research Sponsor: None.

9532 Poster Session (Board #298), Fri, 8:00 AM-11:00 AM

Residual circulating tumor DNA (ctDNA) after two months of therapy to predict progression-free and overall survival in patients treated on S1403 with afatinib +/- cetuximab. *First Author: Philip C. Mack, Icahn School of Medicine at Mount Sinai, New York, NY*

Background: ctDNA from patient plasma has demonstrated diagnostic utility in non-small cell lung cancer (NSCLC). Longitudinal changes in mutant allele frequency (MAF) have great potential to refine clinical management on targeted therapies. **Methods:** S1403 was a first-line phase II study of afatinib w or w/o cetuximab in pts with EGFR-mutant NSCLC. Between March, 2015 and April, 2018, 174 pts were randomized with 168 determined to be eligible. The study closed early due to futility. Plasma specimens were prospectively collected at baseline, Cycle 3 Day 1 (C3D1; 8 weeks) and at progression, and processed for batch analysis of ctDNA by next-generation sequencing (Guardant 360). A complete case analysis approach was used. The Kaplan-Meier method was used to estimate survival distributions, a Cox model to estimate hazard ratios and confidence bounds, and the log-rank test to compare distributions. A landmark analysis was used to assess predictive value of ctDNA clearance at C3D1. **Results:** 104 patients (62%) had analyzable baseline plasma specimens available, with *EGFR* mutations detected in 83 (80%). PFS was significantly shorter for pts with *EGFR* ctDNA positivity at baseline (p = 0.03) (Table) compared to those with no detectable ctDNA, likely a prognostic effect. Kinetic changes in ctDNA MAFs were analyzed in 79 pts with matching baseline and C3D1 specimens. Of 62 cases with detectable ctDNA at baseline, 68% (42/62) became undetectable at C3D1 ("ctDNA clearance"); ctDNA clearance relative to residual ctDNA was associated with significantly longer PFS (p = 0.00001) and OS (0.003) (Table). To date, 29 pts had matching *at-progression* samples. T790M mutations were observed at progression in 6/29 (24%) cases. Other putative emergent resistance factors include: a *TACC3-FGFR3* and an *EML4-ALK* fusion, *MET* exon 14 skipping, multiple *MET* amplifications and *NF1* frameshift mutations. **Conclusions:** Clearance of *EGFR* ctDNA after 60 days of therapy was associated with a substantial and statistically significant improvement in subsequent PFS and OS. Incorporation of ctDNA kinetics into routine clinical care represents a promising platform to identify patients with inferior outcomes on TKIs and detect targetable emergent resistance mechanisms. Research Sponsor: Boehringer Ingelheim; Eli Lilly, U.S. National Institutes of Health.

Baseline				
	Detectable	**Not-detectable**	**HR**	**p-value**
PFS	10.2 (7.3-13.5)	14.7 (10.1-NR)	1.80 (0.29-2.01)	**0.03**
OS	30.2 (25-NR)	NR	2.10 (0.82-5.39)	**0.10**
Landmark				
	Clearance at C3D1	**Residual at C3D1**	**HR**	**p-value**
PFS	15.1	2.8	0.24 (0.13-0.44)	**0.00001**
OS	27.2	15.0	0.30 (0.14-0.66)	**0.003**

9533 Poster Session (Board #299), Fri, 8:00 AM-11:00 AM

Effect of performance status on survival with pembrolizumab monotherapy in advanced non-small cell lung cancer (NSCLC). *First Author: Kartik Sehgal, Beth Israel Deaconess Medical Center, Boston, MA*

Background: Pembrolizumab (P) is now widely used as standard of care (SOC) in advanced NSCLC. We sought to identify prognostic factors influencing survival with it in a real-world setting. **Methods:** We conducted a retrospective cohort study of with advanced NSCLC patients who initiated treatment with SOC P monotherapy at our center from 2/11/16 to 10/15/19 (data cutoff 1/15/20). Patient demographic, clinicopathologic, therapeutic and outcomes data were extracted. Survival time was defined from start of P. Cox proportional hazards and logistic regression were utilized. **Results:** Of 74 patients with median follow up of 83.9 weeks, 30 (40.5%) were alive at cutoff. Patient characteristics at start of therapy were: 36 (48.6%) female, median age 68.5 yr (range 33-87), 10 (13.5%) with symptomatic brain metastases; 54 (72.9%) treatment-naïve, 29 (39.2%) with ECOG performance status (PS) ≥2. Tumor characteristics were: 53 (71.6%) with PD-L1 tumor proportion score (TPS) ≥50%, median PD-L1 TPS 75% (range 1-100), tumor mutational burden (TMB) tested in only 37 (50%) patients, median TMB 8 mut/mB (range 1-62). Any grade immune-related adverse events (irAE) occurred in 33 (44.6%) patients, while 16 (21.6%) received systemic steroids. Median survival was 43.3 wks (95% CI 29-104.1). Multivariable regression showed ECOG PS of ≥2 as the strongest risk factor for death (Table). We next evaluated differences in characteristics of patients who were alive vs dead within 12 wks of starting P, by which initial response assessments are completed in routine practice. ECOG PS was the only significantly different baseline variable, even after multivariable adjustment (p = 0.002). **Conclusions:** ECOG PS of ≥2 is a poor prognostic risk factor associated with P monotherapy in advanced NSCLC. Though comprising a clinically significant subset of patients in real-world, they were not included in landmark trials (KEYNOTE-024 & 042). Prospective evaluation is warranted. Research Sponsor: U.S. National Institutes of Health.

	Univariate Hazard ratio for death (95% CI)	p	Multivariable Hazard ratio for death (95% CI)	p
ECOG PS ≥2 / 0-1	3.72 (1.99 – 6.95)	< 0.001	3.63 (1.80 – 7.31)	< 0.001
Any grade irAE, No / Yes	3.36 (1.72 – 6.58)	< 0.001	3.16 (1.59 – 6.28)	0.001
Symptomatic brain metastases, Yes / No	1.83 (0.84 – 3.9)	0.13	1.70 (0.74 – 3.95)	0.21
Age	1.02 (0.99 – 1.06)	0.11	1.01 (0.97 – 1.04)	0.78
PD-L1 TPS	0.99 (0.99 – 1.01)	0.56	1.01 (0.99 – 1.02)	0.25
Ever smoker, No / Yes	1.78 (0.75 – 4.26)	0.19		
Prior therapy / Treatment-naïve	1.02 (0.52 – 1.99)	0.96		
TMB (limited availability)	0.91 (0.83 – 0.99)	0.04		
Systemic steroids for irAE, No / Yes	1.19 (0.59 – 2.42)	0.63		

9534 Poster Session (Board #300), Fri, 8:00 AM-11:00 AM

Distinct genomic instability landscape of lung adenocarcinoma associated with treatment and metastasis. *First Author: Chuanxin Wu, Department of Medical Oncology, Cancer hospital of Guangzhou Medical University, Guangzhou, China*

Background: Lung adenocarcinoma (LUAD) is the most common subtype of non-small cell lung cancer (NSCLC). Genomic instability, defined as genome-wide copy number alterations, is a key pathogenic signature which occurs at the early stage of most cancers and is associated with an increased risk of recurrence or death. We examined the pattern of genomic instability in primary and metastatic LUAD. **Methods:** We performed deep targeted sequencing (425 genes) of 3395 tissue samples and whole exome sequencing (WES) of 60 tissue samples from LUAD patients. Whole-genome doubling (WGD) and arm level aneuploidy were analyzed to uncover correlation with clinical phenotypes and other genomic alterations including driver mutations, tumor mutation burden (TMB), and microsatellite instability (MSI). **Results:** Overall, targeted sequencing revealed that WGD occurred in 64.33% LUAD samples, which was comparable with WES results. Compared to primary site, metastasis exhibited higher proportion of WGD (1.14 fold). Specifically, liver metastasis has the highest WGD percentage among metastasis sites (~87.5%; 1.40 fold increase compared to primary). Interestingly, patients who received tyrosine kinase inhibitors (TKI) had higher frequency of WGD than patients without TKI treatment. In addition, TMB was higher in WGD^+ patients but MSI status was not significantly different between groups. Arm-level aneuploidy was prevalent in this cohort. The most common amplification events were 7p gain (62%), 5p gain (54%), and 8q gain (53%); top deletion events were 19p loss (47%), 15q loss (42%), and 10 q loss (41%). Patients with EGFR or TP53 mutation were more likely to have aneuploidy compared to wildtypes. Subgroup analysis showed distinct patterns of aneuploidy among metastasis sites, suggesting organ-specific alterations. Evolution analysis showed 7p gain was an early event common in primary tumor whereas metastatic tumor had multiple distinct evolutionary trajectories following 7p gain. Several copy number signatures were associated with specific TKI and chemotherapies. For example, TKI-naïve tumors lacked 7p gain but had 19p loss as the most common alteration. **Conclusions:** The genomic landscape of LUAD was characterized by widespread large-scale copy number alterations including WGD and chromosomal aneuploidy. Metastasis had elevated level of aneuploidy compared to primary tumors which were specific to metastatic site. Copy number signature associated with different treatments may contribute to distinct long-term survival and side effects among patients. Research Sponsor: None.

9535 Poster Session (Board #301), Fri, 8:00 AM-11:00 AM

Prediction of the molecular status in non-small cell lung cancer based on metastatic pattern: A free webtool powered by artificial intelligence. *First Author: Benjamin Besse, Gustave Roussy Université Paris Sud, Villejuif, France*

Background: Molecular characterization of metastatic lung adenocarcinomas is mandatory but might be hampered by the quantity of tissue, restricted access to molecular platforms or limited economical resources. Our aim was to develop a tool supported by the hypothesis that radiological patterns of pts could help predict the rate of positivity of the most common oncogenic drivers. **Methods:** We defined an algorithm based on a molecularly defined cohort of 656 pts with stage IV lung adenocarcinoma. Two radiologists centrally reviewed the baseline imaging. Clinical data were retrospectively collected. There were 135 *EGFR* mutations, 81 *ALK* fusions, 47 *BRAF* mutations, 141 *KRAS* mutations, and 146 pan-negative tumors for these 4 oncogenic drivers. Univariate correlation analyses were performed to define an algorithm predicting the molecular testing positivity based on the metastatic pattern. Subsequently, an online tool was developed. This study was approved by our institutional review board. **Results:** Metastatic patterns correlated with the genomic drivers when compared to the pan-negative group. In the *EGFR* group, pleural metastases were more frequent (32% vs. 20%; p = 0.021), whereas adrenal and node metastases less frequent (6% vs.23%; p < 0.001 and 11% vs. 23% respectively; p = 0.011). In the *ALK* group, there were more brain and lung metastases (respectively 42% vs. 29%; p = 0.043 and 37% vs. 24% respectively; p = 0.037). In the *BRAF* group, pleural and pericardial metastases were more common (47% vs. 20%; p < 0.001 and 11% vs. 3% respectively; p = 0.04) and bone metastases less common (21% vs. 42%; p = 0.011). Lymphangitis was more frequent in *EGFR*, *ALK* and *BRAF* groups (6%, 7% and 15% vs. 1%; p = 0,016, p = 0,009 and p < 0,001 respectively). A free online access to the algorithm is now available after registration at http//tactic-ct.fr. Physicians enter age, sex, smoking status and the sites of metastases at diagnosis (present/absent/unknown). A mutation score is calculated, reflecting the % of chance to find an oncogenic driver. On the website, contributors can also enter new cases and an artificial intelligence will refine the algorithm and expand the number of oncogenic drivers. **Conclusions:** Our free access tool allows establishing a hierarchy in the molecular testing based on simple clinical and radiological information. Continual learning from new cases entered in the database will increase the sensitivity of the tool. This tool might save time, tumor tissue, economical resources and accelerate access to personalized treatment. Research Sponsor: Digital Tech Year program of CentraleSupélec, University Paris-Saclay.

9536 Poster Session (Board #302), Fri, 8:00 AM-11:00 AM

Interaction between CAF and CD8+ T cells in non-small cell lung cancer affects prognosis and efficacy of immunotherapy. *First Author: Xinlong Zheng, Fujian University of Traditional Chinese Medicine, Fuzhou, China*

Background: Cancer-related fibroblasts (CAFs) are important components of the tumor microenvironment (TME) and play a key role in tumor progression. There is growing evidence that CAF levels in tumors are highly correlated with treatment response and prognosis. However, the effect of CAFs on immunotherapy response remains unknown. **Methods:** RNA-seq and clinical data were downloaded from TCGA and GEO. The SVA package *ComBat* function was used to remove batch effects. The ssGSEA algorithm was used to assess the level of cell infiltration in each sample. OS (overall survival) and DFS (disease free survival) were analyzed using the Kaplan–Meier method. GO enrichment analysis was used to assess the biological processes of subgroup differential genes. The Tumor Immune Dysfunction and Exclusion (TIDE) algorithm and subclass mapping were used to predict the clinical response to immune checkpoint blockade. **Results:** We evaluated the infiltration abundance of 24 types of immune cells and fibroblasts in 1768 NSCLC samples and found that almost all IMFRs (immune cells / fibroblasts) are beneficial to the prognosis. This phenomenon is called "CAFs-mediated immune resistance pattern (CMIRP)". We evaluated the infiltration abundance of 24 types of immune cells and fibroblasts in 1768 NSCLC samples and found that almost all IMFRs (immune cells / fibroblasts) are beneficial to the prognosis. This phenomenon is called "CAFs-mediated immune resistance pattern (CMIRP)". The prognosis according to CD8+ T cells was not strong, but CD8+ T cells / fibroblasts (CFR) were significant protective prognostic factors [n = 1588; hazard ratio (HR), 0.66; 95% confidence interval (CI), 0.56–0.78; P < 0.001]. Multivariate analysis revealed that the CFR was an independent prognostic biomarker. The TCGA pan-cancer cohort confirmed the widespread presence of CMIRP in cancer. We further defined the CFR high and CFR low subgroups. CFR high samples were enriched with immune activation pathways including T cell activation, cytolysis, and antigen presentation, while CFR low was associated with immunosuppression including activation of transforming growth factor β, epithelial-mesenchymal transition, and angiogenesis pathways. Finally, we combined TIDE and submap to speculate that CFR is a potential prognostic marker of immunotherapy for NSCLC. **Conclusions:** We proposed the term "CMIRP" to shed light on a more accurate assessment of immune status. CFR is a potential marker for prognosis and predictive efficacy of immunotherapy in NSCLC. Research Sponsor: None.

9537 Poster Session (Board #303), Fri, 8:00 AM-11:00 AM

Brigatinib in Japanese ALK positive NSCLC patients previously treated with ALK tyrosine kinase inhibitors: J-ALTA. *First Author: Tatsuya Yoshida, Department of Thoracic Oncology, National Cancer Center Hospital, Tokyo, Japan*

Background: Brigatinib is an ALK inhibitor with demonstrated activity against ALK resistance mutations. To evaluate efficacy and safety in Japanese patients with ALK-positive non-small cell lung cancer (NSCLC), a prospective, single-arm, phase 2 study was conducted. We report the efficacy and safety of brigatinib in patients who have progressed on alectinib with or without prior crizotinib and of those who previously received up to two ALK tyrosine kinase inhibitors (TKIs) with or without prior chemotherapy. **Methods:** A safety evaluation lead-in was followed by an expansion stage of an ALK TKI-naïve and two ALK TKI-refractory cohorts. The refractory cohorts included patients with stage IIIB, IIIC, or IV NSCLC with ALK rearrangements. This report describes efficacy results from the post-alectinib patients in the expansion cohort and safety results from all refractory patients. The primary endpoint was confirmed objective response rate (ORR) assessed by IRC, secondary endpoints included duration of response (DoR), progression-free survival (PFS), disease control rate (DCR), and intracranial ORR (iORR). Brigatinib was administered at 180 mg QD with 90 mg QD lead-in for the first 7 days, and efficacy was evaluated every 8 weeks. **Results:** A total of 72 patients were enrolled in 28 sites, including a cohort of 47 patients with prior alectinib, with/without crizotinib between January 2018 and September 2019. The primary analysis of brigatinib in this cohort (data cut-off date 26 September 2019) demonstrated an IRC-assessed, confirmed ORR of 30% and a median DoR of 6.1 months. The median PFS was 7.3 months. Clinically meaningful intracranial efficacy was also observed (see table). Grade ≥3 TEAEs included blood creatine phosphokinase increase (18.1%), lipase increase (13.9%), hypertension (11.1%), amylase increase (4.2%), and pneumonitis (1.4%). Brigatinib also showed anti-tumor activity in patients with refractory secondary mutations in the ALK kinase domain, including G1202R, I1171N, V1180L, and L1196M. **Conclusions:** Brigatinib showed clinically meaningful efficacy in Japanese patients refractory to prior alectinib (first line or post crizotinib), regardless of prior chemotherapy. The safety profile of brigatinib was consistent with prior studies and no new safety findings were identified. Clinical trial information: NCT03410108. Research Sponsor: Takeda Pharmaceutical Company Ltd.

Endpoint	Value, 95% CI
ORR	30.6%, 16.530, 44.165
DCR	78.7%, 64.336, 89.297
DoR, median	6.1 months, 3.8, not reached
PFS, median	7.3 months, 3.7, not reached
iORR	25.0%, 3.185, 65.086

9538 Poster Session (Board #304), Fri, 8:00 AM-11:00 AM

Early pulmonary function changes associated with brigatinib initiation. *First Author: Terry L. Ng, Division of Medical Oncology, University of Colorado, Anschutz Medical Campus, Aurora, CO*

Background: Phase I-III studies reported symptomatic pulmonary toxicity within the first week of initiating brigatinib in 6% patients post-crizotinib and 3% in TKI naive patients with standard dosing (90mg QD for 7 days then 180mg QD as tolerated). A prospective observational study of pulmonary function testing (PFT) on initiating brigatinib was conducted. **Methods:** Patients PS≤2, with resting O2 sats on RA ≥90% and Hg ≥10 g/dL, without significant heart/lung disease or steroid use initiating brigatinib 90 mg QD were eligible. PFT with DLCO, Borg dyspnea and 6-minute walk tests were performed at baseline (prior to brigatinib), and on day 2 (D2), 8 (D8), and 15 (D15) of brigatinib. D15 analyses were initially as clinically indicated but became mandatory if DLCO had not returned to baseline by D8. Peripheral blood was collected at baseline, D2 and D8 for CyTOF analysis. The primary endpoint was the incidence of Early Onset Pulmonary Events (EOPEs), defined as a DLCO reduction of ≥ 20% from baseline. An interim analysis was performed on the first 10 patients due to a higher than expected incidence of DLCO reduction. **Results:** D2 and D8 measurements were captured in all 10 patients, D15 in 7 patients. Ninety percent (9/10) of patients experienced DLCO reduction with nadir occurring on D2 in 4/9 and on D8 in 5/9 patients. Median DLCO nadir was −13.33% from baseline (range: −34.44 to −5.00). Three patients (30%) met EOPE criteria, all on D8, all without symptoms. Brigatinib was not held and all 10 patients escalated to 180mg on D8. Despite continued dosing, 4/9 patients recovered DLCO to baseline or above by D15 (2/3 EOPEs cases), 2/9 recovered above nadir but below baseline by D15 (1/3 EOPE case), and 3/9 did not have improvement from nadir values but no D15 assessment was performed. Dyspnea and 6-minute walk test did not correlate with DLCO changes. Patients who experienced an EOPE had significantly higher levels of activated neutrophils (pERKhi) at baseline. On the day of the EOPE event, patients who met EOPE criteria had significantly higher levels of activated neutrophils and fewer activated CD4+ effector memory T cells. **Conclusions:** Modest DLCO reduction occurred in 90% (9/10) patients during the first 8 days of brigatinib-dosing without associated symptoms. When rechecked on D15, DLCO improved in 100% patients (6/6) despite continued dosing and standard dose escalation at D8. Patients unlikely to tolerate even this modest, short-lived change should consider shallower step-up dosing or alternative drugs. CyTOF analysis suggests levels of pretreatment neutrophils may be a biomarker for developing EOPEs. Clinical trial information: NCT03389399. Research Sponsor: Takeda Oncology.

9539 Poster Session (Board #305), Fri, 8:00 AM-11:00 AM

PD-L1 tumor proportion score and clinical benefit from first-line pembrolizumab in patients with advanced nonsquamous versus squamous non-small cell lung cancer (NSCLC). *First Author: Deborah Blythe Doroshow, Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY*

Background: The predictive value of PD-L1 tumor proportion score (TPS) on NSCLC tumor cells as a biomarker for response to PD-(L)1 inhibitors is well established. However, its histology specific value in advanced (a) squamous (Sq) versus nonsquamous (NS) cancers remains unclear. Here, we used real world data to assess the differential value of PD-L1 TPS as a predictive biomarker for overall survival (OS) after first-line pembrolizumab (P) in patients (pts) with Sq versus NS NSCLC. **Methods:** Inclusion criteria for this analysis of the Flatiron Health EHR-derived de-identified database required that pts were diagnosed with aNSCLC, tested for PD-L1 TPS and received a numerical result, had no alteration in *EGFR*, *ALK*, or *ROS*, and received first-line, single agent P. The primary endpoint was overall survival (OS) from the first dose of P in patients with TPS ≥ 50% (H) compared to patients with TPS < 50% (L). Due to the violation of the proportional hazards assumption, a generalized gamma model of OS was used, adjusting for demographic variables and estimated median OS and their confidence intervals with the bootstrap method. The PD-L1-histology interaction was examined by comparing the differences in median OS (H vs. L) between Sq and NS patients. **Results:** Of 1560 pts with NSCLC treated from 1/2011 – 5/2019, 1055 had NS and 405 Sq. No meaningful differences in age, gender, or smoking history were seen between PD-L1 H and L pts with either histology. Among NS pts, H had significantly longer OS than L, with unadjusted hazard ratio (HR) of 0.71 (95% CI: 0.53 - 0.94; p = 0.018). Among Sq pts, H was not associated with longer OS than L, with unadjusted HR 0.89 (95% CI: 0.64 - 1.25; p = 0.514). Based on the generalized gamma model, PD-L1 H in Sq patients was associated with a 0.19 year improvement in median OS (95% CI: -0.22-0.49, P = 0.283), whereas PD-L1 H in the NS group was associated with a 0.70 year improvement in OS (95% CI: 0.34-1.05, P < 0.001). The median improvements between the Sq and NS patients were significantly different (P = 0.034), after adjusting for demographic variables. **Conclusions:** PD-L1 TPS of ≥ 50% predicted longer OS in pts with NS NSCLC treated with first-line P compared to pts whose tumors had a TPS of < 50%. However, no relationship between PD-L1 TPS and OS after first-line P was seen in patients with Sq NSCLC. These data suggest that PD-L1 may not be an appropriate predictive biomarker for checkpoint inhibitor use in NSCLC with squamous histology. Research Sponsor: None.

9540 Poster Session (Board #306), Fri, 8:00 AM-11:00 AM

SRC-homology 2 domain-containing phosphatase 2 (SHP2) in epidermal growth factor receptor (EGFR)-mutant lung adenocarcinoma (LUAD). *First Author: Rafael Rosell, Catalan Institute of Oncology, Barcelona, Spain*

Background: Epidermal growth factor (EGFR)-mutant lung adenocarcinomas (LUADs) display impaired phosphorylation of extracellular signal-regulated kinase (ERK) and SRC-homology 2 domain-containing phosphatase 2 (SHP2) in comparison with EGFR wild-type LUADs. However, the function of SHP2 in early EGFR-mutant LUADs and EGFR wild-type LUADs has not been reported. We posit that SHP2 mRNA expression could be a predictive marker in resected EGFR-mutant LUADs versus EGFR wild-type patients (pts). **Methods:** We examined 267 resected LUADs from Japan and Spain. mRNA expression levels of AXL, MET, CDCP1, STAT3, YAP1 and SHP2 were analyzed by quantitative reverse transcriptase polymerase chain reaction (PCR). EGFR mutant cell lines were investigated for their activity of SHP2. **Results:** Among the 267 enrolled pts, 100 (37.3%) were EGFR-mutant LUADs. Five-year recurrence-free survival (RFS) and overall survival (OS) were lower for EGFR-mutant LUADs with high SHP2 mRNA levels (hazard ratio = 1.83 and 2.28, respectively. p = 0.03 and p = 0.04). However, SHP2 was not associated with RFS nor OS in the 167 wild-type EGFR LUADs. In EGFR-mutant cells, RMC-4550 (SHP2 inhibitor) plus erlotinib showed synergism via inhibition of AKT (S473) and ERK1/2 (T202/Y204). While erlotinib translocates SHP2 (Y542) into the nucleus, either RMC-4550 alone, or in combination with erlotinib, relocalizes SHP2 into the cytoplasm membrane, limiting AKT and ERK activation. **Conclusions:** High SHP2 mRNA is related to shorter RFS and OS in EGFR-mutant LUADs, but not in EGFR wild-type LUADs. The findings indicate that the addition of SHP2 inhibitors could improve adjuvant therapy in EGFR-mutant LUADs. Research Sponsor: None.

9541 Poster Session (Board #307), Fri, 8:00 AM-11:00 AM

An FDA analysis of the association of tumor growth rate and overall and progression-free survival in metastatic non-small cell lung cancer (NSCLC) patients. *First Author: Yutao Gong, U.S. Food and Drug Administration, Silver Spring, MD*

Background: Previous studies have suggested that tumor growth rate (g), estimated using prostate-specific antigen values, is associated with overall survival (OS) in prostate cancer (Wilkerson, 2016). We performed a retrospective pooled analysis in non-small cell lung cancer (NSCLC) to investigate the extent to which g values estimated using radiological tumor measurements in clinical trials are associated with survival. **Methods:** We identified 24 randomized clinical trials submitted to FDA between 2013 and 2019 investigating either immune checkpoint inhibitor (ICI) or targeted therapy (TT) in pts with metastatic NSCLC. Of 9934 patients (pts) enrolled, 5532 pts (2401, 1189, and 1942 pts treated with ICI, TT, and chemotherapy respectively) had sufficient data to derive a valid g. The g was evaluated by both type and line of therapy. Pts were then grouped according to quartiles of g, with Q1 being the lowest. We calculated OS and progression-free survival (PFS) for each group via the Kaplan-Meier method, and used the Cox model for group comparison. **Results:** Median g was 9.7E-4, 1.4E-3, and 2.2E-3/day, and median OS was 34.2, 21.3, and 15.3 months (mo), in pts treated with TT, ICI, and chemotherapy, respectively, regardless of lines of therapy. When treated with the same type of therapy, pts receiving 2nd line therapy had a higher median g than those receiving 1st line. The median survival and log-rank hazard ratios for pts treated with 1st line ICI monotherapy are shown in the Table. **Conclusions:** TT is associated with the lowest median g, followed by ICI, and then chemotherapy, perhaps due to patient selection, better inherent biology/natural history, or favorable results of TT on selected tumors. Regardless, we found that g is inversely associated with survival, across treatment types. This relationship is also observed in pts treated with the same type and line of therapy (for example, 1st line ICI), where Q1 has the longest survival, followed by Q2, Q3, and then Q4. In summary, our exploratory analysis suggests that g derived from radiological tumor measurements in NSCLC may relate to survival. Prospective studies are needed to evaluate if g might be an earlier endpoint compared to classical response criteria. Research Sponsor: None.

		OS		PFS	
	N	Median (mo)	Hazard Ratio	Median (mo)	Hazard Ratio
Q1	110	NR (NR, NR)	1	32.5 (21.5, NR)	1
Q2	109	26.1 (22.9, NR)	1.8 (1.1, 3.1)	13.1 (10.4, 18.7)	2.3 (1.6, 3.4)
Q3	109	16.7 (13.5, 22.4)	4.6 (2.8, 7.3)	6.1 (4.2, 7.1)	6.6 (4.5, 9.8)
Q4	109	8.7 (7.2, 12.9)	6.8 (4.3, 10.7)	3.4 (2.1, 4.1)	11.0 (7.2, 16.9)

*NR = Not Reached

9542 Poster Session (Board #308), Fri, 8:00 AM-11:00 AM

ctDNA levels before treatment predict survival in non-small cell lung cancer patients treated with a tyrosine kinase inhibitor. *First Author: Mariano Provencio-Pulla, Department of Medical Oncology, University Hospital Puerta de Hierro-Majadahonda, Madrid, Spain*

Background: Currently there is an intense debate concerning therapeutic strategies in EGFR positive NSCLC patients with advance disease. Osimertinib is superior to standard EGFR Tyrosine Kinase Inhibitors (TKIs) as first line treatment. However, it is yet unclear whether this option is superior to sequential treatment of a 1st or 2nd generation TKI followed by osimertinib. In order to clarify this issue it is important to identify which patients are at high risk of progression disease. **Methods:** This is a prospective, multicentre, cross-sectional study promoted by Spanish Lung Cancer Group. 698 plasma samples from 196 advanced NSCLC patients with tumors harboring an EGFR activating mutation and treated with a first line TKI (afatinib, gefitinib, erlotinib or osimertinib) were analyzed. Plasma samples were prospectively collected before treatment (T0), after 3 months of treatment (T3), after 6 months of treatment (T6) and at first disease progression. EGFR mutations were analyzed by dPCR. Multivariate Cox proportional hazards analysis was used to determine the significance of ctDNA in the prediction of prognosis. **Results:** The median follow up was 19.8 months. At baseline patients with plasma EGFR sensitizing mutations at allele frequency (AF) $\geq$ 10% had worse OS and PFS than patients in which the opposite occurred (HR = 1.86; 95 %CI: 1.09-3.17, and HR = 1.65; 95 %CI: 1.07-2.58, respectively). Noteworthy, median OS and PFS time were 18.6 and 8.8 months respectively, in patients with plasma AF$\geq$10% before treatment initiation compared to 37.9 and 12.4 months for patients with plasma AF $<$ 10%. Similar results were obtained when a cutoff of AF$\geq$ 5% was used (HR = 1.73; 95%CI: 1.02-2.94 for OS, and HR = 1.72; 95%CI: 1.13-2.61 for PFS). Patients who remained ctDNA-positive after 3 months of treatment exhibited also poorer outcomes (HR = 3.24; 95%CI: 1.77-5.94 for OS, and HR = 3.1; 95%CI: 1.91-5.03 for PFS). In the same way, detectable levels of ctDNA after 6 months of treatment predicted shorter OS and PFS (HR = 3.3; 95%CI: 1.53-7.13 and HR = 2.62; 95%CI: 1.62-4.25, respectively). **Conclusions:** ctDNA levels significantly predict survival. Moreover, ctDNA levels before treatment initiation can be useful to assess patient's progression risk which is not possible to assess otherwise facilitating treatment decision making. Research Sponsor: Boehringer Ingelheim.

9543 Poster Session (Board #309), Fri, 8:00 AM-11:00 AM

Racial diversity of genomic alterations in lung adenocarcinomas. *First Author: Huashan Shi, Mayo Clinic, Jacksonville, FL*

Background: Lung cancer is the leading cause of cancer related death in the United States in all racial groups. However, the overall death rate from lung cancer is different among white, black and Asian. Although differences in socioeconomic status and treatments received might be the contributing factors, the biology, particularly genomic alteration of cancer might also have an important impact. To date, the differences of genomic alterations among all racial patients are poorly understood. **Methods:** The American Association for Cancer Research (AACR) Project Genomics Evidence Neoplasia Information Exchange (GENIE, version 7.0) database was analyzed. A total of 8908 patients with lung adenocarcinoma (LUAD) were identified. Among them, 5652 patients who had comprehensive sequencing results (gene panel $\geq$ 275) were selected for further analysis. Patients with unknown race, undefined and Pacific Island (only 3 patients) were excluded. Finally, 5360 patients were included in the study. The prevalence and distribution of genomic alteration cross all racial groups were analyzed. **Results:** Overall 5951 samples from 5360 patients were collected (85.7% white, 7.9% Asian, 4.7% black, 0.2% Native American and 1.4% other). Most patients have only one sample. The median mutation counts in white, black, Asian, Native American and others are 7, 6, 5, 5, 7 respectively (Kruskal–Wallis test, $P<$ 0.001). Asian have significantly higher rates of insertion and deletions than other races (14.8% of Asian versus 9.8% of white, 10.7% of black, 10.4% of Native American, 11.1% of other; Pearson's chi-square test, $<$0.001). TP53, EGFR, KRAS and STK11 are the most frequent alterations in white, black and other. EGFR, TP53, KRAS and APC are the most frequent alterations in Asian. STK11 mutations are rare in both Asian and Native American. Native Americans have more alterations of LRP1B, ARID2 and ATM, although the patients' number remains small. ATM and KEAP1 mutations are also common in white and black. EGFR is the highest discrepancy gene in racial distribution. 78.9% Asian, 47.7% black, 36.4% of native American had EGFR alteration in comparison to 29.6% in white (Fisher's exact test, $P < 0.001$). KRAS is the second highest discrepancy gene in racial distribution. 11.6% Asian, 26.3% black, 27.3% of Native American had KRAS alteration in comparison to 36.1% in white (Fisher's exact test, $P<$ 0.001). **Conclusions:** Our study demonstrated the potential diversity of genomic alterations across all racial groups with potential impact on therapeutic decisions. Research Sponsor: Paul Calabresi Career Development Award for Clinical Oncology (K12) - National Cancer Institute Awardee: Yanyan Lou.

9544 Poster Session (Board #310), Fri, 8:00 AM-11:00 AM

Characterization of KRAS mutations (mt) in non-small cell lung cancer (NSCLC). *First Author: Stephen V. Liu, Georgetown University, Washington, DC*

Background: KRAS is the most commonly mutated oncogene in NSCLC and the development of direct KRAS inhibitors has renewed interest in this molecular subtype. However, there are several different KRAS mts, representing unique biology and different prognostic and therapeutic impact. A more comprehensive understanding of the genomic landscape relative to each KRAS mt subset will help guide therapeutic development. **Methods:** Molecular profiles of 17,113 NSCLC specimens were obtained using next-generation sequencing of 592 genes (Caris Life Sciences) and classified based on presence and types of KRAS mt. Incidence of KRAS mts was noted across the cohort and by histology. Co-occurring genomic alterations, tumor mutational burden (TMB) and PD-L1 IHC (22C3, TPS score) were analyzed by KRAS mt type. **Results:** Across the entire cohort, 4706 (27%) of samples harbored a KRAS mt (Table). The most common was G12C (40%), followed by G12V (19%) and G12D (15%). The prevalence of KRAS mt was 37.2% among adenocarcinoma and only 4.4% in squamous. High TMB, defined by $>$ 10 mts/Mb, varied across the different KRAS mt types, most common in G13X (68.3%) and least common in G12D (43.2%). PD-L1 expression also varied. G12C was the most likely to be PD-L1 positive, with 65.5% TPS $>$ 1%, and the most likely to be PD-L1 high, with 41.3% TPS $>$ 50%. STK11 was mutated in 8.6% of KRAS wild type NSCLC but more frequently noted in every KRAS subtype, with the highest rate in G13X (36.2%) and the lowest in G12D(14.2%). TP53 mts were more frequent in KRAS wild type NSCLC (73.6%), with the highest rate among KRAS mutants at 55.4% (G12other) and the lowest at 36.8% (Q61X). NF1 was noted to be mutated in 21.4% of KRAS G13X cases, while all other KRAS mts had a lower frequency of NF1 mts than KRAS wild type (11.5%). **Conclusions:** KRAS mts are relatively common in lung adenocarcinoma and KRAS G12C is the most common variant. The different KRAS mts have different co-occurring mutations and a different genomic landscape. KRAS G12C was associated with the highest rate of PD-L1 expression. The clinical relevance of these differences in the context of therapeutic intervention warrants investigation. Research Sponsor: None.

	KRAS WT	KRAS G12C	KRAS G12V	KRAS G12D	KRAS G13X	KRAS Q61X	KRAS G12A	KRAS G12other
Incidence	12407	1882	915	684	327	313	298	210
TMB > 10 mut/Mb	50.1%	58.1%	55.3%	43.2%	68.3%	51.2%	52.3%	65.0%
PDL1 > 1%	52.1%	65.5%	58.2%	62.7%	57.7%	62.6%	61.5%	56.4%
PDL1 > 50%	25.9%	41.3%	35.2%	35.3%	35.0%	36.7%	36.3%	28.2%
STK11 mutant	8.6%	23.0%	23.6%	14.2%	36.2%	26.2%	23.4%	29.2%
KEAP1 mutant	4.2%	6.3%	5.7%	3.7%	13.1%	5.1%	6.0%	5.7%
TP53 mutant	73.6%	48.9%	46.0%	44.0%	52.8%	36.8%	43.1%	55.4%

9545 Poster Session (Board #311), Fri, 8:00 AM-11:00 AM

Real-world performance of blood-based host immune profiling in first-line immunotherapy treatment in advanced-stage non-small cell lung cancer. *First Author: R. Brian Mitchell, Virginia Cancer Inst, Midlothian, VA*

Background: Immune checkpoint inhibition (ICI) has improved outcomes for many treatment-naïve advanced non-small cell lung cancer (NSCLC) patients. However, better biomarkers are needed to predict patient response and guide treatment decisions considering added toxicity and higher cost of combination treatments. A prospectively designed, observational study assessed the ability of a clinically validated, blood-based, host immune classifier (HIC) to predict ICI therapy outcomes. **Methods:** The study (NCT03289780) includes 33 US sites having enrolled over 3,000 NSCLC patients at any stage and line of therapy. All enrolled patients are tested and designated HIC-Hot (HIC-H) or HIC-Cold (HIC-C) prior to therapy initiation. An interim analysis of secondary and exploratory endpoints was performed after 12- 18 months (mo) follow-up with the first 2,000 enrolled patients. We report the overall survival (OS) of HIC-defined subgroups comprising advanced stage (IIIB and higher) NSCLC patients treated with first-line regimens (284 ICI containing treatments, 877 total first-line patients). **Results:** In a real-world clinical setting, OS of advanced stage NSCLC treatment-naïve patients receiving platinum-based chemotherapy (n = 392) did not differ significantly from patients receiving any type of ICI containing regimen (n = 284); 11.7 mo vs. 14.4 mo; hazard ratio (HR) = 0.94 [95% confidence interval (CI): 0.76–1.17], p = 0.59. HIC-H patients experienced longer survival than HIC-C across multiple regimens, including ICI. For all ICI, median OS (mOS) was not reached for HIC-H (n = 196, CI: 15.4 mo–undefined) vs. 5.0 mo (n = 88, CI: 2.9 mo–6.4 mo) for HIC-C patients (HR = 0.38 [CI: 0.27–0.53], p $<$ 0.0001). Similar results were seen in the ICI only (16.8 mo vs. 2.8 mo; n = 117, HR = 0.36 [CI: 0.22–0.58], p $<$ 0.0001) and ICI/chemotherapy combination subgroups (unreached vs. 6.4 mo; n = 161, HR = 0.41 [CI: 0.26–0.67], p = 0.0003). In the PD-L1 high cohort (PD-L1 $\geq$50%), mOS for HIC-H was not reached (n = 81, CI: 13.9 mo–undefined) vs. 3.9 mo (n = 41, CI: 2.1 mo–7.8 mo) for HIC-C (HR: 0.39 [CI: 0.24-0.66], p = 0.0003). HIC results were independent of PD-L1 score (p = 0.81) and remained predictive of OS in first-line ICI-treated patients when adjusted for PD-L1 and other covariates by multivariate analysis (HR = 0.40 [CI: 0.28-0.58], p $<$ 0.0001). **Conclusions:** Blood-based host immune profiling may provide clinically meaningful information for selecting NSCLC patients for two common ICI containing regimens independent of and complementary to PD-L1 score. Research Sponsor: Biodesix, Inc.

9546 Poster Session (Board #312), Fri, 8:00 AM-11:00 AM

Tumor antigen expression and survival of patients with previously treated advanced non-small cell lung cancer (NSCLC) receiving viagenpumatucel-L (HS-110) plus nivolumab. *First Author: Daniel Morgensztern, Washington University School of Medicine in St. Louis, St. Louis, MO*

Background: Viagenpumatucel-L (HS-110) is an allogeneic cellular vaccine derived from a human lung adenocarcinoma cell line transfected with gp96-Ig fusion protein. Gp96-Ig functions as an antigen chaperone for dendritic cell activation and direct CD8+T cell expansion via cross presentation. DURGA is a multi-cohort study evaluating HS-110 plus anti-PD-1 mAbs in patients (pts) with advanced NSCLC. We report on Cohort A, which enrolled previously-treated pts who had not received an anti-PD(L)1 prior to study entry. **Methods:** Primary objectives were safety and objective response rate (ORR). Overall Survival (OS) was a secondary endpoint. Pts received 1 X 10^7 HS-110 cells intradermally every week for 18 wks and nivolumab until tumor progression. To determine cancer testis antigen (CTA) overexpression from baseline pt tumor samples, hybrid-capture RNA-seq libraries were prepared from macrodissected formalin fixed paraffin embedded tumor tissue and sequenced on an Illumina NovaSeq 6000. Gene-level transcripts were quantified using the Salmon software package. **Results:** 47 pts were enrolled into Cohort A. ORR and clinical benefit rate (CR + PR + SD) were 21% and 43%, respectively, with a 17.2 month median duration of response. Median OS was 28.7 months (mos), with a median follow up of 15.7 mos. One and 2-year survival were 57% and 36%, respectively. A prespecified exploratory analysis of CTA expression level in baseline pt tumor tissue was performed. 50% of pts shared at least 8 of the 39 total antigens overexpressed by HS110. Although there was no difference in ORR between these groups, mOS was higher in pts with tumors that shared $\geq$ 8 antigens with HS-110 (not reached (NR) [95%CI: 10.3 mos, NR] vs 6.7 mos [95%CI: 1.4 mos, NR]), p = 0.028. Pts whose tumors expressed the ZNF492 antigen also had improved OS (NR [95%CI: 11.6 mos, NR] vs 7.2 mos [95%CI: 1.6 mos, NR]), p = 0.03. All pts experienced at least one adverse event (AE), and the most common AEs were fatigue (28%), arthralgia (19%) and cough (17%). There were 2 grade 5 AEs not related to treatment. **Conclusions:** The combination of HS-110 and nivolumab appears safe and well tolerated. OS was improved in pts whose tumors express $\geq$ 8 shared antigens with HS110, as well as in those who specifically expressed ZNF492. Further exploration of antigen expression as a predictor for treatment outcome with HS110 plus nivolumab is ongoing. Clinical trial information: NCT02439450. Research Sponsor: Heat Biologics.

9547 Poster Session (Board #313), Fri, 8:00 AM-11:00 AM

Circulating and tumor-associated neutrophil subtypes discriminate hyper-progressive disease (HPD) from conventional progression (PD) upon immune checkpoint inhibitors (ICI) in advanced non-small cell lung cancer (NSCLC) patients (pts) and in vivo models. *First Author: Roberto Ferrara, Medical OnIstituto Nazionale Dei Tumori di Milano, Milan, Italy*

Background: HPD occurs in $\simeq$10-25% of NSCLC pts upon single-agent ICI and correlates with poor prognosis. High circulating neutrophil count and neutrophils/lymphocytes ratio have been associated with shorter survival and HPD in NSCLC pts. In mouse lung cancer models, interleukin-17 (IL-17) promoted tumour growth upon ICI increasing intratumoral neutrophils. The role of specific circulating and/or tumour-associated neutrophils in driving HPD is currently unknown. **Methods:** NSCLC pts treated with single agent ICI were assessed for HPD and circulating neutrophils' phenotype. Conventional PD was defined by RECIST 1.1. HPD required 3 tumour assessments (2 before ICI, 1 upon ICI) and was defined as delta tumour growth rate (TGR) (TGR upon ICI – TGR before ICI) $>$ 50% and/or TGR ratio (TGR upon ICI/ TGR before ICI) $\geq$2. Correlations with continuous variables were performed by Mann-Whitney test. Circulating low density neutrophils (LDNs) subtypes were assessed by flow cytometry (FC) on peripheral blood mononuclear cells (PBMCs) from fresh blood samples. LDNs were defined as $CD66b^+CD15^+$ cells among $CD11b^+$ PBMCs. Immature subtypes were defined as $CD10^-$ and $CD10^-CD16^-$ LDNs. The occurrence of HPD upon anti-PD-1 treatment was tested in C57BL/6 immune competent mice bearing Lewis Lung Carcinoma and treated with anti-murine PD-1. Tumour associated neutrophils' phenotype was assessed by FC. **Results:** Of 52 NSCLC, 65% were $>$ 65 years, 83% had stage IV, 25% PD-L1 on tumour cells $\geq$50%, 67% received 1st line ICI. PD and HPD occurred in 21 (40%) and 5 (10%) pts, respectively. Before ICI start, HPD pts had higher circulating immature neutrophils measured as median percentage of $CD10^-$ LDNs [41.9 (min 26.7; max 83.5) vs 10.1 (min 0.69; max 79.3), p = 0.01] and of $CD16^-$ cells among $CD10^-$ LDNs [93 (min 89.5; max 98.4) vs 86.3 (min 24.2; max 99), p = 0.03] compared to conventional PD pts. PD and HPD occurred in 17 (71%) and 3 (12.5%) of 24 immune competent mice treated with anti-murine PD-1. The median percentage of IL-17^+ tumour associated neutrophils ($Gr1^{high}Ly6C^{low}$) was significantly higher in HPD compared to PD mice [0.25 (min 0.14; max 0.63) vs 0.06 (min 0.02; max 0.32), p = 0.02]. **Conclusions:** Circulating immature ($CD10^-$ and $CD10^-$ $CD16^-$) LDNs and IL-17^+ tumour associated neutrophils discriminate HPD from conventional PD upon ICI in NSCLC pts and in vivo models, respectively. Functional characterization of specific neutrophil subsets is ongoing. Research Sponsor: IASLC Young Investigator Award 2019 and ASCO Merit Award 2019.

9548 Poster Session (Board #314), Fri, 8:00 AM-11:00 AM

Radiotherapy to augment pembrolizumab responses and outcomes in metastatic non-small cell lung cancer: Pooled analysis of two randomized trials. *First Author: James William Welsh, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: In metastatic non-small cell lung cancer (mNSCLC), the clinical trials NCT02492568 and NCT02444741 are the only known randomized comparisons of pembrolizumab alone versus pembrolizumab combined with radiation therapy (RT). When the trials were analyzed individually, some potential benefit was observed in the combination therapy group, but the relatively small sample size of each trial limited the detection of potential differences in response rates and outcomes. Hence, we perform a pooled analysis of these two randomized trials to validate and explore whether RT improves mNSCLC patient responses to immunotherapy. **Methods:** This was a pooled analysis of two randomized trials (NCT02492568 and NCT02444741) of pembrolizumab with or without RT for mNSCLC. Endpoints included the out-of-field overall response rate (ORR) and disease control rate (DCR), progression-free survival (PFS), overall survival (OS), and subgroup analysis of the different RT schemes. **Results:** In all, 131 patients were analyzed (n = 66 pembrolizumab; n = 65 pembrolizumab/RT (iRT)). ORR was 21% in the pembrolizumab arm vs. 38% in the iRT arm (p = 0.01); DCR was 53% in the pembrolizumab arm vs. 67% in the iRT arm (p = 0.0009); PFS was 4.4 m vs 8.3 m (p = 0.046); and OS was 9.2 m vs 19.2 m (HR 0.66; p = 0.040). Ablative RT (24Gy/3 fractions and 50Gy/4 fractions) had better ORRs of 48% and 54%, respectively, compared to 18% for non-ablative RT (45Gy/15 fractions) and 20% for pembrolizumab alone (p $<$ 0.05, respectively). **Conclusions:** The addition of RT to immunotherapy significantly increased the ORR of unirradiated lesions and was additionally associated with significant improvements in PFS and OS. Ablative RT was associated with response rates significantly higher than those of non-ablative RT, possibly due to a detrimental effect of non-ablative RT on ALC. These hypothesis-generating findings require dedicated, large-volume, and randomized studies for corroboration. Clinical trial information: NCT02492568 and NCT02444741. Research Sponsor: Merck Sharp & Dohme.

9549 Poster Session (Board #315), Fri, 8:00 AM-11:00 AM

Long-term responders to PD-1 blockade in patients with advanced non-small cell lung cancer (NSCLC). *First Author: Jia Luo, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Long-term response – the plateau of the survival curve – is the transcendent benefit from PD-1 blockade. However, only a subset of responses achieve substantial durability. The frequency, characteristics, and predictors of long-term responders (LTR) to PD-1 blockade are not well known and may differ from short-term responders (STR). **Methods:** Patients with advanced NSCLC treated with anti-PD-1/PD-L1 therapy from two institutions (MSK and DFCI) were examined. Responses were assessed by RECIST. LTR was defined as PR/CR lasting $\geq$ 24 months. STR was defined as PR/CR lasting $<$ 12 months. Comparisons were also made to patients with progressive disease (PD). PD-L1 expression was assessed by IHC. TMB was assessed by targeted NGS; high TMB was defined as $\geq$ median of the cohort. A subset had detailed molecular profiling by MSK-IMPACT. Fisher's exact and Mann-Whitney U tests were used to compare features, and the log-rank test was used to compare survival. **Results:** Of 2318 patients (MSK n = 1536, DFCI n = 782), 126 (5.4%, 95% CI 4.6-6.4%) achieved LTR, with similar rates in both cohorts. STR occurred in 139 (6%). Overall survival was longer in LTR compared to STR (median NR vs 19.6 months, HR 0.07, $p <$ 0.001). LTR had deeper responses compared to STR (median best overall response -69% vs -46%, $p < 0.001$). Patients with LTR were younger ($<$ 65 years old) and had increased TMB ($\geq$ median mut/Mb) compared to both STR and PD ($p = 0.006$, $p = 0.03$; $p < 0.001$, $p < 0.001$). The rate of LTR was enriched among patients with both high TMB/high PD-L1 compared to those with low TMB/low PD-L1 (9% vs 1%, OR 9.2, $p < 0.001$), while STR was similar in both groups (7% vs 6%). 2% of patients with sensitizing EGFR mutations (n = 243) achieved LTR. Loss of function variants in ARID1A (14% vs 2%), PTEN (8% vs 0%), and KEAP1 (12% vs 2%) were enriched in LTR compared to STR ($p < 0.05$ for each). Among patients with KRAS mutations, the rate of LTR was higher in those with co-mutation with TP53 compared to STK11 (11% vs 2%, $p = 0.01$). **Conclusions:** Long-term response (LTR, ongoing response $\geq$ 24 months) to PD-1 blockade is an uncommon but profound clinical outcome in metastatic lung cancers. Younger age and high TMB correlate with LTR; the combination of high TMB/high PD-L1 enriches for LTR but not STR. Features predicting long term response may be distinct from those predicting initial response. Research Sponsor: T32-CA009207, NIH-T32, Investigational Cancer Therapeutics Training Program Grant.

9552 Poster Session (Board #318), Fri, 8:00 AM-11:00 AM

Comparative efficacy of chemoimmunotherapy versus immunotherapy alone in the front-line treatment of advanced non-small cell lung cancer: A systematic review and network meta-analysis. *First Author: Ranjan Pathak, Section of Medical Oncology, Yale School of Medicine, New Haven, CT*

Background: Immune checkpoint inhibitors (ICI) and combination chemotherapy (chemo) plus ICI (Chemo-ICI) have been shown in RCTs to have improved OS compared to chemo in the 1L treatment of advanced NSCLC. However, the benefit of chemo-ICI compared with ICI alone is unknown. **Methods:** Systematic review using MEDLINE, Embase and Cochrane CENTRAL was done to identify relevant studies up to December 2019. Phase 3 RCTs that evaluated the efficacy of 1L ICI or chemo-ICI and reported outcomes stratified by PD-L1 status ($<$1%, 1-49%, $\geq$50%) were included. ICI was defined as single-agent PD-1 axis inhibitor or dual checkpoint blockade with PD-1 axis inhibitor plus CTLA-4 inhibitor. Comparison for PD-L1$<$1% included chemo-ICI vs ipi/nivo and for PD-L1 1-49% and PD-L1$>$50% included chemo-ICI vs ipi/nivo or single-agent ICI. OS, PFS, and ORR were extracted. Network meta-analysis (NMA) was done in Bayesian random-effects regression models. **Results:** Ten phase 3 RCTs (7971 screened) involving 7,218 patients assigned to ICI (pembro or atezo or ipi/nivo) or chemo-ICI (platinum-doublet + atezo, pembro, or nivo) were included. In PD-L1 $<$1% patients, NMA comparing chemo-ICI with ipi/nivo failed to show a statistically significant difference in OS, PFS or ORR. In PD-L1 1-49% patients, there was no significant difference between chemo-ICI vs ICI in OS or ORR; PFS could not be analyzed due to lack of available data. In PD-L1 $>$50% patients, chemo-ICI was associated with improved PFS and ORR compared to ICI alone, but without any OS difference (Table). **Conclusions:** Although the addition of chemo to ICI appears to improve ORR and PFS in PD-L1 $\geq$50% patients when compared to ICI alone, chemo-ICI does not confer an OS benefit in the 1L treatment of NSCLC patients regardless of PD-L1 status. Prospective trials comparing chemo-ICI, ICI monotherapy, and combination ICI are needed to confirm these findings. OS, PFS and ORR with chemo-ICI vs ICI. Research Sponsor: None.

PD-L1 status	Comparison	OS (HR, 95% CrI)	PFS	ORR (OR, 95% CrI)
PD-L1 <1%	Chemo-ICI vs ipi/nivo	1.23 (0.74-1.99)	0.94 (0.53-1.60)	1.38 (0.40-5.05)
PD-L1 1-49%	Chemo-ICI vs ICI overall	0.83 (0.44-1.50)	NA	2.40 (0.66-9.10)
	Chemo-ICI vs ipi/nivo	0.82 (0.34-1.92)	NA	NA
	Chemo-ICI vs ICI monotherapy	0.84 (0.34-2.00)	NA	2.30 (0.65-8.20)
PD-L1 ≥50%	Chemo-ICI vs ICI overall	0.92 (0.66-1.30)	0.64 (0.47-0.88)	2.10 (1.20-3.50)
	Chemo-ICI vs ipi/nivo	0.88 (0.53-1.49)	0.66 (0.39-1.15)	2.27 (0.91-5.31)
	Chemo-ICI vs ICI monotherapy	0.95 (0.64-1.40)	0.63 (0.44-0.96)	2.00 (1.10-3.80)

9553 Poster Session (Board #319), Fri, 8:00 AM-11:00 AM

Clinical performance of a comprehensive novel liquid biopsy test for identifying non-small cell lung cancer (NSCLC) patients for treatment with osimertinib. *First Author: Jhanelle Elaine Gray, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL*

Background: Genotyping is required to identify cancer patients (pts) eligible for targeted therapy; however, many do not receive biomarker testing, in part due to limitations associated with tissue-only genotyping practices and the growing list of biomarkers recommended to be tested. Liquid biopsy overcomes many of these limitations but is not yet fully adopted. We report here the clinical performance of a comprehensive liquid biopsy test based on next generation sequencing (NGS) of circulating tumor DNA (ctDNA) for the identification of NSCLC patients with *EGFR* exon 19 deletions (ex19del) or L858R mutations (*EGFR*m) or *EGFR* T790M, eligible for treatment with osimertinib. **Methods:** 441 (79%) of 556 pts randomized in FLAURA (NCT02296125; first-line osimertinib vs comparator EGFR TKI in *EGFR*m NSCLC) and 300 (72%) of 419 pts from AURA3 (NCT012151981; osimertinib vs chemotherapy in NSCLC pts with T790M at progression on EGFR TKI) were retrospectively tested with Guardant360 (G360), a 74-gene ctDNA NGS assay assessing single nucleotide variants, insertion-deletions, amplifications, and fusions in genes relevant to targeted therapy selection as well as microsatellite instability. Progression-free survival (PFS) of pts with *EGFR*m or T790M detected by G360 was compared to pts detected by the cobas EGFR Mutation Test (cobas) using tissue or plasma with an unadjusted cox model. **Results:** Treatment with osimertinib was associated with a significant PFS benefit relative to control therapy in NSCLC pts with *EGFR*m (FLAURA) and T790M (AURA3) detected using G360 (Table). Observed clinical benefit for pts with *EGFR*m or T790M detected by G360 was similar to that for pts with *EGFR*m or T790M identified by cobas using tissue or plasma specimens. **Conclusions:** This analysis demonstrates that G360 accurately identifies pts for osimertinib therapy while simultaneously providing comprehensive genotyping for other therapeutic molecular targets. The application of NGS liquid biopsy has the potential to increase rates of pts genotyped and access to precision medicine. Research Sponsor: AstraZeneca.

Pivotal study (*EGFR* mutations)	PFS Hazard Ratio (95% CI)	p-value
FLAURA (ex19del/L858R)		
G360	0.42 (0.31, 0.55)	< 0.0001
cobas plasma	0.45 (0.35, 0.58)	< 0.0001
cobas tissue	0.43 (0.34, 0.54)	< 0.001
AURA3 (T790M)		
G360	0.39 (0.28, 0.57)	< 0.0001
cobas plasma	0.42 (0.28, 0.62)	< 0.0001
cobas tissue	0.37 (0.29, 0.48)	< 0.0001

9554 Poster Session (Board #320), Fri, 8:00 AM-11:00 AM

Phase III study of tislelizumab plus chemotherapy vs chemotherapy alone as first-line (1L) treatment for advanced squamous non-small cell lung cancer (sq NSCLC). *First Author: Jie Wang, National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China*

Background: Tislelizumab is an anti-PD-1 antibody engineered to minimize binding to FcγR on macrophages to abrogate antibody-dependent phagocytosis. Tislelizumab in combination with chemotherapy has demonstrated a manageable tolerability profile and preliminary efficacy as 1L treatment for NSCLC. **Methods:** In this open-label phase 3 study (NCT03594747), Chinese pts with histologically confirmed stage IIIB or IV sq NSCLC were randomized (1:1:1) to receive IV Q3W: tislelizumab (200 mg, D1) + paclitaxel (P; 175 mg/m^2, D1) and carboplatin (carb; AUC 5, D1) (*Arm A*); tislelizumab + *nab*-P (100 mg/m^2; D1, 8, and 15) and carb (AUC 5, D1) (*Arm B*); or P (175 mg/m^2, D1) and carb (AUC 5, D1) (*Arm C*). Chemotherapy was administered for 4-6 cycles followed by tislelizumab. Patients were stratified by tumor stage and PD-L1 expression. The primary endpoint, PFS per RECIST v1.1, was assessed by Independent Review Committee; key secondary endpoints included OS, ORR, DoR, and safety/tolerability. **Results:** Across 360 pts, median PFS was significantly improved with tislelizumab plus chemotherapy (*Arms A* and *B*) compared with chemotherapy alone (*Arm C*) (Table). As of 6 Dec 2019, ORRs were higher and median DoRs were longer in *Arms A* and *B* vs *Arm C*. Across all arms, median OS was not reached and median number of treatment cycles were comparable. Adverse events (AEs) leading to discontinuation of any treatment were reported in 12.5%, 29.7%, and 15.4% of pts in *Arms A*, *B*, and *C*, respectively. The most commonly reported grade $\geq$3 AEs were hematologic in nature (eg, neutropenia) and consistent with known chemotherapy AEs. Serious treatment-related AEs (TRAEs) were reported in 72 pts (37.5% [*A*]; 38.9% [*B*]; 23.6% [*C*]); TRAEs leading to death were reported in 6 pts (n=1 [*A*]; n=2 [*B*]; n=3 [*C*]), none of which were solely attributed to tislelizumab. **Conclusions:** As 1L treatment for advanced sq NSCLC, addition of tislelizumab to P/carb or *nab*-P/carb chemotherapy significantly improved PFS and showed higher ORR and longer DoR than chemotherapy alone. The safety profile is in line with the known profiles of tislelizumab, chemotherapy, and underlying NSCLC; no new safety signals were identified with addition of tislelizumab to chemotherapy. Clinical trial information: NCT03594747. Research Sponsor: BeiGene, Ltd.

	Arm A (n=120)	*Arm B* (n=119)	*Arm C* (n=121)
Median PFS, mo (95% CI)	7.6 (6.0-9.8)	7.6 (5.8-11.0)	5.5 (4.2-5.7)
Stratified HR (95% CI)	0.52 (0.4-0.7)	0.48 (0.3-0.7)	NA
***P*-value**	0.0001	<0.0001	
ORR, % (95% CI)	72.5 (63.6, 80.3)	74.8 (66.0, 82.3)	49.6 (40.4, 58.8)
Median DoR, (95% CI)	8.2 (5.0, NE)	8.6 (6.3, NE)	4.2 (2.8, 4.9)

9556 Poster Session (Board #322), Fri, 8:00 AM-11:00 AM

Primary efficacy and biomarker analyses from the VISION study of tepotinib in patients (pts) with non-small cell lung cancer (NSCLC) with *MET*ex14 skipping. *First Author: Xiuning Le, Department of Thoracic Head and Neck Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Preliminary tepotinib data showed durable activity in pts with NSCLC with *MET*ex14 skipping prospectively identified by liquid (L+) or tissue (T+) biopsy. Having met target enrollment of ≥60 L+ pts & ≥60 T+ pts, we report primary data. **Methods:** VISION Cohort A enrolled pts with advanced *EGFR/ALK* wt, *MET*ex14 skipping NSCLC (asymptomatic brain metastases [BM] allowed), who received oral tepotinib 500 mg QD. On-study treatment decisions were based on investigator assessment (INV) of response. Primary endpoint was objective response rate (ORR) by independent review committee (IRC) analyzed in 3 primary ITT sets: L+ and/or T+, L+, T+. 2ary endpoints included ORR by INV, duration of response (DOR), disease control rate (DCR), PFS, OS, & safety. Preplanned analyses were performed in pts with BM at baseline (BL). BL/on-treatment ctDNA plasma samples (L+) were analyzed using a 73-gene NGS panel (Guardant360). Deep molecular responses (MR), defined as > 75% depletion of *MET*ex14, were compared with objective responses (OR). **Results:** By data cut-off (1 Oct 19) 151 pts received tepotinib (safety set); 99 L+/T+, 66 L+, 60 T+ pts comprised the 3 ITT sets with ≥6-month [m] allowed-up. Across treatment lines (n = 44 1L, n = 55 ≥2L), primary ORR & mPFS [95% CI] in 99 L+/T+ pts were 43% [34–54] & 8.6 m [6.9–11.0] by IRC and 56% [45–66] & 9.5 m [6.7–13.5] by INV. ORR was similar in L+ or T+ pts (table) or in T+L− pts (n = 25): 40% [21–61] by IRC and 48% [28–69] by INV. Only 2 pts were T−L+. Outcomes were also comparable in pts with BM (n = 11): IRC ORR 55% [23–83] & mPFS 10.9 m [8.0–ne]. 34/51 pts (67%) with matched BL/on-treatment L+ samples had deep MR strongly associated with clinical response: 32/34 pts (94%) with MR had disease control (INV), including 29/34 pts (85%) with OR; 2/34 pts had progressive disease. Further biomarker data will be presented. Grade ≥3 treatment-related adverse events (TRAEs) were reported by 37/151 pts (25%). 13 pts (9%) discontinued due to TRAEs. **Conclusions:** Tepotinib is a promising targeted therapy with durable clinical activity and manageable toxicity in pts with *MET*ex14 skipping NSCLC L+ or T+, including pts with BM. High ORR & DCR in pts with ctDNA molecular responses support that MET inhibition in *MET*ex14+ tumor cells can lead to clinical benefit. Clinical trial information: NCT02864992. Research Sponsor: Merck KGaA.

	L+		T+	
	66		60	
N	**IRC**	**INV**	**IRC**	**INV**
[95% CI]				
ORR %	44 [32–57]	56 [43–68]	47 [34–60]	62 [48–74]
mDOR m	11.1 [8.3–ne]	16.4 [7.3–21.5]	12.4 [9.7–ne]	16.4 [7.0–21.5]
DCR %	64 [51–75]	70 [57–80]	70 [57–81]	78 [66–88]
mPFS m	8.5 [5.1–11.0]	8.5 [5.6–11.2]	11.0 [7.8–17.1]	12.2 [6.3–17.7]
Immature mOS m	19.1 [9.5–ne]		19.7 [12.8–ne]	

9557 Poster Session (Board #323), Fri, 8:00 AM-11:00 AM

Genetic profiling and the response to RET inhibitors in RET fusion positive non-small cell lung cancer (NSCLC) identified by international genomic screening project (LC-SCRUM-Asia). *First Author: Kaname Nosaki, National Cancer Center Hospital East, Kashiwa, Japan*

Background: *RET* fusions are targetable oncogenic drivers in 1 – 2 % of NSCLC, yet no RET inhibitors are approved. Selective RET inhibitors, such as LOXO-292 and BLU-667, are currently in development. The impact of co-occurring mutation on outcome in RET-TKI therapy remains largely unknown. **Methods:** In an international genome screening project in Asia (LC-SCRUM-Asia), 161 cancer-related genes have been analyzed by a next-generation sequencing (NGS) system, Oncomine™ Comprehensive Assay. The therapeutic efficacy and survival of *RET* fusion+ NSCLC were evaluated using a large-scale clinicogenomic database in the LC-SCRUM-Japan. **Results:** From Feb 2013 to Dec 2019, a total of 7177 patients with non-squamous NSCLC were enrolled. *RET* fusion were detected in 167 patients (2.3 %). Median age was 61 years (range: 29 - 85), 60 % were female, 61 % were never-smokers, 99 % had adenocarcinoma, and 78 % had stage IIIB/IV disease. Based on our database, the median overall survival was 37 months. 62 patients received RET inhibitor therapy. *RET* fusions was identified by NGS assay (KIF5B-RET: 75, CCDC6-RET: 30, Others: 2) in 107 patients. Co-occurring genomic alterations were detected in 62 (58 %) patients, the median number of co-mutations was 1 (range 0 - 4). The most common co-occurring mutations in tumor involved *TP53* (31; 29 %), *STK11* (6; 6 %), *CDKN2A* (5; 5 %) and *TSC2* (5; 5 %). In 23 patients treated with RET inhibitor (unapproved drugs), there was a strong association between co-occurring mutation and time to treatment discontinuation (TTD) in RET inhibitor therapy; HR 2.75 (95%CI 1.71 - 15.6, P = 0.0096). **Conclusions:** *RET* rearrangements continue to represent a rare but high unmet need disease. Co-occurring mutation was significantly associated with shorter TTD. Our data is the largest cohort of advanced-stage *RET* fusion+ NSCLC profiled by NGS to date. Co-occurring mutation should be evaluated in the development of novel targeted therapies for *RET* fusion+ NSCLC. Research Sponsor: None.

9558 Poster Session (Board #324), Fri, 8:00 AM-11:00 AM

Two-year follow-up of bintrafusp alfa, a bifunctional fusion protein targeting TGF-β and PD-L1, for second-line (2L) treatment of non-small cell lung cancer (NSCLC). *First Author: Byoung Chul Cho, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, South Korea*

Background: Bintrafusp alfa (M7824) is a first-in-class bifunctional fusion protein composed of the extracellular domain of the TGF-βRII receptor (a TGF-β "trap") fused to a human IgG1 mAb blocking PD-L1. Interim analysis of a global phase 1 study (NCT02517398) found an objective response rate (ORR) of 27.5% and a manageable safety profile in patients with NSCLC who received bintrafusp alfa 1200 mg in the 2L setting; median overall survival (OS) was not reached. Here we present the longest efficacy and safety follow-up in a cohort receiving bintrafusp alfa. **Methods:** Patients with advanced NSCLC unselected for PD-L1 expression level who progressed after first-line standard treatment (no prior immunotherapy) were randomized to receive bintrafusp alfa 500 or 1200 mg (n = 40 each) Q2W until disease progression, unacceptable toxicity or trial withdrawal. The primary objective was best overall response (BOR) per RECIST 1.1; secondary and exploratory objectives include safety and OS, respectively. **Results:** As of October 15, 2019, a total of 40 patients received bintrafusp alfa at the recommended phase 2 dose of 1200 mg Q2W for a median of 17 (range, 2-136) weeks, with a median follow-up of 128 weeks; 18 patients were still alive, 3 patients had an ongoing response, and 1 patient remained on treatment. Results for the 1200 mg dose cohort showed an ORR of 27.5%, and a median duration of response of 18 months. The 18- and 24-month progression-free survival and OS rates were 18.4% and 11.0%, and 49.7% and 39.7%, respectively. Duration of response rates at 18 and 24 months were 42.4% and 21.2%, respectively. Median OS in patients with positive (≥1%) PD-L1 expression was 21.7 months; 6 of 7 patients with high (≥80% with Ab clone 73-10, which is equivalent to ≥50% with 22C3) PD-L1 expression were still alive. The overall safety profile has remained consistent since the interim analysis, with no new safety signals or deaths and 1 additional treatment-related discontinuation (blood alkaline phosphatase increased). **Conclusions:** After two years of follow-up, bintrafusp alfa continues to show manageable safety with durable responses and encouraging long-term survival, especially in patients with high PD-L1 expression. A study evaluating bintrafusp alfa vs pembrolizumab as first-line treatment for NSCLC is ongoing in patients with high PD-L1 expression (NCT03631706). Clinical trial information: NCT02517398. Research Sponsor: Merck KGaA, Darmstadt, Germany, Pharmaceutical/Biotech Company.

9560 Poster Session (Board #326), Fri, 8:00 AM-11:00 AM

Nivolumab (NIVO) plus ipilimumab (IPI) with two cycles of chemotherapy (chemo) in first-line metastatic non-small cell lung cancer (NSCLC): CheckMate 568 Part 2. *First Author: Justin F. Gainor, Massachusetts General Hospital, Boston, MA*

Background: In Part 1 of the phase II CheckMate 568 study (NCT02659059), NIVO + IPI was active and tolerable in patients (pts) with advanced NSCLC. The addition of chemo to dual immune checkpoint inhibitor therapy may further improve initial disease control. We report results from Part 2 of CheckMate 568, which evaluates NIVO + IPI combined with 2 cycles of chemo in pts with advanced treatment-naive NSCLC. **Methods:** Adult pts with untreated stage IV NSCLC received NIVO 360 mg Q3W + IPI 1 mg/kg Q6W combined with 2 cycles of histology-based platinum-doublet chemo, followed by NIVO + IPI without chemo until disease progression/unacceptable toxicity for ≤ 2 years. The primary endpoints were dose-limiting toxicity (DLT) within the first 9 weeks and safety/tolerability. Treatment was considered safe if ≤ 25% of at least 22 evaluable pts had a DLT. DLTs included but were not limited to: uncontrolled grade 3 non-skin treatment-related adverse events (TRAEs), grade 4 TRAEs, grade 2 treatment-related pneumonitis not resolved within 14 days, and treatment-related hepatic function abnormalities. **Results:** In total, 36 pts received treatment; 97% of pts completed 2 cycles of chemo combined with NIVO + IPI. Three pts discontinued IPI while continuing NIVO. Minimum follow-up was 14.9 months. Only 1 (3%) pt experienced a DLT (transient, asymptomatic grade 3 AST and ALT elevation) within the first 9 weeks. The elevation occurred on cycle 1, day 21 and resolved 2 weeks later with discontinuation of IPI, delay of NIVO, and treatment with prednisone; chemo was continued throughout and NIVO was restarted thereafter without recurrent toxicity. Grade 3–4 TRAEs occurred in 21 (58%) pts. Eight (22%) pts experienced a TRAE leading to discontinuation, most commonly colitis, encephalopathy, pneumonitis, and arthralgia (each in 2 [6%] pts); these events occurred outside of the 9-week window for DLT assessment. The most common select TRAEs (defined as AEs of potential immunologic causes) were skin related (18 [50%] pts); the most common grade 3–4 select TRAEs were endocrine (3 [8%] pts), skin related, gastrointestinal, and pulmonary (each in 2 [6%] pts). No treatment-related deaths occurred. Updated safety in addition to efficacy data will be presented. **Conclusions:** In pts with untreated advanced NSCLC, the addition of 2 cycles of platinum-doublet chemo to NIVO + tumor-optimized IPI was tolerable. No unexpected safety signals were observed. Clinical trial information: NCT02659059. Research Sponsor: Bristol-Myers Squibb.

9561 Poster Session (Board #327), Fri, 8:00 AM-11:00 AM

Soluble BTN2A1 as a potential predictive biomarker of immune checkpoint inhibitor efficacy in advanced non-small cell lung cancer (NSCLC). *First Author: Philippe Rochigneux, Institut Paoli-Calmettes, CRCM U1068, Marseille, France*

Background: Medical treatment of lung cancer has irreversibly changed since the development of immune checkpoint inhibitors (ICI). However, immune biomarkers of efficacy are still lacking. Preliminary data in leukemia and pancreatic cancer showed that soluble immune checkpoints are associated with a reduced overall survival (OS). This led us to explore the prognostic and predictive value of soluble immune checkpoints in non-small cell lung cancer (NSCLC) patients treated with chemotherapy or ICI. **Methods:** We analyzed 90 advanced NSCLC patients. The pilot cohort (Rennes University Hospital, France), included 48 patients treated with platinum doublets (n = 33) or ICI (n = 15) (LOC/11-16 protocol). The confirmation cohort (Paoli-Calmettes Institute) included 42 patients treated with ICI (nivolumab or pembrolizumab) in a longitudinal prospective setting (Immunosup trial, NCT03595813). In both cohorts, enzyme-linked immunosorbent assays (ELISA) were performed in baseline plasma samples for soluble forms of PD-1, PD-L1, global BTN3, BTLA, BTN3-A1 and BTN2A1. Soluble ICI levels were linked to clinical data using Kaplan-Meier, log-rank and Cox proportional-hazards models. Cut-points were determined using maxstat package for survival, R software R 3.6.2. **Results:** Five soluble immune checkpoints correlated and clustered together in unsupervised analysis (PD-1, PD-L1, global BTN3, BTLA, BTN3-A1), but were not associated with ICI efficacy. In patients treated with ICI, in the pilot and confirmation cohort, a high baseline plasmatic concentration of soluble BTN2A1 was significantly associated with an improved OS (confirmation cohort with a BTN2A1 cut-point of 3.55 ng/ml: HR = 0.30, 95%CI = 0.12-0.74, p = 0.0057, median OS in $BTN2A1^{low}$ = 7.6 months and median OS in $BTN2A1^{hi}$ = 19.5 months). On the contrary, in patients treated with chemotherapy, soluble BTN2A1 concentration was not associated with overall survival. **Conclusions:** In advanced NSCLC patients, a high baseline plasmatic concentration of soluble BTN2A1 was correlated with improved outcomes for ICI, but not for chemotherapy, suggesting that baseline soluble BTN2A1 level is a potential predictive biomarker of ICI efficacy. Additional studies are ongoing to confirm this finding. Research Sponsor: Institut Paoli Calmettes and Rennes University Hospital.

9562 Poster Session (Board #328), Fri, 8:00 AM-11:00 AM

A phase Ib study of abemaciclib in combination with pembrolizumab for patients (pts) with stage IV Kirsten rat sarcoma mutant (KRAS-mut) or squamous non-small cell lung cancer (NSCLC) (NCT02779751): Interim results. *First Author: Jean-Louis Pujol, Centre Hospitalier Universitaire, Maladies Respiratoires, Montpellier, France*

Background: Abemaciclib is an orally administered, selective small molecule cyclin-dependent kinase 4 and 6 inhibitor. In preclinical models, abemaciclib induced intratumor immune inflammation and synergized with PD-1 blockade to enhance antitumor efficacy in anti-PD-L1 refractory disease. Here, we report the safety and antitumor activity of abemaciclib plus the approved NSCLC treatment pembrolizumab in 2 cohorts for pts with nonsquamous and squamous NSCLC. **Methods:** Eligible pts for this non-randomized, open-label, multicohort, phase 1b study were either chemotherapy-naive with ≥ 1% tumor cell (TC) PD-L1 staining, *KRAS*-mut nonsquamous NSCLC (Cohort A) or had a squamous subtype and received ≤ 1 prior platinum-containing chemotherapy regimen (Cohort B) for metastatic NSCLC. Primary endpoint was safety; secondary objectives included objective response rate (ORR), progression-free survival (PFS), and overall survival (OS). **Results:** Twenty-five pts with NSCLC were enrolled in each cohort. Most pts (68%) in Cohort B had received 1 prior line of chemotherapy. Safety profiles observed in both cohorts were largely consistent with previous reports for abemaciclib and pembrolizumab monotherapy. Grades 3/4 AEs in Cohorts A and B, respectively, included ALT increase (6 pts [24%]/ 0 pts), diarrhea (3 pts [12%]/ 0 pts), neutropenia (3 pts [12%]/ 0 pts), and pneumonitis (3 pts [12%]/ 1 pt [4%]). Six pts in Cohort A (24%) and 2 pts in Cohort B (8%) had a confirmed partial response for a disease control rate (CR+PR+SD) of 52% and 64%, respectively. In Cohort A, the ORR in pts with strong (≥50% TC) PD-L1 staining (n = 13) was 31% vs. 17% in pts with weak (1-49% TC) PD-L1 expression (n = 12). Median PFS and OS were 7.6 months (95% CI: 1.6, NR) and 22.0 months (95% CI: 9.9, NR) in Cohort A and 3.3 months (95% CI: 1.4, 5.2) and 6.0 months (95% CI: 3.7, 13.1) in Cohort B, respectively. **Conclusions:** Abemaciclib plus pembrolizumab resulted in a numerical higher rate of transaminase elevations and pneumonitis. Antitumor activity was remarkable in the *KRAS*-mut nonsquamous NSCLC but not noticeably higher as compared to historical data for pembrolizumab monotherapy. Clinical trial information: NCT02779751. Research Sponsor: Eli Lilly and Company.

9563 Poster Session (Board #329), Fri, 8:00 AM-11:00 AM

Randomized phase II study of pembrolizumab (P) alone versus pegilodecakin (PEG) in combination with P as first-line (1L) therapy in patients (pts) with stage IV non-small cell lung cancer (NSCLC) with high PD-L1 expression (CYPRESS 1). *First Author: David R. Spigel, Sarah Cannon Research Institute, Nashville, TN*

Background: Pembrolizumab (P) is an immune checkpoint inhibitor (CPI) approved to treat 1L advanced NSCLC pts with high PD-L1 expression. PEG + CPI has demonstrated promising efficacy in NSCLC pts in a phase I trial (IVY; NCT02009449; Naing et al., 2019 *Lancet Oncol*), providing rationale for this randomized phase II trial (CYPRESS 1; NCT03382899). **Methods:** CYPRESS 1 was an open label phase II trial, for treatment-naïve, ECOG 0-1, PD-L1 high (22C3 clone TPS ≥ 50%), Stage IV NSCLC pts, without known EGFR/ALK mutations. Pts were randomized 1:1 to arm P (received 200mg IV on day 1 of a 21-day cycle) v. arm PEG+P (received P as above + PEG daily of 0.8 mg if weight ≤80kg and 1.6mg if weight> 80 kg up to 35 cycles in each arm). Pts were stratified by tumor histology and must have no prior history of cancer or prior CPI therapy. Primary endpoint was ORR (per RECIST v1.1 by investigator) Secondary endpoints included PFS, OS, and safety. Exploratory endpoints included ORR and PFS by blinded independent central review (BICR). Immune activation biomarkers (baseline and change from baseline) were assessed by serum immunoassay, IHC, and sequencing. **Results:** As of Dec 6, 2019, 101 pts were randomized to PEG+P (n=51) or P (n=50). Median follow-up time was 10.0 months (95% CI [8.4, 11.1]). Results for PEG+P versus P were: ORR per investigator was 47% v. 44% (p=0.76), ORR per BICR was 53% v. 46%(p=0.78), mPFS per investigator was 6.3 v. 6.1 months with HR = 0.94 (95% CI [0.54, 1.63];p=0.82), mPFS per BICR was 6.4 v. 7.2 months with HR = 1.10 (95%CI [0.62, 1.96]; p=0.74), and mOS was 16.3 months v. not reached with HR = 1.36 (95% CI [0.66, 2.77]; p-value=0.40). Gr ≥3 treatment related adverse events (TRAEs) were 62% for PEG+P versus 19% for P. Gr ≥3 TRAEs with ≥10% incidence included anemia (20% vs. 0%) and thrombocytopenia (12% vs. 2%). Biomarker data on immunostimulatory signals of the IL-10R pathway will be included. **Conclusions:** Adding PEG to P did not lead to improvement in ORR, PFS, or OS, in 1L advanced NSCLC with high PD-L1 expression. PEG+P arm demonstrated expected safety profile but overall higher toxicity compared to pembrolizumab alone. Clinical trial information: NCT03382899. Research Sponsor: Eli Lilly and Company.

9564 Poster Session (Board #330), Fri, 8:00 AM-11:00 AM

RELAY+: Exploratory study of ramucirumab plus gefitinib in untreated patients (pts) with *epidermal growth factor receptor* (*EGFR*)-mutated metastatic non-small cell lung cancer (NSCLC). *First Author: Makoto Nishio, Thoracic Medical Oncology, The Cancer Institute Hospital of Japanese Foundation for Cancer Research, Tokyo, Japan*

Background: The phase III randomized part of the RELAY study (Part B; RELAY; NCT02411448) showed a significant improvement in progression-free survival (PFS) for ramucirumab (RAM) plus erlotinib (ERL) vs placebo plus ERL in 449 untreated pts with *EGFR*-mutated metastatic NSCLC (median PFS: 19.4 vs 12.4 months; stratified hazard ratio: 0.59, 95% CI: 0.46–0.76, p<0.0001; 1-year PFS rate: 71.9% vs 50.7%). Here we report initial results from RELAY+ (additional cohort of RELAY; Part C), an open-label, single-arm, exploratory study evaluating RAM plus gefitinib (GEF) in East Asian pts. **Methods:** Previously untreated East Asian pts with metastatic NSCLC and *EGFR* exon 19 deletions (Ex19del) or exon 21 substitution mutation (Ex21.L858R) received RAM (10 mg/kg Q2W) plus GEF (250 mg/day) until disease progression or unacceptable toxicity. The 1-year PFS rate (primary endpoint, assuming a 1-year PFS rate of 55% for RAM+GEF), tumor response, biomarkers, and safety were assessed. *EGFR* T790M status (baseline/30-day follow-up) was assessed in liquid biopsy samples by Guardant360 NGS. **Results:** In total, 82 pts were enrolled (Japan: 68; Taiwan: 8; Korea: 6); 65.9% were female, 65.9% were never-smokers, and 43.9% had Ex19del. With median follow-up of 13.8 months (range: 2.6–20.2; censoring rate: 58.5%), the overall 1-year PFS rate (95% CI) was 65.0% (52.4–75.1), 67.2% (48.6–80.3) in pts with Ex19del (n=36), and 63.4% (45.0–77.1) in pts with Ex21.L858R (n=46). The objective response rate was 70.7% (95% CI: 59.6–80.3), disease control rate was 98.8% (95% CI: 93.4–100.0), and duration of response was immature at this point in time with a censoring rate of 56.9% where the median point estimate was 13.6 months (95% CI: 11.1–18.2). Post-progression *EGFR* T790M was seen in 7 of 9 (78%; 95% CI: 45.3–93.7) pts with 30-day follow-up NGS results in which *EGFR* activating mutation was detected. Grade ≥3 treatment-emergent adverse events reported in >5% of pts were ALT increased (23.2%), hypertension (22.0%), and AST increased (12.2%). **Conclusions:** With a 1-year PFS rate of 65.0%, the primary endpoint of RELAY+ was met. The efficacy of RAM+GEF in RELAY+ was similar to that of RAM+ERL in RELAY, and the safety profile of the combination was similar to that of the individual drugs. Clinical trial information: NCT02411448. Research Sponsor: Eli Lilly and Company.

9566 Poster Session (Board #332), Fri, 8:00 AM-11:00 AM

Phase Ib study of BI 836880, a VEGF/Ang2-blocking nanobody, in combination with BI 754091, an anti-PD-1 antibody: Initial results in patients (pts) with advanced non-small cell lung cancer (NSCLC). *First Author: Nicolas Girard, Institut Curie, Institut du Thorax Curie-Montsouris, Paris, France*

Background: Preclinical studies show that combining anti-VEGF/Ang2 with anti-PD-1 therapy promotes an immunopermissive state supportive of T-cell-mediated tumor cell destruction. BI 836880 is a humanized bispecific nanobody that targets VEGF and Ang2, and BI 754091 is an anti-PD-1 antibody. Each has shown manageable safety and preliminary activity as monotherapy. Here, we report initial results from a Phase Ib study assessing BI 836880 in combination with BI 754091. **Methods:** In Part 1 (dose escalation), pts with locally advanced or metastatic (m) non-squamous NSCLC who progressed during/after completion of ≥2 cycles of platinum-based chemotherapy (CT) ± a checkpoint inhibitor (CPI) were enrolled. Pts received BI 836880 (cohorts of 360, 500 and 720 mg intravenously [iv] 3-weekly [q3w]) plus fixed-dose BI 754091 (240 mg iv q3w). Dose escalation was guided by Bayesian logistic regression models with overdose control. Primary endpoint in Part 1 was maximum tolerated dose (MTD)/recommended phase 2 dose (RP2D), based on dose-limiting toxicities (DLTs) in Cycle 1. Initial safety and efficacy results of Part 1 are reported here. Part 2 will assess safety and efficacy in 6 expansion cohorts: mNSCLC after CPI monotherapy; mNSCLC after CT + CPI; mSCLC after CT ± CPI; immunotherapy-resistant m-melanoma; recurrent glioblastoma after 1st-line CT; and hepatocellular carcinoma after prior sorafenib or lenvatinib ± subsequent CPI. **Results:** 12 pts received BI 836880 plus BI 754091 (8 male; median age 59.5 years; 8 had received prior CPI). 4 pts remain on treatment (including 1 treated for 15 cycles). 1 pt had a DLT during Cycle 1 (360 mg; G3 pulmonary embolism). All pts experienced an adverse event (AE; any-cause; safety data cut-off Nov 2019), most commonly (all%/G3%) hypertension (58/25), vomiting (42/0), nausea (33/0), and asthenia (33/0). Hypertension was transient. No G4 AEs were reported; one G5 AE occurred (general physical health deterioration). 5 pts had immune-related AEs (G2 hypothyroidism in 2 pts; G2 pruritus, G1 papular rash, and G2 vomiting). To date (Jan 2020), 2 pts have achieved partial response; 1 pt (500 mg dose; CPI-naïve) had 58% target lesion reduction, and 1 (720 mg; prior CPI) had 35% target lesion reduction. 8 pts had stable disease. **Conclusions:** MTD/RP2D was BI 836880 720 mg plus BI 754091 240 mg q3w. The combination had a manageable safety profile, and preliminary anti-tumor activity was observed. Expansion cohorts are ongoing. Equal contribution: JA and BH Clinical trial information: NCT03468426. Research Sponsor: Boehringer Ingelheim.

9567 Poster Session (Board #333), Fri, 8:00 AM-11:00 AM

Phase II randomized trial of first-line pembrolizumab and vorinostat in patients with metastatic NSCLC (mNSCLC). *First Author: Andreas Nicholas Saltos, Department of Thoracic Oncology, Moffitt Cancer Center and Research Institute, Tampa, FL*

Background: Histone deacetylase inhibitors may enhance tumor immunogenicity through various mechanisms including induced expression of T cell chemokines. A previous phase I trial demonstrated the combination of pembrolizumab (P) with vorinostat (V) in mNSCLC was well tolerated with signals of activity in ICI-pretreated pts. We initiated a randomized trial in the first-line setting with the primary objective to determine if the combination had superior ORR compared to pembrolizumab monotherapy. **Methods:** Pts with treatment-naïve mNSCLC and 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] or 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 analysis of CD8+ TIL, scored using a 0-3 scale in tumor beds. Here we report results after a preplanned interim analysis for efficacy, with accrual ongoing to a planned total of 39 patients per arm. **Results:** Between 7/2017 – 1/2019, 49 pts were enrolled, with 47 pts evaluable for response (24 in Arm A and 23 in Arm B). Median age was 69 (range 47 - 87), 49% female, ECOG PS 0/1 in 11%/89%. PD-L1 TPS was ≥50% in 13/24 (54%) of pts in Arm A, and in 13/23 (57%) of pts in Arm B. The most common TRAEs in Arm A included diarrhea (13%), fatigue (8%), and pruritus (8%). 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 anorexia (43%), fatigue (43%), nausea (35%) and increased creatinine (35%). 1 pt in Arm B experienced grade ≥ 3 irAE (1 grade 3 pneumonitis). Pre-treatment CD8+ TIL were not significantly different between Arm A and Arm B (p = 0.85) with the majority of tumors in both arms having a low TIL score of 1 (65% Arm A and 73.7% Arm B). A significant increase from pre-treatment to on-treatment TIL scores was seen in both Arm A (p = 0.001) and Arm B (p = 0.002). The ORR in Arm B pts with low pre-treatment TIL (score = 1) pts was substantially higher (66.7%) than in Arm A (33.3%), suggesting the combination may be especially beneficial against low TIL tumors. **Conclusions:** The combination arm had a considerably higher ORR compared to pembrolizumab monotherapy, with a manageable toxicity profile. The combination of pembrolizumab plus vorinostat in mNSCLC warrants further investigation. Clinical trial information: NCT02638090. Research Sponsor: Merck, Other Government Agency.

Best response:	Arm A N = 24	Arm B N = 23	P value
PR	6 (25%)	11 (48%)	p = 0.135
SD	8 (33%)	10 (43%)	
PD	10 (42%)	2 (9%)	
DCR	14 (58%)	21 (91%)	p = 0.017

9568 Poster Session (Board #334), Fri, 8:00 AM-11:00 AM

Outcomes to first-line pembrolizumab in patients with PD-L1-high (≥50%) non-small-cell lung cancer and a poor performance status. *First Author: Joao Victor Machado Alessi, Hospital Sírio-Libanês, São Paulo, Brazil*

Background: Patients with non-small cell lung cancer (NSCLC) and a poor Eastern Cooperative Oncology Group performance status (ECOG PS) have been excluded from immunotherapy clinical trials. We sought to evaluate clinical outcomes to first-line pembrolizumab in patients with advanced NSCLC, a PD-L1 tumor proportion score (TPS) of ≥50%, and an ECOG PS of 2. **Methods:** We performed a multicenter retrospective analysis of patients with metastatic NSCLC and a PD-L1 tumor proportion score (TPS) of ≥50% (negative for genomic alterations in *EGFR* and *ALK*) who received treatment with first-line commercial pembrolizumab. Clinical outcomes were compared in patients based on ECOG PS. **Results:** Among 234 patients, 83.3% (N = 195) had an ECOG PS of 0 or 1, and 16.7% (N = 39) had an ECOG PS of 2. The baseline clinicopathological characteristics were balanced between the ECOG PS 0-1 vs 2 groups in terms of age, sex, tobacco use, histology, *KRAS* mutation status, presence of other potentially targetable driver mutations (*BRAF*, *MET*, *HER2*, *RET*), history of central nervous system (CNS) disease, and PD-L1 TPS distribution. Compared to patients with an ECOG PS of 0-1, patients with an ECOG PS of 2 had a significantly lower objective response rate (ORR 43.1% vs 25.6%; P = 0.04), a numerically shorter median progression free survival (mPFS 6.6 months vs 4.0 months; P = 0.09), and a significantly shorter median overall survival (mOS 20.3 months vs 7.4 months; P < 0.001). Upon disease progression, patients with an ECOG PS of 2 were significantly less likely to receive second-line systemic therapy compared to patients with an ECOG PS of 0-1 (55.5% vs 14.3%, P < 0.001). **Conclusions:** Although a subset of patients with an ECOG PS of 2 can respond first-line pembrolizumab, clinical outcomes in this population are poor, and use of second-line systemic therapy is infrequent. Research Sponsor: None.

9569 Poster Session (Board #335), Fri, 8:00 AM-11:00 AM

Angiogenesis inhibitor plus erlotinib versus erlotinib alone as first-line for advanced non-small cell lung-cancer harboring EGFR mutation. *First Author: Thierry Landre, UCOG-HUPSSD-APHP, Paris, France*

Background: Erlotinib is indicated in first line treatment for patients with Non-Small-Cell-Lung cancer (NSCLC) harbouring EGFR mutation. Addition of anti-VEGF in combination with erlotinib in this setting is controversial. **Methods:** We performed a meta-analysis of randomized trials comparing VEGF inhibitor plus erlotinib with erlotinib alone in first line treatment for advanced NSCLC harbouring EGFR mutation. The outcomes included overall survival (OS), progression-free survival (PFS) objective response rate (ORR), and median duration of response (DOR). A fixed-effect model was used. **Results:** Four studies evaluated bevacizumab + erlotinib (ARTEMIS, NEJ026, J025667, Stinchcombe et al), and one study evaluated ramucirumab + erlotinib (RELAY). These five eligible studies included 1230 non-squamous NSCLC patients (654 with Ex19del and 568 with Leu858Arg);. Most of the patients were women (63%), Asian (85%) and non-smokers (60%), with a median age of 64 years. The combination (anti-VEGF + erlotinib) was significantly associated with improvement of PFS (hazards ratio [HR]: 0.59, 95%CI: 0.51-0.69, p < 0.00001). Improvement in PFS was seen across all subgroups analyzed. Interim analysis of OS (HR: 0.90, 95%CI; 0.68-1.19, p = 0.45) and ORR (odds ratio [OR], 1.19, 0.91-1.55, p = 0.21) were not statistically significant. DOR was statistically longer with combination (p < 0.005). **Conclusions:** For patients with untreated advanced NSCLC with EGFR mutation, the anti-VEGF combination with erlotinib, compared with erlotinib alone, is associated with significantly improved PFS and DOR, but mature data for OS are needed to confirm the benefit of this strategy. Research Sponsor: None.

9570 Poster Session (Board #336), Fri, 8:00 AM-11:00 AM

Osimertinib in non-small cell lung cancer (NSCLC) with atypical EGFR activating mutations: A retrospective multicenter study. *First Author: Jingran Ji, University of California Davis Comprehensive Cancer Center, Sacramento, CA*

Background: Osimertinib (osi) is a 3rd generation EGFR tyrosine kinase inhibitor (TKI) approved for first line (1L) treatment of metastatic NSCLC harboring EGFR Exon 19 del and L858R (representing > 80% of EGFR activating mutations) or in NSCLC with $EGFR^{T790M}$ (the most common resistance mutation to 1st or 2nd generation TKI). However, it has not been well-studied in EGFR-mutant NSCLC harboring less common EGFR activating mutations such as G719X, L861Q, S768I, and exon 20 insertion (ins), among others. **Methods:** We conducted a multi-institution, retrospective study approved on institutional IRB protocols in a series of patients (pts.) with metastatic NSCLC treated with osi who harbored at least one atypical EGFR mutation, excluding those with concurrent L858R, Exon 19 del, or T790M. Kaplan-Meier analyses were generated with SPSS, v25 (IBM Corp., USA). Response was assessed by RECIST 1.1 in evaluable pts. Time on osi was employed as a surrogate endpoint for clinical benefit in this retrospective analysis. **Results:** Fifty-one NSCLC pts with uncommon EGFR mutations were identified among six US institutions. Pt characteristics: 72.5% women, median age 65 yo (44-83 yo), 82.3% ECOG PS 0-1, 43.1% never smoker, 100% lung adenocarcinoma, 58.8% Caucasian, 25.5% Asian, 3.9% Black, 2.0% Hispanic, and 9.8% Other. The most frequent mutations were L861Q (35.3%, N = 18), G719X (27.5%, N = 14), and Exon 20 ins (15.7%, N = 8). Osi was used in the 1L setting in 39.2% (N = 20). Median time on osi was 7.1 months (mo.) in the overall cohort (95% CI, 5.4 to 8.8 mo.) and 8.9 mo. (95% CI, 7.0 to 10.8 mo.) in pts receiving 1L osi. Patients harboring G719X (N = 4) and L861Q (N = 10) mutations had a median time on 1L osimertinib of 5.8 mo. and 19.3 mo., respectively. One patient's tumor had an EGFR exon 19 ins and was on 1L osi with a partial response for 16.8 months. Two patients with Exon 20 ins were on 1L osi for 9.3 mo. and 8 mo., respectively. **Conclusions:** In this largest known clinically annotated dataset of patients with atypical EGFR-mutations treated with osi, activity was noted, though 1L clinical benefit on osi appears lower in this multicenter US cohort than in E19del or L858R. These results are comparable to the recently published prospective phase II trial (*Cho et al*, 2019) conducted in Korea. Patients with L861Q and Exon 19 insertion appeared to benefit the most from osi in this time on treatment retrospective analysis. More detailed analysis of this cohort is planned and further prospective studies are warranted to determine clinical benefit of osi amongst diverse atypical EGFR-mutations. Research Sponsor: None.

9571 Poster Session (Board #337), Fri, 8:00 AM-11:00 AM

Intracranial anti-tumor activity of lazertinib in patients with advanced NSCLC who progressed after prior EGFR TKI therapy: Data from a phase I/II study. *First Author: Sang-We Kim, Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea*

Background: Lazertinib (YH25448) is a highly mutant-selective, irreversible 3rd-generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) that targets the activating EGFR mutations (Del19 and L858R), as well as the T790M mutation, while sparing wild type. Brain metastasis (BM) are common in patients (pts) with advanced NSCLC. Lazertinib showed a high blood-brain barrier penetration profile in pre-clinical studies. We report intracranial response data in pts with advanced NSCLC from a Phase I/II study of lazertinib (NCT03046992). **Methods:** Pts with advanced NSCLC, who had progressed after prior EGFR-TKI therapy, were enrolled in an open-label, multicenter, phase I/II study with dose-escalation, dose-expansion and dose-extension phases. Brain MRI was done in all pts at baseline. Pts with asymptomatic BM were eligible for enrollment. Intracranial anti-tumor activity of lazertinib was analysed in pts with BM present on baseline brain scan. Pre-defined intracranial endpoints included objective intracranial response rate (OIRR) and intracranial progression-free survival (IPFS) by independent central review (ICR). The brain metastasis full analysis population included pts with measurable and/or non-measurable BM lesion present on baseline brain scan; the brain metastasis population evaluable for response included only pts with measurable BM lesion. **Results:** As of 30 Sep 2019, a total of 181 pts received at least one dose of lazertinib 20-320 mg across 7 dose levels. Of those, 64 pts (56% female, median age 63, 86% T790M mutation positive by central testing) were included in the brain metastasis full analysis population; Intracranial disease control rate (IDCR) was 90.6% (58/64; 95% CI 83.5, 97.8) and median IPFS was not reached (95% CI 14.0, NR). In the brain metastasis population evaluable for response, a total of 22 pts were included; OIRR and IDCR were 54.5% (12/22; 95% CI 33.7, 75.4) and 90.9% (20/22; 95% CI 78.9, 100), respectively. In 13 pts (7.2%) out of 181 pts, brain was the first site of disease progression by existing and/or new lesions. **Conclusions:** Lazertinib demonstrated clinically meaningful activity against BM, aligned with preclinical data. Clinical trial information: NCT03046992. Research Sponsor: Yuhan Corporation, Other Government Agency.

9572 Poster Session (Board #338), Fri, 8:00 AM-11:00 AM

Efficacy and safety of lazertinib 240 mg as the clinical dose in patients with EGFR T790M mutant NSCLC: Data from a phase I/II study. *First Author: Ki Hyeong Lee, Division of Medical Oncology, Department of Medicine, Chungbuk National University Hospital, Chungbuk National University College of Medicine, Cheongju, South Korea*

Background: Lazertinib (YH25448) is a highly mutant-selective, irreversible 3rd-generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) that targets the activating EGFR mutations (Del19 and L858R), as well as the T790M mutation, while sparing wild type. We report the efficacy and safety results of lazertinib 240 mg as recommended phase 2 dose (RP2D) from a phase I/II study of lazertinib (NCT03046992). **Methods:** Patients (pts) with advanced NSCLC, who had progressed after prior EGFR-TKI therapy were enrolled in an open-label, multicenter, phase I/II study with dose-escalation (20-320 mg), dose-expansion (40-240 mg) and dose-extension phases. Pts were assessed for safety, tolerability, pharmacokinetics and efficacy. For dose-expansion and extension phases, tumors had to be T790M mutation-positive (T790M+). Of all 78 pts assigned to lazertinib 240 mg dose level across all phases, 76 pts with centrally confirmed T790M+ were included for efficacy analysis. **Results:** As of 30 Sep 2019, a total of 78 pts (49% female, median age 62) received at least one dose of lazertinib 240 mg. The median duration of follow-up was 9.6 months and 44 pts were ongoing at data cut-off. Of 78 pts, 76 pts with centrally confirmed T790M+ showed the objective response rate (ORR) 57.9% (95% CI 46.8, 69.0), the disease control rate (DCR) 89.5% (95% CI 82.6, 96.4), the median progression-free survival (PFS) 11.0 months (95% CI 5.6, 16.4) and the median duration of response (DoR) 13.8 months (95% CI 9.6, NR) by independent central review (ICR), respectively. Two pts (3%) experienced a confirmed complete response. The investigator-assessed ORR, DCR, median PFS and median DoR were 72.4% (95% CI 62.3, 82.4), 94.7% (95% CI 89.7, 99.8), 13.2 months (95% CI 9.6, not reached) and 11.8 months (95% CI 8.4, not reached), respectively. The most common treatment-emergent adverse events (TEAEs) at the 240 mg dose regardless of its causality were rash (35%), pruritus (33%) and paraesthesia (32%), which were mostly mild (Grade ≥3 rash: 1%; no Grade ≥3 pruritus or paraesthesia). TEAEs leading to dose reduction and dose discontinuation were observed in 13% (10/78) and 8% (4/78), respectively. Drug related TEAEs of grade ≥3 were observed in 6% (5/78). **Conclusions:** Lazertinib 240 mg has a favorable safety profile, and exhibits promising anti-tumor activity in pts with EGFR T790M+ NSCLC. Clinical trial information: NCT03046992. Research Sponsor: Yuhan Corporation, Other Government Agency.

9573 Poster Session (Board #339), Fri, 8:00 AM-11:00 AM

Study of anlotinib combined with icotinib as the first-line treatment in non-small cell lung cancer (NSCLC) patients harboring activating EGFR mutations (ALTER-L004). *First Author: Dingzhi Huang, Tianjin Medical University Cancer Institute and Hospital, Tianjin, China*

Background: Anti-angiogenic monoclonal antibodies plus EGFR TKIs have previously shown to prolong PFS in patients with EGFR-mutated NSCLC (JO25567 and NEJ026). Unlike bevacizumab, anlotinib is more convenient with orally administered and can inhibit more targets. Monotherapy using anlotinib has significantly prolonged median PFS and OS compared with the placebo values for third-line treatment or beyond in advanced NSCLC. We conducted a study to investigate the activity of anlotinb combined with icotinib, an oral EGFR TKI. **Methods:** This is a prospective, single-arm, multicenter clinical trial. Patients with locally advanced and/or metastatic IIIB, IIIC or IV non-squamous NSCLC are enrolled. Patients with EGFR exon 19 deletion and/or exon 21 L858R mutation who have not received prior therapies are eligible. The regimen consists of anlotinib (12 mg p.o, qd, day 1 to 14 every 21-day cycle) and icotinib (125mg p.o, tid). The primary endpoint is PFS. Secondary endpoints are OS, ORR, DCR and safety. **Results:** Between Jul 2018 and Dec 2019, 35 patients were enrolled in five centers and treated with anlotinb and icotinib. At data cutoff (Jan 7, 2020), patients were followed up for a median of 6.01 months.32 tumors were analyzed with 30 evaluable. Preliminary efficacy results: ORR was 59% (0 CR, 19 PR), DCR was 88% (0 CR, 19 PR, 9 SD). 26 patients are still receiving treatment and the longest exposure was 14 cycles. 10 (67%) of 15 patients with exon 19 deletions and 9 (53%) of 17 patients with L858R mutations achieved an objective response. 18 patients harbored aberrations in additional oncogenic drivers (PIK3CA or AKT1) and/or tumor suppressors (TP53, RB1, and PTEN) with an ORR of 72%. Upon analyses, AEs were observed in 97% (34/35) of patients. No Gr 5 AEs were reported. The most common Grade 3 AEs were hypertension (6 [17%]), hypertriglyceridemia (2 [6%]), diarrhea (1 [3%]), hyperuricemia (1 [3%]), hand and foot skin reaction (1 [3%]), asthenia (1 [3%]), and acute coronary syndrome (1 [3%]). Hypertriglyceridemia was the only grade 4 AE (2 [6%]). Three patients had to adjust treatment dosage. **Conclusions:** The strategy of anlotinib plus icotinib showed encouraging efficacy for previously untreated, EGFR-mutated advanced NSCLC patients. The combination was well tolerated and the AEs were manageable. The follow-up time is not sufficient and the PFS and OS outcomes need further evaluation. Clinical trial information: NCT03736837. Research Sponsor: None.

9574 Poster Session (Board #340), Fri, 8:00 AM-11:00 AM

Nazartinib (EGF816) in patients with treatment-naïve *EGFR*-mutant non-small cell lung cancer (NSCLC): Updated phase II results. *First Author: Daniel Shao-Weng Tan, National Cancer Centre Singapore, Singapore, Singapore*

Background: Prior data from a phase I/II study showed durable responses, including efficacy in brain lesions, and a tolerable safety profile with nazartinib in treatment (tx)-naïve patients (pts) with *EGFR*-mutant (mut), locally advanced (adv)/metastatic NSCLC. Here we report updated phase II results, including overall survival (OS). **Methods:** Tx-naïve adult pts with activating *EGFR*-mut (L858R or ex19del), stage IIIB/IV adv NSCLC with neurologically stable and controlled brain metastasis (BM) received oral nazartinib 150 mg once daily (continuous schedule). Primary endpoint: overall response rate (ORR) by BIRC per RECIST v1.1; secondary endpoints: disease control rate (DCR), duration of response (DOR), time to response, progression-free survival (PFS), OS, and safety. **Results:** At data cut-off (Nov 1, 2019), 45 pts were enrolled (median [range] age: 64 [28–83] years; 26 pts [58%] ECOG PS 1; 18 pts [40%] had baseline BM). *EGFR* mutations: 56% ex19del, 40% L858R, 4% other. 26/45 pts (58%) discontinued tx, with the primary reason being progressive disease in 19 pts (42%); 2 pts (4%) discontinued tx due to AEs. Median (range) follow-up for OS: 25 (0–33) months (mo); and for PFS: 17 (0–33) mo. ORR by BIRC: 69%; median PFS by BIRC: 18 mo; median OS was NE and at 33 mo, 56% of pts were alive (Table). BIRC results by baseline BM are shown in the Table. Median (range) duration of exposure: 24 (0–34) mo. Most frequent AEs (≥20% all grade, all causality): diarrhea (47%), maculopapular rash (38%), pyrexia (29%), cough and stomatitis (27% each), decreased appetite and pruritus (24% each), and dermatitis acneiform (22%). Most frequent grade 3/4 AEs (≥10%, all causality): maculopapular rash (5 pts [11%]; all grade 3) and increased lipase (5 pts [11%]; 1 pt with grade 4; no clinical pancreatitis AE was observed). **Conclusions:** After additional follow-up, median OS was still not reached and the safety profile was manageable. Nazartinib is a promising 3rd generation EGFR TKI for tx-naïve pts with adv *EGFR*-mut NSCLC, including pts with baseline BM. Clinical trial information: NCT02108964. Research Sponsor: Novartis Pharmaceuticals.

	BM – Yes N=18	BM – No N=27	All Pts N=45
ORR, n (%) (95% CI)	12 (67) (41–87)	19 (70) (50–86)	31 (69) (53–82)
DCR, n (%) (95% CI)	18 (100) (82–100)	23 (85) (66–96)	41 (91) (79–98)
Median DOR, mo (95% CI)	15 (9–25)	NE (15–NE)	25 (14–NE)
Events, n (%)	9 (75)	6 (32)	15 (48)
24-mo rate, % (95% CI)	33 (10–59)	65 (38–83)	52 (33–68)
Median PFS, mo (95% CI)	17 (11–21)	NE (15–NE)	18 (15–NE)
Events, n (%)	12 (67)	12 (44)	24 (53)
24-mo rate, % (95% CI)	27 (8–50)	51 (30–69)	42 (26–56)
Median OS, mo (95% CI)			NE (23–NE)
Events, n (%)			15 (33)
33-mo rate, % (95% CI)			56 (33–74)

9575 Poster Session (Board #341), Fri, 8:00 AM-11:00 AM

Tepotinib in patients (pts) with NSCLC with *MET* exon 14 (*MET*ex14) skipping: Health-related quality of life (HRQoL). *First Author: Paul K. Paik, Thoracic Oncology Service, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: In the phase II VISION study (NCT02864992) tepotinib had promising efficacy (response rate of 40–50% & median duration of response >1 y) and tolerable safety in pts with advanced NSCLC with *MET*ex14 skipping (3–4% of NSCLC), who are typically elderly with poor prognosis. Pt reported outcomes (PROs) of HRQoL are described here. **Methods:** Pts with advanced NSCLC positive for *MET*ex14 skipping by tissue or liquid biopsy received oral tepotinib 500 mg once daily; PROs were assessed using QLQ-LC13 (lung cancer symptoms), EORTC QLQ-C30 (Global health status [GHS] & 5 functional scales), and EQ-5D-5L (VAS). Questionnaires were completed at baseline (BL) and every 6 weeks (Wk); results were scored from 0–100 (minimal clinically important difference [MCID] ≥10 points). Mean change from BL was analyzed at Wk 12 (predefined analyses). **Results:** By 19 Jul 19 cut-off, 130 pts across treatment lines were enrolled (median age 74.2 y), with PROs available for 129. Questionnaire completion rates were 90.1% at Wk 12. Symptom burden at BL was moderate for advanced NSCLC; mean change from BL for PROs are shown in the table (better functioning: lower QLQ-LC13 or higher QLQ-C30 scores). For the QLQ-LC13 symptoms, mean changes from BL indicated a meaningful improvement in coughing, with a median time to improvement (2.8 months) paralleling the onset of objective response (within first 3 months), and a numerical improvement in dyspnea (–2.3 at Wk 12) and chest pain (–4.2 at Wk 12). QLQ-C30 values remained stable over treatment as did EQ-5D-5L scores (higher=better): mean (standard deviation, SD) change from BL score (60 [20.4]) was 6 (18.6) at Wk 6 and 5 (20.9) at Wk 12. **Conclusions:** In this first analysis of PROs in pts with advanced NSCLC with *MET*ex14 skipping with a moderate symptom burden, treatment with tepotinib led to a clinically meaningful improvement in coughing symptoms, while maintaining HRQoL. Coupled with the efficacy and safety profile, the predefined HRQoL analysis from the VISION study supports tepotinib as a promising treatment option for this elderly population with *MET*ex14+ NSCLC. Clinical trial information: NCT02864992. Research Sponsor: Merck KGaA.

			Mean change (SD):	
MCID: ≥10 points		**BL mean (SD)**	**Wk 6**	**Wk 12**
QLQ-LC13	Cough	36.0 (29.6)	–14.2 (28.6)	–11.6 (32.3)
	Dyspnea	31.4 (25.2)	–4.0 (15.5)	–2.3 (19.9)
	Chest pain	19.8 (27.7)	–8.4 (20.6)	–4.2 (25.0)
QLQ-C30	GHS	53.2 (24.4)	10.0 (21.6)	6.7 (20.5)
	Functional scales			
	Physical	31.0 (24.6)	–2.1 (16.4)	–0.3 (16.7)
	Role	34.5 (32.1)	–3.8 (25.5)	–4.8 (29.6)
	Cognitive	20.1 (23.7)	–2.0 (17.5)	1.3 (22.7)
	Emotional	30.0 (24.0)	–6.4 (19.9)	–7.1 (20.3)
	Social	27.7 (30.1)	–8.4 (24.9)	–3.7 (27.2)

9576 Poster Session (Board #342), Fri, 8:00 AM-11:00 AM

Lung-MAP (SWOG S1400): Design, implementation, and lessons learned from a biomarker-driven master protocol (BDMP) for previously-treated squamous lung cancer (sqNSCLC). *First Author: Mary Weber Redman, Fred Hutchinson Cancer Research Center, Seattle, WA*

Background: S1400, a BDMP, was designed to address an unmet need in sqNSCLC, run within the National Clinical Trials Network of the National Cancer Institute using a public-private partnership (PPP). The goal of was to establish an infrastructure for biomarker-screening and rapid evaluation of targeted therapies in biomarker-defined groups leading to regulatory approval. **Methods:** S1400 included a screening part using the FoundationOne assay and a clinical trial part with biomarker-driven studies (BDS) and "non-match" studies (NMS) for patients not eligible for any BDS. Patients could be screened (SaP) at progression or pre-screened (PreS). **Results:** Between June 2014 and January 2019, 1864 patients enrolled (711 PreS, 1079 SaP), 1674 with biomarker results, and 653 registered to a study with 217 to BDS and 436 to NMS. Six BDS and 3 NMS were initiated in small subsets with all BDS and 2 NMS completed within 2-3 years (see Table). Completed BDS have not demonstrated activity with 0-2 responses. On S1400I, Nivolumab and ipilimumab did not improve survival. Response with durvalumab (S1400A) was 16%. **Conclusions:** Lung-MAP met its goal to quickly answer targeted and other novel therapy questions in rare sqNSCLC subpopulations, answering questions that likely would not have been otherwise feasible, thereby demonstrating value. Activated just prior to the success of PD-(L)1 therapies in sqNSCLC, the trial had to undergo major design changes. Lessons learned include the need to update based on new science and that the PPP collaboration was essential to success. Lung-MAP continues now with new BDS and NMS in all NSCLC as of January 2019. Clinical trial information: NCT02154490. Research Sponsor: U.S. National Institutes of Health, Public-private partnership through Foundation for the NIH.

Clinical studies.

	Biomarker/Population	Therapy	Design	N	Endpoint	Open Date, Duration
S1400A	Immune-checkpoint inhibitor naive (ICIN)	Durvalumab	Single arm phase 2 (SAP2)	116	Response by RECIST 1.1 (R)	6/14 18 months(mths)
S1400B	PI3KCA	Taselisib	SAP2	26	R	6/14 30 mths
S1400C	Cell Cycle Gene Alterations	Palbociclib	SAP2	36	R	6/14 27 mths
S1400D	FGFR	AZD4547	SAP2	27	R	6/14 28 mths
S1400E	c-MET by IHC	Rilotumumab + Erlotinib versus (v) Erlotinib	Phase 2/3	9	R	6/14 5 mths
S1400F	NMS, PD-(L)1 exposed	Durvalumab + Tremelimumab	SAP2	30 acquired ICI resistant (AR) 36 primary ICI resistant (PR)	R	AR: 10/17 25 mths PR: 10/17 On-going
S1400G	Homologous recombinant repair deficiency genes	Talazoparib	SAP2	51	R	2/17 17 mths
S1400I	NMS ICIN	Nivolumab + Ipilimumab v. Nivolumab	Phase 3	275	Overall survival	12/15 28 mths
S1400K	c-MET by IHC	ABBV-399	SAP2	28	R	2/18 10 mths

9577 Poster Session (Board #343), Fri, 8:00 AM-11:00 AM

Clinicopathologic characteristics and immunotherapy outcomes in SMARCA4-mutant (mut) non-small cell lung cancer (NSCLC). *First Author: Joao Victor Machado Alessi, Dana-Farber Cancer Institute, Boston, MA*

Background: The catalytic unit of the SWI/SNF chromatin remodeling complex is encoded by the SMARCA4 gene, which is mutated in ~10% of NSCLCs. We sought to characterize the clinicopathologic characteristics and outcomes to immune checkpoint inhibition in SMARCA4-mutant NSCLC. **Methods:** We collected clinicopathologic and genomic data from patients with NSCLC that had undergone targeted next generation sequencing (NGS) by OncoPanel at the Dana-Farber Cancer Institute. SMARCA4 frameshift, nonsense, and splice-site mutations were considered pathogenic, as were missense mutations if predicted to be pathogenic by Mutation Assessor and Polyphen-2. Clinical outcomes to immune checkpoint inhibition among SMARCA4-mutant NSCLCs were retrospectively assessed. **Results:** Of 2690 patients with NSCLC, 8% (N = 211) harbored SMARCA4 mutations. Clinicopathological characteristics were balanced between SMARCA4 mut and SMARCA4 wild-type (wt) in terms of age, histology, and PD-L1 expression. We observed a male predominance (P = 0.03), greater use of tobacco (P < 0.001), a higher tumor mutational burden (TMB) (P < 0.001), a higher prevalence of advanced disease (P < 0.001), and a lower prevalence of concurrent targetable driver mutations (P < 0.001) in SMARCA4mut vs SMARCA4wt NSCLCs. Among 513 patients with nonsquamous NSCLC who received immune checkpoint inhibitors, 11% (N = 57) harbored SMARCA4 mutations. From the start of immunotherapy, we observed no difference in overall response rate (ORR 21.5% vs 19.3%; P = 0.3), median progression free survival (mPFS 3.2 months vs 2.1 months; P = 0.4), or median overall survival (mOS 12.0 months vs 8.2 months; P = 0.09) in SMARCA4wt vs SMARCA4mut NSCLC, respectively. However, among KRASmut NSCLC, a concurrent SMARCA4 mut conferred a significantly lower ORR (23.1% vs 0.0%; P = 0.02), a significantly shorter mPFS (4.8 months vs 1.7 month; HR: 0.31 [95% CI: 0.15-0.61]; P < 0.001), and a significantly shorter mOS (15.6 months vs 2.7 months; HR: 0.25 [95%CI: 0.12-0.49]; P < 0.001). The deleterious effect of SMARCA4 mut on immunotherapy outcomes in KRAS mut NSCLC was maintained when controlling for concurrent STK11 mut. **Conclusions:** SMARCA4 mutations define a genomic subset of NSCLC with unique clinicopathologic characteristics, and confer worse outcomes to immunotherapy in KRAS mut NSCLC. Research Sponsor: None.

9578 Poster Session (Board #344), Fri, 8:00 AM-11:00 AM

***FOXO3* polymorphisms were correlated with gefitinib-induced hepatotoxicity in patients with non-small cell lung cancer.** *First Author: Shaoxing Guan, Laboratory of Drug Metabolism and Pharmacokinetics, School of Pharmaceutical Sciences, Sun Yat-sen University, Guangzhou, China*

Background: Drug-induced liver injury (DILI) is one of the most safety concern in drug development and clinical therapy. Severe hepatotoxicity of gefitinib often leads to acute/chronic liver injury, drug discontinuation and further treatment failure, however, the mechanism of gefitinib-induced hepatotoxicity remains unclear. *AKT1/FOXO3* regulates expression of genes involved in multiple biological/pathological processes in liver cells, including apoptosis, oxidative stress, and cell-cycle transition, as well as expression of autophagy-related (Atg) genes. Therefore, we investigated the correlation between single nucleotide polymorphisms (SNP) in *AKT1/FOXO3* and gefitinib-induced hepatotoxicity in patients with advanced non-small cell lung cancer (NSCLC). **Methods:** A total of 172 advanced NSCLC patients with activating *EGFR* mutations were enrolled and administered with gefitinib 250mg daily. 22 tag SNPs in *AKT1/FOXO3* were selected by Heploview 4.2 and sequenced by Agena MassARRAY System. The associations between polymorphisms of *AKT1/FOXO3* and gefitinib-induced hepatotoxicity were analyzed by Chi square test. This study was approved by the ethical committee of Sun Yat-Sen University Cancer Center. **Results:** *FOXO3* rs4946935 and *FOXO3* rs75544369 were found to be associated with gefitinib-induced hepatotoxicity in NSCLC patients. *FOXO3* rs4946935 AA carriers have higher risk of developing gefitinib-induced hepatotoxicity than those with *FOXO3* rs4946935 AG/GG. ($P = 0.018$, OR = 12.414, 95%CI (1.53-100.711)). Patients with *FOXO3* rs75544369 GA have higher risk of developing hepatotoxicity with *P* of 0.0002 (OR = 5.241, CI%(1.85-14.851)), or developing severe hepatotoxicity with *P* of 0.033 (OR = 2.963, 95%CI (1.090-8.059)), than those with *FOXO3* rs75544369 GG. **Conclusions:** *FOXO3* rs4946935 and *FOXO3* rs75544369 are predictive biomarkers for gefitinib-induced hepatotoxicity in NSCLC patients. The mechanism underlying the association between *FOXO3* polymorphisms and gefitinib-induced hepatotoxicity are worth investigating in further studies. Clinical trial information: NCT01994057. Research Sponsor: National Natural Science Foundation of China.

9579 Poster Session (Board #345), Fri, 8:00 AM-11:00 AM

Is checkpoint inhibitor pneumonitis underreported in patients with advanced non-small cell lung cancer (NSCLC) on PD-1 inhibitor monotherapy? *First Author: Benjamin Oren Spieler, University of Miami Miller School of Medicine, Miami, FL*

Background: For patients with advanced non-small cell lung cancer (NSCLC), immunotherapy (ImT) has led to improvements in survival and quality of life. Checkpoint inhibitor pneumonitis (CIP) is an uncommon but sometimes life-threatening adverse event. While CIP is a diagnosis of exclusion, many oncologists believe the incidence of CIP is underreported. Radiomics, an image analysis technique that can extract imperceptible information from radiographic images, has been incorporated into predictive models for many cancers. Recent studies suggest that radiomic analysis of pre-ImT imaging can predict CIP. We hypothesized that for patients with advanced NSCLC treated with Nivolumab monotherapy, the rate of CIP is underreported and radiomics features can identify CIP that was clinically misclassified. **Methods:** From an IRB-approved database (DB) of 159 patients with advanced NSCLC treated with Nivolumab, chart review identified 8 patients diagnosed with CIP of any grade (5%). 42 additional patients from the same DB without diagnosis of CIP were randomly selected for analysis. For all 50 patients, uninvolved lung in the last pre-ImT CT imaging study was segmented, delineated, and analyzed for radiomics features associated with CIP. A logistic regression model incorporating radiomics assigned a CIP probability score to every patient. **Results:** Six radiomics features correlated with CIP (*p*-values range from 0.02 to 0.03). Each feature had an AUC of ~0.79 (range 0.789 to 0.794) showing large effect size, with odds ratios greater than 3.50 (4 features) or less than 0.3 (2 features). The radiomics-based probability model assigned 7/42 patients (17.5%) without clinical diagnosis of CIP a greater than 50% probability of CIP. Chart review revealed that 6/7 "misclassified" patients exhibited symptoms or radiographic features highly suggestive of CIP within 5 months of initial immunotherapy treatment. These indications originally had been attributed to disease progression, overshadowed by more severe symptoms or simply mislabeled (e.g. a case of recall pneumonitis was described as "radiation pneumonitis"). **Conclusions:** For patients with advanced NSCLC treated with nivolumab, the incidence of checkpoint-inhibitor pneumonitis (CIP) is underreported and radiomics features can help identify CIP that has been clinically misclassified. Future directions include expansion of this study across the full database, correlation of radiomics features with blood biomarkers, and the inclusion of tumor burden as an additional covariate in the analysis. Research Sponsor: None.

9580 Poster Session (Board #346), Fri, 8:00 AM-11:00 AM

Indirect comparison of TAK-788 vs real-world data outcomes in refractory non-small cell lung cancer (NSCLC) with *EGFR* exon 20 insertions. *First Author: Leora Horn, Vanderbilt-Ingram Cancer Center, Nashville, TN*

Background: Currently approved epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) are ineffective in patients (pts) with *EGFR* exon 20 insertion NSCLC. TAK-788 is an EGFR TKI with potent and selective preclinical inhibitory activity against *EGFR* exon 20 insertions, and has demonstrated preliminary efficacy in a single-arm phase 1/2 clinical trial (NCT02716116). We performed an indirect comparison of real-world outcomes with clinical trial data for this subset of pts to determine whether TAK-788 provides superior efficacy over standard treatment options. **Methods:** We compared efficacy in pts with refractory NSCLC with *EGFR* exon 20 insertions treated with TAK-788 160 mg qd (1–7 prior lines) from the ongoing clinical trial (data cut Mar 1, 2019) vs real-world data (RWD) in the second-line setting from the US Flatiron Health electronic health record–derived database (Jan 2011–Jun 2018). This analysis was conducted using an unadjusted data set, as well as by applying propensity score modeling with inverse probability of treatment weighting (IPTW) to adjust for group differences in key baseline characteristics. Progression-free survival (PFS) and objective response rate (ORR) were compared between groups. **Results:** A total of 99 pts were included, n=28 TAK-788 and n=71 RWD; mean age 62/65 y; male 25%/46%; Asian 18%/10%; former smoker 39%/45%; brain metastases 43%/34%. In the RWD, there was no consistent regimen for second-line treatment (including 29.6% immuno-oncologic agents, 25.4% EGFR TKI, 10% docetaxel). Baseline characteristics were comparable after weighting. PFS and ORR showed statistically significant improvements with TAK-788 vs RWD (Table). Specifically, after weighting, median PFS for TAK-788 vs RWD is 7.3 vs 3.5 mo, and ORR is 43% vs 13%. **Conclusions:** Despite a more heavily pretreated pt population, the efficacy of TAK-788 in pts with refractory NSCLC with *EGFR* exon 20 insertions appears better than other second-line treatment options used in the real-world setting. Clinical trial information: NCT02716116. Research Sponsor: Millennium Pharmaceuticals, Inc., a wholly owned subsidiary of Takeda Pharmaceutical Company Limited.

	TAK-788 (n=28)	RWD Unweighted (n=71)	RWD Weighted (n=71)
PFS[a] median, mo (95% CI)	7.3 (4.4, NE)	3.7 (2.6, 5.9)	3.5 (2.3, 5.9)
HR (95% CI)		0.50 (0.27, 0.92)	0.44[b] (0.22, 0.91)
Log-rank *P*		0.0235	0.0098
ORR, % (95% CI)	43 (25, 63)	14 (7, 24)	13 (0.4, 25)
Rate difference, % (95% CI)		29 (9, 49)	30 (8, 52)
OR (95% CI)		4.58 (1.68, 12.48)	5.14[c] (1.35, 19.65)
P		0.0030	0.0167

[a]Per investigator RECIST 1.1 for TAK-788 and clinician-reported tumor growth for RWD. [b]Cox regression model with IPTW. [c]Logistic regression model with IPTW. HR, hazard ratio; NE, not estimable; OR, odds ratio.

9581 Poster Session (Board #347), Fri, 8:00 AM-11:00 AM

SPRING: A Worldwide Innovative Network (WIN) Consortium phase I study of triple therapy (avelumab, axitinib, and palbociclib) in advanced non-small cell lung cancer (NSCLC) with genomic and transcriptomic correlates. *First Author: Benjamin Maurice Solomon, Avera Cancer Institute, Sioux Falls, SD*

Background: The Worldwide Innovative Network (WIN) Consortium has developed the Simplified Interventional Mapping System (SIMS) algorithm in order to predict treatment response by comparing tumor and normal tissue biopsies on both genomic and transcriptomic platforms. SPRING is the first trial to assess a SIMS-based tri-therapy regimen in advanced non-small cell lung cancer (NSCLC). **Methods:** Patients with advanced NSCLC (no *EGFR* or *ALK* alterations; no *ROS1* alterations if tested; PD-L1 unrestricted; $\leq$2 prior therapy lines) were treated with avelumab, axitinib, and palbociclib (3+3 dose escalation design). Tumor and normal endobronchial mucosal biopsies were obtained on all patients for retrospective SIMS algorithm validation. **Results:** Fifteen patients were treated: 6 at dose level 1 (DL1); 6, dose level 2 (DL2); 3, dose level 3 (DL3). Three dose-limiting toxicities (DLTs) at least possibly drug-related occurred: 1 DLT at DL2 (Grade 3 (G3) infusion reaction); 2 patients with DLTs at DL3 (1 with G3 hand/foot syndrome and G3 fatigue and 1 with G5 respiratory failure). Among 14 evaluable patients, the partial response (PR) rate was 28.6% (4/14 patients including 2/6 patients at DL1; two PRs in patients who failed prior pembrolizumab; two PRs in patients with PD-L1 $<$ 1%). The maximum tolerated dose was avelumab 10 mg/kg IV q2weeks, axitinib 5 mg PO BID continuous, palbociclib 75 mg PO daily on days 8-28 of a 28 day cycle (DL2). DL2 was above the recommended phase II dose (RP2D), since 5/6 patients treated at DL2 required later treatment delays and/or dose reductions, mostly due to neutropenia. To further evaluate DL1, 3 patients were added to this cohort (total of 6). Since no DLTs were seen at DL1, and 5 of 6 patients did not require dose reduction, DL1 (avelumab 10 mg/kg IV q2weeks, axitinib 3 mg PO BID continuous, palbociclib 75 mg PO daily on days 8-28 of a 28 day cycle) is the RP2D. **Conclusions:** The RP2D was determined to be dose level 1. This triplet showed antitumor activity in patients with NSCLC, including those progressing on prior pembrolizumab. SIMS algorithm correlates of response are being assessed. Clinical trial information: NCT03386929. Research Sponsor: ARC Foundation for cancer research, Villejuif, France, Pharmaceutical/Biotech Company.

9582 Poster Session (Board #348), Fri, 8:00 AM-11:00 AM

Final analysis of KEYNOTE-189: Pemetrexed-platinum chemotherapy (chemo) with or without pembrolizumab (pembro) in patients (pts) with previously untreated metastatic nonsquamous non-small cell lung cancer (NSCLC). *First Author: Delvys Rodriguez-Abreu, Complejo Hospitalario Universitario Insular Materno-Infantil de Gran Canaria, Universidad de Las Palmas de Gran Canaria, Las Palmas De Gran Canaria, Spain*

Background: The phase III KEYNOTE-189 study (NCT02578680), showed significant improvements in OS and PFS with pembro + chemo vs placebo + chemo in pts with previously untreated metastatic nonsquamous NSCLC without sensitizing *EGFR/ALK* mutations. We report the protocol-specified final analysis of KEYNOTE-189. **Methods:** Pts were randomized 2:1 to receive 35 cycles of pembro 200 mg Q3W (n = 410) or placebo Q3W (n = 206) plus 4 cycles of pemetrexed (pem) and carboplatin/cisplatin followed by maintenance pem. Pts in the placebo + chemo arm could crossover to pembro upon PD. PFS and OS were primary endpoints; ORR was a secondary endpoint. PFS2 (time from randomization to objective tumor progression on next-line treatment/death), was an exploratory endpoint. **Results:** At data cutoff (May 20, 2019), median (range) time from randomization to data cutoff was 31.0 (26.5–38.8) mo. 17 pts in the pembro + chemo arm and 1 pt in the placebo + chemo arm were receiving initially assigned treatment; 84 pts crossed over to pembro. Median (95% CI) OS (22.0 [19.5–24.5] vs 10.6 [8.7–13.6] mo; HR 0.56 [95% CI, 0.46–0.69]) and PFS (9.0 [8.1–10.4] vs 4.9 [4.7–5.5] mo; HR 0.49 [95% CI, 0.41–0.59]) were longer with pembro + chemo vs placebo + chemo (Table). The 2-y OS rate was 45.7% vs 27.3% and the 2-y PFS rate was 22.0% vs 3.4%. ORR was 48.3% with pembro + chemo vs 19.9% with placebo + chemo. 56 pts in the pembro + chemo arm completed 35 cycles of pembro among whom ORR was 85.7% (4 CR, 44 PR, 8 SD) and median OS was not reached. 292 (72.1%) pts in the pembro + chemo arm and 135 (66.8%) pts in the placebo + chemo arm had grade 3–5 AEs. **Conclusions:** Pembro + chemo continued to show improved outcomes in OS, PFS, ORR and PFS2 compared with placebo + chemo, with manageable toxicity. These findings support first-line pembro + chemo in pts with previously untreated metastatic nonsquamous NSCLC. Clinical trial information: NCT02578680. Research Sponsor: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

HR (95% CI)	All pts N = 616	PD-L1 TPS ≥50% n = 202	PD-L1 TPS 1-49% n = 186	PD-L1 TPS < 1% n = 190
OS	0.56 (0.46–0.69)	0.59 (0.40–0.86)	0.66 (0.46–0.96)	0.51 (0.36–0.71)
PFS	0.49 (0.41–0.59)	0.35 (0.25–0.49)	0.53 (0.38–0.74)	0.67 (0.49–0.93)
PFS2	0.50 (0.41–0.61)	0.52 (0.36–0.75)	0.57 (0.40–0.81)	0.47 (0.33–0.66)

9583 Poster Session (Board #349), Fri, 8:00 AM-11:00 AM

A phase Ib study of a novel c-MET, AXL and VEGFR-2 inhibitor ningetinib and gefitinib combination therapy in Chinese EGFR-TKI resistant NSCLC with T790M negative. *First Author: Hongyun Zhao, Department of Medical Oncology, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Sun Yat-sen University Cancer Center, Sun Yat-sen University, Guangzhou, China*

Background: Ningetinib is a novel tyrosine kinase inhibitor, targeted at c-Met, Axl, VEGFR-2, Mer and Flt3. This phase Ib trial (NCT03758287) evaluated the safety, determined the recommended phase II dose (RP2D), and further explored the pharmacokinetic and efficacy of Ningetinib + Gefitinib in EGFR-TKIs acquired resistant NSCLC patients (pts) with T790M negative. **Methods:** Chinese Pts with advanced or metastatic NSCLC, acquired resistant to at least one EGFR-TKI, T790M negative were enrolled. Pts received Ningetinib 30, 40, 60 mg + Gefitinib 250mg orally once daily in dose-escalation (n = 12) by a Fibonacci 3+3 design. Expansion phase (n = 74, enrollment is ongoing) started at tolerated dosage. Safety, RP2D were primary endpoints; PK, antitumor activity were secondary endpoints. Non-mandatory tumor samples at baseline were collected for exploratory objectives. **Results:** Totally, 86 eligible pts were enrolled between Nov 2016 and Dec 2019, and received treatment (Ningetinib 30 mg, n = 36; 40 mg, n = 46; 60 mg, n = 4), with median age 56.7 years, 36% with baseline brain metastasis, 66%/33%/1% prior 1/2/3 lines EGFR-TKI treatment, respectively. Treatment-related adverse events (TRAEs) occurred in 82 (95%) pts, grade 3/4 in 32 pts (37%). Most common TRAEs (≥30%) were myocardial enzyme elevation (all grade 74.4%; grade 3-4 0%), transaminase elevation (73.3%; 2.3%), skin rash (60.5%; 3.5%), albuminuria (44.2%; 0%), coagulation abnormalities (mostly asymptomatic Fbp decrease; 37.2%; 15.1%), diarrhea (33.7%; 2.3%) and hypertension (32.6%; 11.6%). Two Dose limited toxicities were observed at 60 mg dosage (both were grade 3 Fbg decrease), RP2D was decided at 40 mg. Of 84 efficacy evaluable pts, ORR was 19.1% (16 PR), DCR was 91.7% (61 SD, 7 PD). Totally, 65 (75.6%) progression events occurred at data cut-off (9 Jan 2020), the median PFS for all pts was 4.4 months (95%CI 3.7-4.6). No PFS differences were found between pts grouped by 3rd TKIs history or brain metastasis. C-Met gene amplification by FISH was conducted in 72 pts (83.7%). Pts with higher gene copy number (GCN) responded better in treatment, ORR in the GCN ≥6 (n = 11), GCN ≥5 (n = 16) and GCN ≥3 (n = 37) subgroups was 36.4%, 25.0% and 21.6% respectively. **Conclusions:** Ningetinib was well tolerated at 30 mg and 40 mg dosage with Gefitinib 250 mg, the RP2D for Ningetinb was 40 mg. This combination therapy showed promising anti-tumor activity in prior EGFR-TKIs acquired resistant NSCLC pts with T790M negative. C-Met GCN was the potential efficacy biomarker. Clinical trial information: NCT03758287. Research Sponsor: HEC R&D Center, Sunshine Lake Pharma Co., Ltd.

9584 Poster Session (Board #350), Fri, 8:00 AM-11:00 AM

Genomic characterization of metastatic lung cancers. *First Author: Hui Yu, Department of Medical Oncology, Fudan University Shanghai Cancer Center; Department of Oncology, Shanghai Medical College, Fudan University, Shanghai, China*

Background: Lung carcinomas are most often diagnosed at stage IV, with metastases, which contribute to 90% of deaths of patients. Enormous efforts have been made in previous studies in seek of underlying mechanisms and treatments that prevent or cure metastases. However, few comprehensive conclusions have been drawn on organ-specific genomic landscapes and molecular dependencies of lung cancer metastases, largely due to limited sample sizes. **Methods:** We employed massive targeted next generation sequencing (NGS) with a panel covering 425 cancer-related genes on 10409 samples from 8619 patients with lung cancer, including 8479 from primary tumors and 1930 from metastases to the brain, liver, pleura, bones, and lymph nodes. We investigated single nucleotide variants (SNVs), copy number variants (CNVs), structural variations (SVs), mutational signatures, and other genomic characteristics at all primary and metastatic sites. With data of primary-metastatic tumor pairs, we also examined genomic evolutionary patterns. **Results:** Our data revealed that metastases harbored more instable and complicated genomes. Most SNVs (5/6), CNVs (41/47), and SVs (2/3) that showed significant differences of prevalence between primary tumors (PTs) and metastases (MTs) were MT-enriched. Among them, we identified a novel MT-enriched event, *PTK2* amplification (2.33 folds), as well as known ones including mutations of *TP53*, *ARID1A*, and *BRCA1* (1.23, 1.74, and 2.29 folds), and amplifications of *MYC*, *RICTOR*, and *EGFR* (2.04, 2.15, and 1.59 folds). In addition, almost all actionable CNV alterations (6/7) showed higher frequencies in MTs. *ALK* fusions and *EGFR* mutations, which indicate distinct target therapies, exhibited opposite preference in MTs and PTs, respectively. We also identified MT site-specificity of alterations, such as *NF2*, *TSC2*, and *LRP1B* mutations enriched in the brain, *BRAF* and *GNAS* mutations absent in the liver, and APOBEC-associated mutational signatures enriched in lymph nodes. Moreover, we unraveled organ-specific patterns of genomic evolutionary trajectories in metastatic diseases. **Conclusions:** The genomic profile and evolutionary pattern of metastatic lung cancer differed from that of primary tumors. The identification of site-specific characteristics that may have empowered directional metastasis, such as *NF2*, *TSC2*, and *LRP1B* mutations in the brain and APOBEC-associated mutational signatures in lymph nodes, may guide personalized disease management, design of clinical trials, and/or discovery of therapeutic targets for metastatic lung cancer at different body regions. Research Sponsor: None.

9585 Poster Session (Board #351), Fri, 8:00 AM-11:00 AM

A phase I, dose-escalation and expansion study of TQ-B3139, a novel ALK TKI, in Chinese ALK or ROS1 positive advanced non-small cell lung cancer (NSCLC). *First Author: Yuxiang Ma, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Department of Medical Oncology, Sun Yat-sen University Cancer Center, Guangzhou, China*

Background: TQ-B3139 is a novel ALK inhibitor with activity 3-7 folds higher than Crizotinib against a broad range of ALK mutations. This phase I study (NCT03099330) is to investigate the safety, and determine the recommended phase II dose (RP2D), and pharmacokinetic (PK), clinical efficacy of TQ-B3139 in Chinese NSCLC patients. **Methods:** Patients with advanced NSCLC and failed at least one systemic anti-cancer treatment were enrolled. TQ-B3139 was administered orally from 50mg~100mg qd and 200, 300, 400, 500, 600 and 800mg bid, using a PK-guided modified Fibonacci 3+3 dose escalation design. The dose-escalation evaluated patients in 28-day cycles, dose limited toxicities (DLTs) was observed at first cycle. Dose-expansion phase started at dose level which objective response occurs. Treatment was continued until disease progression, death or unacceptable toxicity. **Results:** Between July 2017 and May 2019, totally 63 patients (59 ALK+, 4 ROS1+) were enrolled. Sixteen patients had prior ALK inhibitor therapy (11 Crizotinib, 5 Ensartinib), and 23 (36.5%) with baseline brain metastasis. Totally, 62 (98.4%) patients experienced treatment-related adverse events (TRAEs), grade 3-4 TRAEs were observed in 21 (33.3%) patients. One DLT occurred in the 800mg bid dose cohort (grade 3 nausea and vomiting). Top 3 common TRAEs were nausea (all grade 87.3%; grade 3-4 3.2%), diarrhea (84.1%, 6.4%), transaminase elevation (65.1%, 4.8%). AUC and C_{trough} at steady state increased proportionally from 200mg to 600mg bid. Absorption saturation was observed in 800mg bid. Base on the safety and PK results, PR2D was decided at 600mg bid. Overall ORR was 73.0% (2 CR, 44 PR); DCR was 85.7% (8 SD). Objective response was observed from dose level 200mg bid cohort, ORR and DCR at ≥200mg bid was 78.0% and 89.8%. For ALK TKI-naïve and -resistant patients, the ORR was 78.7% (37/47) and 56.3% (9/16) respectively. For patients with measurable baseline brain metastasis, the ORR for brain lesions was 80.0% (8/10). At data cut-off (23 Jan 2020), 32 events (50.8%) occurred, the median PFS for all patients was 12.1 months (95%CI 8.5-15.6), for patients at ≥200mg bid dose was 12.2 months. The median PFS was not reached for -naive patients (6 months PFS rate 74.5%, 95%CI 68.1-80.9), and 5.6months (95%CI 1.6-9.5) for ALK TKI-resistant patients. **Conclusions:** TQ-B3139 was well tolerated in Chinese NSCLC patients with high antitumor activity. RP2D was established at 600mg bid. A randomized phase III trial of TQ-B3139 versus Crizotinib in advanced ALK-TKI naïve NSCLC patients is underway. Clinical trial information: NCT03099330. Research Sponsor: CHIA TAI TIANQING PHARMACEUTICAL GROUP CO., LTD.

9586 Poster Session (Board #352), Fri, 8:00 AM-11:00 AM

High-dose osimertinib for CNS progression in EGFR+ non-small cell lung cancer (NSCLC): A multi-institutional experience. *First Author: Andrew Piper-Vallillo, Beth Israel Deaconess Medical Center, Boston, MA*

Background: High-dose osimertinib 160 mg QD (osi160) has activity in osi-naïve, EGFR+ NSCLC pts with CNS or leptomeningeal disease (LMD) per the BLOOM trial, but the role of dose-escalation for CNS progression (PD) and/or LMD that develops while on 80 mg QD (osi80) is unclear. We describe here our multi-institutional experience with osi160. **Methods:** 105 pts from 8 institutions with advanced EGFR+ NSCLC treated with osi160 were retrospectively reviewed. To assess the CNS efficacy of dose escalation for CNS PD, we focused on pts who escalated from osi80 to osi160 for CNS PD without the addition of chemo and/or RT during dose escalation (cohort A, 24 pts). We also examined osi escalation for CNS PD while receiving chemo and/or RT (cohort B, 34 pts) and those who started on osi160 for CNS PD as the initial osi dose without overlapping therapies (cohort C, 11 pts). Radiographic responses were clinically assessed via chart review of scan reports. Kaplan-Meier analysis was used for time-to-event endpoints. We defined median duration of CNS disease control (MedDurCNSCon) on osi160 as time from the start of osi160 to CNS PD or discontinuation of osi160. **Results:** Among the 105 pts, 69 (26M, 43F; median age 57) EGFR+ NSCLC pts (29 del19, 31 L858R, 9 other) received osi160 for CNS PD between 10/2013 and 1/2020. Median lines of therapy pre-osi was 1 (range 0-8). While all 69 pts had CNS PD at the start of osi160, 61 (90%) had isolated CNS/LMD PD, without systemic PD. In cohort A, osi160 monotherapy had a MedDurCNSCon of 3.8 mos (95% CI, 1.7 – 5.8). Cohort A pts with isolated LMD (11) had MedDurCNSCon 5.8 mos (95% CI, 1.7 – 9) while those with parenchymal mets only (11) had MedDurCNSCon of 2 mos (95% CI, 1 - 4.9). In cohort B, osi160 in combination with RT (22) and/or chemo (14), had a MedDurCNSCon of 5.1 mos (95% CI, 3.1 – 6.5). In cohort C, osi160 monotherapy had a MedDurCNSCon of 4.2 mos (95% CI, 1.6 – NA). Pts on osi160 had no severe or life-threatening side effects. **Conclusions:** In this real-world cohort of EGFR+ NSCLC pts with CNS and/or LMD PD on osi80, dose escalation to 160 provided modest benefit with median 3.8 mos added CNS disease control. Dose escalation appeared more effective in pts with LMD versus parenchymal disease (MedDurCNSCon of 5.8 vs 2 mos). Treatment intensification with osi escalation plus RT and/or chemo appeared to confer about 1 month additional CNS disease control (power for comparison limited). Osi naïve pts started at 160 for CNS PD derived similar benefit. While limited by small numbers and retrospective design, this study suggests we need improved strategies to optimally manage CNS PD arising on osi80. Research Sponsor: None.

9587 Poster Session (Board #353), Fri, 8:00 AM-11:00 AM

IMpower150: Exploratory analysis of brain metastases development. *First Author: Federico Cappuzzo, Azienda Unità Sanitaria Locale della Romagna, Ravenna, Italy*

Background: In the global phase III IMpower150 study (NCT02366143), atezolizumab (atezo) + bevacizumab (bev) + chemo (carboplatin + paclitaxel [CP] (ABCP) showed significant improvements in PFS and OS vs BCP in patients with chemotherapy-naive metastatic NSCLC (Socinski et al. *N Engl J Med* 2018). Because bev has been shown to delay or prevent brain metastases progression in NSCLC (Fu et al. *J Chemother* 2016; Ilhan-Mutlu et al. *Mol Can Ther* 2016), exploratory analyses were conducted to assess the development of brain metastases in patients treated with ABCP, BCP and atezo + CP (ACP) in IMpower150. **Methods:** A total of 1202 patients (intention-to-treat [ITT] population) were randomized 1:1:1 to receive ABCP, ACP or BCP. Doses were given every 3 weeks: atezo 1200 mg, bev 15 mg/kg, carboplatin AUC 6 mg/mL/min and paclitaxel 200 mg/m^2. Co-primary endpoints were investigator-assessed PFS and OS in ITT–wild-type (no *EGFR* or *ALK* alterations) patients. Exploratory analyses included the rate and time to development (TTD) of new brain metastases in the ITT population, regardless of the presence of baseline brain metastases, as well as safety. Brain scans were performed as clinically indicated, and analyses were based on investigator assessments. **Results:** With a minimum follow-up of 32.4 months in the ITT population (data cutoff: September 13, 2019), 100 patients had developed brain metastases, with the highest rate of new brain lesions seen in the ACP (11.9%) vs the ABCP (7.0%) and BCP (6.0%) arms (table). Median TTD was not reached in any arm; a trend toward delayed TTD was seen in the ABCP vs BCP arm (HR, 0.68 [95% CI: 0.39, 1.19]). Among patients with and without brain metastases, 17 (35.4%) and 155 (44.0%) in the ACP arm, 18 (64.3%) and 207 (56.7%) in the ABCP arm and 10 (41.7%) and 183 (49.5%) in the BCP arm had Grade 3-4 treatment-related adverse events, respectively. **Conclusions:** The ACP arm had the highest rate of new brain lesions, whereas the ABCP and BCP arms had similar, lower rates. Taken together with the trend toward delayed development of new brain lesions with ABCP, the data suggest that adding atezo to BCP may not reduce the rate of new brain lesion development but may delay the time to new lesion development. No new safety signals were observed in this exploratory analysis. Clinical trial information: NCT02366143. Research Sponsor: F. Hoffmann-La Roche, Ltd.

	ACP n = 402	ABCP n = 400	BCP n = 400
New Brain Lesions			
Yes, n (%)	48 (11.9)	28 (7.0)	24 (6.0)
No, n (%)	354 (88.1)	372 (93.0)	376 (94.0)
Time to New Brain Lesions			
Median (range), months	NE (0-46.9)	NE (0-45.9)	NE (0-42.3)
HR (95% CI)	1.55 (0.95, 2.55)	0.68 (0.39, 1.19)	NA
***P* value* (log-rank)**	0.08	0.17	NA

NE, not estimable.
**P* value is for descriptive purpose only.

9588 Poster Session (Board #354), Fri, 8:00 AM-11:00 AM

Plasma-derived cfDNA to reveal potential biomarkers of response prediction and monitoring in non-small cell lung cancer (NSCLC) patients on immunotherapy. *First Author: Francesco Vallania, Freenome, South San Francisco, CA*

Background: Immune checkpoint inhibitors have shown promising results in many advanced cancers, but the response rate remains low. Various molecular and cellular biomarkers, such as elevated tumor-infiltrating cytotoxic T cells and Natural Killer (NK) cells at baseline, are associated with response. Blood-based biomarkers to predict or monitor response remain challenging to develop. Here we investigate the potential of cell-free DNA (cfDNA) biomarkers to predict response to the PD-1 immune checkpoint inhibitor nivolumab in patients with refractory metastatic non-small cell lung cancer (NSCLC). **Methods:** Plasma from stage IV NSCLC patients enrolled in ALCINA (NCT02866149) was collected before (baseline, BL, n = 30) and at week 8 (W8, n = 17) of nivolumab therapy. Response was determined using RECIST 1.1 (responders n = 5; non-responders n = 25). Whole-genome sequencing was performed to characterize cfDNA fragments. Tumor fraction (TF) was assessed using ichorCNA. Cellular composition was estimated by deconvolution of cfDNA co-fragmentation patterns, and transcription factor activity was estimated by measuring binding site accessibility across the genome. **Results:** Although estimated TF at baseline did not predict response to nivolumab, NK cell levels estimated by cell-mixture deconvolution were significantly higher in responders at BL ($p < 0.05$). Furthermore, estimated monocyte levels at W8 strongly correlated with overall survival ($r = 0.75$, $p < 0.0005$, HR = 2.71) and were significantly higher in responders ($p < 0.05$). By evaluating changes in transcription factor binding activity, we identified factors with greater accessibility in non-responders at baseline (DEAF1, THAP11) and W8 (DUX4, PDX-1). **Conclusions:** Plasma cfDNA signatures may be useful for response prediction and monitoring in NSCLC patients on immunotherapy. Our results suggest that changes in the immune system, as reflected by cellular composition and transcriptional activity inferred from cfDNA, may provide biological insights beyond TF alone that may benefit biomarker discovery and drug target identification. Research Sponsor: None.

9589 Poster Session (Board #355), Fri, 8:00 AM-11:00 AM

Therapeutic impact of mutation subtypes and concomitant *STK11* mutations in *KRAS*–mutated non-small cell lung cancer (NSCLC): A result of nationwide genomic screening project (LC-SCRUM-Japan). *First Author: Yutaro Tamiya, National Cancer Center Hospital East, Kashiwa, Japan*

Background: *KRAS* mutations are one of the common oncogene drivers in non-small cell lung cancer (NSCLC), and the development of several targeted drugs for *KRAS*-mutated NSCLC is now ongoing. However, the clinical impact of *KRAS* mutation subtypes or concomitant other gene mutations in NSCLC patients (pts) remains unclear. **Methods:** In a nationwide genomic screening project (LC-SCRUM-Japan), we have prospectively analyzed lung cancer pts for genetic alterations and tumor mutation burden (TMB) by next-generation sequencing system, and for PD-L1 expression by immunohistochemistry (22C3 antibody). The therapeutic efficacy and survival of *KRAS*-mutated non-squamous (non-sq) NSCLC pts were evaluated using a clinico-genomic database of the LC-SCRUM-Japan. **Results:** A total of 5166 non-sq NSCLC pts enrolled from 2015 to 2019. *KRAS* mutations were detected in 794 pts (15%; G12C/G12D/G12V/G12A/G13X/others = 232/186/165/66/61/84). Among the 794 pts, TMB and PD-L1 expression were analyzed in 128 and 79, respectively, and 218 received PD-1/PD-L1 inhibitors (IO) after 1st-line chemotherapy. The median age was 66 years (range, 29-89). 142 pts (65%) were male and 172 (78%) were smokers. Concomitant *STK11* mutations were detected in 33 pts (15%) with no difference in the mutation frequency among *KRAS* mutation subtypes. *KRAS* G12C was significantly associated with high TMB (≥ 10 mut/Mb) ($p = 0.03$), and *KRAS* G12C or G12V with high PD-L1 expression (≥ 50%) ($p = 0.02$). In pts who received IO, median progression-free survival (mPFS) was significantly longer in pts with *KRAS* G12C or G12V than in those with other *KRAS* mutations (4.7 vs 2.0 months, hazard ratio (HR) 0.58 [95%CI 0.43-0.78], $p < 0.01$). Among pts with *KRAS* G12C or G12V, mPFS of IO was significantly shorter in pts with concomitant *STK11* mutations than in those without (1.8 vs. 5.7 months, HR 1.97 [95%CI 1.06-3.41], $p = 0.02$). These correlations were not observed in platinum-containing chemotherapy (Plt-CTx). There were also no significant differences in IO and Plt-CTx efficacies between with and without other concomitant mutations, such as *TP53*, *RB1*, *CDKN2A* and *PTEN* mutations. **Conclusions:** Non-sq NSCLC pts with *KRAS* G12C/V were more sensitive to IO therapies than those with other *KRAS* mutations, but *KRAS* G12C/V-positive pts with concomitant *STK11* mutations were less sensitive than those without. These results could be highly informative in the development of novel targeted therapies for *KRAS*-mutated NSCLC. Research Sponsor: Japan Agency for Medical Research and Development.

9590 Poster Session (Board #356), Fri, 8:00 AM-11:00 AM

Large scale clinico-genomic analyses among patients with BRAF-mutated non-small cell lung cancers (NSCLC) identified by nationwide genomic screening project (LC-SCRUM-Japan). *First Author: Tetsuya Sakai, National Cancer Center Hospital East, Kashiwa-Shi Chiba, Japan*

Background: *BRAF* mutations are functionally classified into three groups, comprisingV600-mutant kinase-activating monomers (class I), kinase-activating dimers (class II), kinase-inactivating heterodimers (class III). The difference of clinical outcomes and concomitant genetic alterations among the three classes in non-small cell lung cancers (NSCLC) are unclear. **Methods:** We have prospectively analyzed NSCLC patients (pts) for cancer-related genes by a next-generation sequencing system, Oncomine™ Comprehensive Assay, in a large-scale genome screening project in Japan (LC-SCRUM-Japan). The clinical characteristics and outcomes of pts with *BRAF*-mutated non-squamous (non-sq) NSCLC were comparatively evaluated among the three classes of *BRAF* mutations. **Results:** A total of 5166 non-sq NSCLC pts were enrolled into the LC-SCRUM-Japan from 2015 to 2019. *BRAF* mutations were detected in 176 pts (3%). Among the 176 pts, 153 (87%) were classified into the three classes according to the mutation variants, including 65 (42%) into class I, 52 (34%) into class II and 36 (24%) into class III. The remaining 23 were not classified into any of the three classes. Compared with class I, class II or class III was significantly associated with smoking ($P = 0.02$ and < 0.01, respectively). Concomitant *RAS* mutations were significantly more frequent in class II and class III than in class I ($P < 0.01$ and $= 0.04$, respectively). The frequency of concomitant *STK11* mutations was significantly higher in class III than in others ($P < 0.01$, respectively). There was no significant difference in the frequency of other oncogene and tumor suppressor gene mutations among the three classes. In the 1st-line platinum-containing chemotherapies for advanced or recurrent cases, median progression-free survival (mPFS) of class III pts was shorter than class I or class II pts (4.2, 11.5 and 4.8 months, I vs III; $P < 0.01$, II vs III; $P = 0.06$). In the treatment with 2nd-4th line PD-1/PD-L1 inhibitors, mPFS was not significantly different among the three classes. Overall survival of class III pts was significantly shorter than class I pts (11.9 vs 35.2 months, $P = 0.03$). **Conclusions:** Concomitant gene mutations and clinical features are largely different among the *BRAF* mutation classes. Especially in class III, concomitant *RAS* and *STK11* mutations are more frequent and clinical outcomes were significantly less favorable. These results suggest the need of novel therapeutic strategy based on the mutation class for *BRAF*-mutated lung cancers. Research Sponsor: None.

9591 Poster Session (Board #357), Fri, 8:00 AM-11:00 AM

Real-world (RW) outcomes for advanced non-small cell lung cancer (aNSCLC) patients (pts) with *EGFR* exon 19 deletions (x19del) stratified by deletion size. *First Author: Sai-Hong Ignatius Ou, Chao Family Comprehensive Cancer Center, University of California Irvine, Orange, CA*

Background: *EGFR* x19dels are well-established targetable drivers in NSCLC. Historically x19dels have been treated as a single group, but it's unclear whether responses vary for distinct subtypes. We compared demographic, clinical and genomic characteristics as well as outcomes to EGFR tyrosine kinase inhibitors (TKIs) for aNSCLC pts with x19dels of varying lengths using a RW Clinico-Genomic Database (CGDB). **Methods:** Eligible pts had a diagnosis of aNSCLC, received care within the Flatiron Health network between 1/2011-9/2019, and had comprehensive genomic profiling (CGP) by Foundation Medicine. Clinical characteristics, treatment history and RW progression were obtained via technology-enabled abstraction as previously described (Singal G, JAMA 2019). x19del length was evaluated for association with overall survival (OS) and RW progression-free survival (rwPFS) with Kaplan-Meier analysis and unadjusted/adjusted (practice type, gender, age at TKI start, EGFR TKI type, race) hazard ratios (HR/aHR) from Cox proportional hazards models adjusted for survival bias. **Results:** Among 6,577 aNSCLC pts, *EGFR* x19dels were detected in 336 cases (5%). E746_A750del was the most frequent (214; 64%) and generally 5 amino acid (aa) deletions (x19del-5) were the most common (241; 72%). Other deletions (x19del-other) of 6 (61; 18%), 3 (20; 6%), 4 (11; 3%) or 8 aa (3; 1%) were also observed. Among pts treated with 1st-line EGFR TKI monotherapy after CGP, the x19del-5 ($n = 70$) cohort was more frequently female compared to x19del-other ($n = 27$) (90% vs 59%, $p = 0.001$). No statistically significant differences in the frequency of co-occurring alterations were observed, specifically for genes associated with response to EGFR TKI response such as *CTNNB1* (14% vs 19%) and *PIK3CA* (10% vs 15%). 1st line EGFR TKIs used were similar for x19del-5 vs x19del-other (43% vs 41% osimertinib, 30% vs 37% erlotinib, 24% vs 22% afatinib, 3% vs 0% gefitinib). x19del-5 pts had similar median rwPFS (10.6 vs 10.6 months, HR: 0.73 [0.41-1.28], aHR:0.78 [0.38-1.59]) and median OS (29.2 vs 24.9 months, HR: 0.64 [0.32- 1.29], aHR: 0.75 [0.32-1.75]) compared to x19del-other. **Conclusions:** In a RW CGDB of 336 aNSCLC pts with *EGFR* x19dels**,** 5 aa x19dels were most common (71%) and 29% of cases had 3, 4, 6 or 8 aa x19dels . For pts included in the treatment cohort, no significant differences in rwPFS or OS were observed. These results suggest that x19del length does not significantly impact clinical outcomes to 1st-line EGFR TKIs. Research Sponsor: None.

9592 Poster Session (Board #358), Fri, 8:00 AM-11:00 AM

Genomic testing among patients (pts) with newly diagnosed advanced non-small cell lung cancer (aNSCLC) in the United States: A contemporary clinical practice patterns study. *First Author: Adam Gondos, F. Hoffmann-La Roche Ltd, Pharmaceutical Division, Personalized Healthcare Center of Excellence, Basel, Switzerland*

Background: We describe contemporary clinical patterns of guideline-mandated genomic testing in newly diagnosed US pts with aNSCLC. **Methods:** From the Flatiron Health electronic health record-derived de-identified database, we included pts with newly diagnosed advanced non-squamous cell carcinoma of the lung between 1.1.2018–6.30.2019 who had received first-line (1L) therapy. We defined inadequate testing as no successful test for at least one of four examined genes: *ALK*, *BRAF*, *EGFR*, and *ROS1*. We grouped pts according to testing received into users of next-generation sequencing (NGS) testing, including a subgroup using comprehensive genomic profiling (CGP, exemplified by Foundation Medicine, Inc.), users of non-NGS testing, and no testing. We describe the following aspects of genomic testing before the start of 1L therapy: occurrence of testing, patterns of use of testing technologies, occurrence of inadequate testing, test failures, percentage of pts with potentially missed targeted therapy with US Food and Drug Administration approval (no positive test and <4 successful tests), and recent trends in genomic testing. **Results:** Among 2971 included pts, 690 (23.2%) had no genomic testing before 1L treatment. Among pts who had a test (n=2281), 59.4% (n=1355) received NGS (CGP: 18.8%, n=429), while 40.6% (n=926) received non-NGS tests only. In the CGP user group, 79.7% of pts received no other type of test, compared with 29.8% of pts in the other NGS group. Inadequate testing was recorded in 13.4% of NGS-tested pts (CGP: 4.9%), compared with 52.5% of pts tested by non-NGS only. Test failures contributed to unsuccessful testing in 4.2% of pts tested by NGS (CGP: 1.2%) and in 6.8% of pts who received non-NGS tests. In the NGS group, 10.1% (CGP: 3.0%) of patients potentially missed a targeted therapy option, compared with 40.3% in the non-NGS group. *EGFR* and *ALK* testing were performed in $\geq$95% of pts, regardless of the testing group; however, only 83.6% and 55.7% of pts received tests for *ROS1* and *BRAF*, respectively, in the non-NGS group. In the latter group, for the first 6 months of 2019, 88.4% and 58.2% of pts were tested for *ROS1* and *BRAF* mutations, respectively. **Conclusions:** Not performing any, or performing only inadequate genomic testing in pts with newly diagnosed aNSCLC remains a concern in clinical practice. The use of NGS, particularly CGP, may help to avoid suboptimal testing, minimize test failures, and improve uptake of testing for newly introduced biomarkers, enabling individualized, targeted therapy. Research Sponsor: F. Hoffmann-La Roche Ltd, Basel, Switzerland.

9593 Poster Session (Board #359), Fri, 8:00 AM-11:00 AM

Updated overall survival (OS) and genomic analysis from a single-arm phase II study of dabrafenib (D) + trametinib (T) in patients (pts) with *BRAF* V600E mutant (Mut) metastatic non-small cell lung cancer (NSCLC). *First Author: David Planchard, Institut Gustave Roussy, Thoracic Team, Villejuif, France*

Background: The phase II multicenter, open label study, which evaluated efficacy and safety of D+T in pretreated (cohort B) and treatment (tx)-naive (cohort C) pts with *BRAF* V600E mut metastatic NSCLC. The results of the primary analysis have been reported. Here, we present an updated survival and genomic analysis data for cohorts B and C. **Methods:** Tx-naïve (n=36) and pretreated (n=57) pts received D 150 mg twice daily + T 2 mg daily. Primary objective: ORR, secondary objectives: PFS, DOR, OS, safety, tolerability and PK of D+T. Tumor samples were centrally tested using a NGS cancer targeted panel (Oncomine Dx Target test, ThermoFisher Scientific). KM curves and Cox regression models were used to evaluate potential associations between baseline genomic landscape and pt efficacy endpoints. **Results:** As of June 22, 2019, median (m) follow-up was 16.3 mo in tx-naïve pts and 16.6 mo in pretreated pts. mOS was 17.3 mo (95% CI: 12.3, 40.2; 3 yr OS: 40%) and 18.2 mo (95% CI: 14.3, 28.6; 3 yr OS: 33%) with 14/36 and 11/57 pts alive in tx naïve and pretreated pts respectively. Detailed efficacy results are presented in table. 57/62 tumor samples retrieved from 93 pts were centrally confirmed to have *BRAF V600E* mut; 5 non-confirmed BRAF tumors (3 pts had PR) were positive for *c-MET* T1010I, *KRAS* G12V, *ALK* fusion and 2 *JAK3* S493C with mPFS of 13.8 mo while OS was NE due to limited data points. Eleven pts (18%) had concomitant somatic mutations and/or genetic alterations in addition to *BRAF* V600E mut: 4 had alterations within PI3K pathway4 had concomitant mutations at *IDH1* R132X, and 3 pts had additional mutations at *BRAF* G466V, *KRAS* G13C and a *cMET* exon 14 skipping, respectively. Pts whose tumors had concomitant genetic alterations, particularly in PI3K pathway, showed a trend towards decreased PFS and OS. Safety profile was similar to previous reported results. **Conclusions:** This update of BRF113928 study reported improved and durable OS rates with combination D+T in *BRAF* V600E mut NSCLC pts. Co-occurring genetic alterations might influence clinical outcomes of such pts. Further validation is ongoing to corroborate current genomic findings. Clinical trial information: NCT01336634. Research Sponsor: Novartis Pharmaceuticals Corporation.

	Tx naive N=36	Pretreated N=57
ORR, n (%)[a]	23 (63.9)	39 (68.4)
95% CI	46.2, 79.2	54.8, 80.1
mDOR, mo[a]	10.2	9.8
95% CI	8.3, 15.2	6.9, 18.3
mPFS, mo[a]	10.8	10.2
95% CI	7.0-14.5	6.9-16.7
mOS, mo	17.3	18.2
95% CI	12.3, 40.2	14.3, 28.6
OS rates, % (95% CI)		
12 mo	74 55, 85	66 52, 77
24 mo	49 32, 65	41 28, 53
36 mo	40 24, 56	33 21, 46
48 mo	NA NA	26 15, 38

[a]Investigator assessment

9594 Poster Session (Board #360), Fri, 8:00 AM-11:00 AM

Patient-reported outcomes (PROs) in the randomized, phase III IMpower110 study of atezolizumab (atezo) vs chemotherapy in 1L metastatic NSCLC. *First Author: Filippo de Marinis, Istituto Europeo di Oncologia IRCCS, Milan, Italy*

Background: IMpower110 (NCT02409342) evaluated atezo (anti–PD-L1) monotherapy as 1L treatment in PD-L1–selected patients (pts) with metastatic NSCLC and met its primary endpoint with statistically significant and clinically meaningful OS benefit in TC3 or IC3 wild-type (WT; *EGFR/ALK*-negative) pts. PROs were prespecified endpoints to assess pt perspectives on overall clinical benefit. **Methods:** Pts were randomized 1:1 to receive atezo 1200 mg IV q3w (Arm A) or platinum-based chemo (Arm B; 4 or 6 21-day cycles). Arm B non-squamous pts received cisplatin (cis) 75 mg/m^2 or carboplatin (carbo) AUC 6 + pemetrexed 500 mg/m^2 IV q3w; Arm B squamous pts received cis 75 mg/m^2 + gemcitabine (gem) 1250 mg/m^2 or carbo AUC 5 + gem 1000 mg/m^2 IV q3w. PROs were assessed by the EORTC Quality of Life Questionnaire Core 30 (QLQ-C30) and lung cancer module QLQ-LC13. Time to confirmed deterioration (TTD) in QLQ-LC13 lung cancer symptoms (secondary endpoint) and change from baseline (BL) in global health status (GHS), functioning and lung cancer symptoms (exploratory endpoints) were analyzed in TC3 or IC3-WT pts. Clinically meaningful change was defined as a $\geq$10-point deterioration from BL. **Results:** Completion rates at BL (atezo, n = 107; chemo, n = 98) were high in both arms for the QLC-C30 (90% atezo, 86% chemo) and the QLC-LC13 (89% atezo, 85% chemo), and remained $>$ 80% at most visits. Mean BL scores for GHS, physical functioning, and role functioning were moderate, symptom burden was low, and all were similar in both arms. No differences in TTD were seen between arms for cough (HR, 0.98; 95% CI: 0.48, 2.03), chest pain (HR, 1.02; 95% CI: 0.47, 2.22), dyspnea (HR, 0.96, 95% CI: 0.57, 1.60), and 3-symptom composite score (HR, 0.92; 95% CI: 0.59, 1.44). Mean change in physical function from BL to wk 42 was modestly improved with atezo and greater than or similar to chemo. No clinically meaningful worsening in dyspnea, cough or chest pain was seen with atezo vs chemo. Mean change in cough and chest pain from BL numerically improved immediately after start of treatment and was maintained to wk 48 with atezo. Fatigue and nausea/vomiting scores numerically improved immediately with atezo and were maintained to wk 48. **Conclusions:** QLQ-C30 and QLQ-LC13 completion rates were high at BL and most study visits. TTD of lung cancer-related symptoms was similar in both arms, indicating pts' low BL symptom burden was maintained for a similar duration. Pts receiving atezo vs chemo sustained numerical improvements in physical function and no worsening in lung cancer-related symptoms. Clinical trial information: NCT02409342. Research Sponsor: F. Hoffmann-La Roche, Ltd.

9595 Poster Session (Board #361), Fri, 8:00 AM-11:00 AM

A phase II study of lorlatinib in patients (pts) with ALK-positive (ALK+) lung cancer with brain-only progression. *First Author: Ibiayi Dagogo-Jack, Massachusetts General Hospital, Boston, MA*

Background: Lorlatinib is a 3rd-generation ALK tyrosine kinase inhibitor (TKI) developed to penetrate the central nervous system (CNS) and overcome resistance to 2nd-generation (2nd-gen) ALK TKIs. In a phase II study, lorlatinib demonstrated significant intracranial (IC) activity after failure of 2nd-gen TKIs. As treatment discontinuation for extracranial (EC) progression can confound assessment of durability of IC response, we performed a phase II study (NCT02927340) to selectively evaluate lorlatinib activity in ALK+ pts with CNS-only disease. **Methods:** Between 11/2016 and 1/2019, 22 pts with IC progression on an ALK TKI with no other sites of measurable disease were enrolled at 2 institutions. Pts received lorlatinib at a starting dose of 100 mg QD. The primary endpoint was the IC disease control rate (DCR) at 12 weeks per modified RECIST v1.1. Secondary endpoints were IC objective response rate (ORR), duration of response (DOR), and progression-free survival (PFS). **Results:** Of the 22 pts enrolled, 21 (95%) had progressed on a 2nd-gen ALK TKI and 14 (64%) had previously received CNS radiation (median 21.1 months between radiation and lorlatinib). Median number of prior ALK TKIs was 2 (range 1-4). As of the data cutoff of 12/15/19, median follow-up was 14 months. At 12 weeks, the IC-DCR was 95%, including 8 pts with stable disease. Best IC ORR was 59% with 6 complete and 7 partial responses. Nine (41%) pts relapsed on study, including 3 IC-only, 5 EC-only, and 1 combined relapse. Four pts continued treatment beyond EC-only progression. Although median IC DOR and PFS were not estimable due to few progression events, the IC progression-free rate at 12 months was 81% (95% CI: 53%-94%). Twelve pts have discontinued study treatment due to progression (n = 6), edema (n = 1), pulmonary hypertension (n = 1), or transition to commercial lorlatinib (n = 4). **Conclusions:** Lorlatinib induces durable intracranial responses in pts with CNS-only progression on 2nd-gen ALK TKIs, suggesting that CNS-specific relapses are primarily driven by ALK-dependent mechanisms. Further studies are needed to characterize the molecular basis of sensitivity to lorlatinib in this unique subgroup of pts with ALK+ lung cancer. Clinical trial information: NCT02927340. Research Sponsor: Pfizer.

9596 Poster Session (Board #362), Fri, 8:00 AM-11:00 AM

Clinical characteristics and anti-PD-(L)1 treatment outcomes of KRAS-G12C mutant lung cancer compared to other molecular subtypes of KRAS-mutant lung cancer. *First Author: Kathryn Cecilia Arbour, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: *KRAS* mutations are identified in approximately 30% of NSCLC. There are no FDA approved targeted therapies for patients with KRAS-mutant non-small cell lung cancer (NSCLC) but novel direct inhibitors of KRAS G12C have shown some activity in early phase clinical trials. We hypothesized that patients with *KRAS*-G12C mutations may have distinct clinical characteristics and responses to systemic therapies compared to patients with non-G12C subtypes. **Methods:** We identified patients with KRAS-mutant lung cancers who underwent next-generation sequencing with MSK-IMPACT, between January 2014 and December 2018. Baseline characteristics were compared with the Chi-square and Fisher's exact test for categorical data and Wilcoxon rank-rum test for continuous data. Overall survival was calculated from time of diagnosis of metastatic/recurrent disease to date of death or last follow up, with left truncation to account for time of MSK-IMPACT. Overall survival was compared between groups using the Cox proportional-hazards model. Response evaluations where performed by independent thoracic radiologists according to RECIST 1. and compared between group with the Fisher's exact test. **Results:** We identified 1194 patients with KRAS-mutant NSCLC, 772 with recurrent or metastatic disease. Of patients with advanced disease, 46% (352/772) had mutations in *KRAS*-G12C and 54% harbored non-G12C mutations (15% G12D, 16% G12V, 8% G12A, 4% G13D). Co-mutation patterns were similar with respect to KEAP1 (p=0.9) and STK11 (p=1.0). Patients with non-G12C mutations had a higher proportion of never smokers (10% vs 1.4% p$<$0.001). The median OS from diagnosis was 13 months for G12C and non-G12C patients (p=0.99). 45% (347/772) received 1L or 2L line treatment with PD-(L)1 inhibitor. RECIST measurements were available for 290/347 cases (84%). ORR with anti-PD-(L)1 treatment was 24% vs 28% in G12C vs non-G12C patients (p=0.5). In patients with PD-L1 50% (n=103), ORR was 39% for G12C vs 58% non-G12C patients (p=0.06). **Conclusions:** KRAS G12C mutations are present in 12% of patients with NSCLC and represent a relevant subtype of NSCLC given KRAS G12C inhibitors now in clinical development. Baseline characteristics including co-mutation patterns are similar between patients with G12C and non-G12C, except for smoking history. The efficacy of KRAS G12C direct inhibitors will need to be compared to other available therapies for KRAS mutant NSCLC (chemotherapy and PD-(L)1 inhibitors) to identify most effective therapeutic strategy. Research Sponsor: None.

9597 Poster Session (Board #363), Fri, 8:00 AM-11:00 AM

A phase II study of osimertinib for patients with radiotherapy-naïve CNS metastasis of non-small cell lung cancer harboring EGFR mutations: The OCEAN study (LOGIK 1603/WJOG 9116L). *First Author: Kazushige Wakuda, Division of Thoracic Oncology, Shizuoka Cancer Center, Sunto-Gun, Shizuoka Prefecture, Japan*

Background: Approximately 15%–30% of patients treated with EGFR-TKIs experience central nervous system (CNS) progression. Although radiotherapy is a standard treatment for CNS metastasis, the efficacy of radiotherapy against CNS is poor. The aim of OCEAN study was to assess the efficacy of osimertinib for patients with radiotherapy-naïve CNS metastasis of NSCLC harboring EGFR mutations. **Methods:** OCEAN study was two-cohort phase II trial, 65 patients (T790M cohort; 40 patients and first-line cohort; 25 patients) with radiotherapy-naïve CNS metastasis of EGFR mutation-positive NSCLC was included. Patients were treated with osimertinib 80 mg once daily. The primary endpoint was the response rate of brain metastasis (BMRR) assessed by the PAREXEL criteria. We set a threshold value of 50% and an expected value of 70% based on the overall response rate (ORR) of AURA trial. Based on one-sided alpha = 0.05 and power = 0.8, the sample size of T790M cohort was calculated to be 40. Key secondary endpoints were progression-free survival (PFS), and ORR, BMRR assessed by the RECIST criteria. We are exploratorily assessing the blood concentration of osimertinib at day 22, which considered to represent steady state. In this report, we present the results of T790M cohort. **Results:** Between October 2016 to July 2019, 40 participants were recruited in the T790M cohort. The median age was 66.5 with 30.0% male. Eight patients had symptomatic CNS metastasis and most patient had multiple CNS metastasis (77.5%). BMRR assessed by PAREXEL criteria was 66.7% (95%CI: 54.3 – 79.1%) and BMRR assessed by RECIST was 70.0% (95%CI, 49.9 – 90.1%). Median PFS was 7.1 months (95%CI, 3.4 – 13.6 months) and ORR assessed by RECIST was 40.5% (95%CI, 24.7 – 57.9%). Treatment related pneumonitis was observed in 4 patients (10.0%). There was no grade 3 or higher toxicities that were found in more than 10%. **Conclusions:** This first study assessed the efficacy of osimertinib for patients with radiotherapy-naïve CNS metastasis of EGFR T790M mutation-positive NSCLC. The OCEAN study met primary endpoint. The results of this study suggested that patients with brain metastasis harboring EGFR T790M mutations had better to receive osimertinib prior to brain radiotherapy. Clinical trial information: 071180017. Research Sponsor: AstraZeneca.

9598 Poster Session (Board #364), Fri, 8:00 AM-11:00 AM

Blood serum amyloid A as potential biomarker of pembrolizumab efficacy for patients affected by advanced non-small cell lung cancer (NSCLC) over-expressing PD-L1: Early results of the FoRECATT Study. *First Author: Vincenzo Di Noia, Medical Oncology, Cliniche Humanitas Gavazzeni, Bergamo, Oncological Sciences, Catholic University of the Sacred Heart, Rome, Italy*

Background: Identifying the patients who may benefit the most from immune checkpoints inhibitors remains a great challenge for clinicians. The tumor-derived Serum Amyloid A (SAA) inhibits the immune-response in melanoma patients. Here we present the early results of FoRECATT study investigating on blood SAA as biomarker of response to upfront pembrolizumab in patients with advanced non-small-cell lung cancer (NSCLC). **Methods:** In this prospective study, patients with PD-L1 $\geq$ 50% receiving upfront pembrolizumab (P cohort) and with PD-L1 0-49% treated with chemotherapy (CT cohort), were evaluated for blood SAA and radiological response at baseline and every 9 weeks. Primary endpoint was response rate (RR) according to Response Evaluation Criteria in Solid Tumors 1.1; secondary endpoints were progression-free (PFS) and overall survival (OS). The most accurate SAA cut-off to predict response was established with ROC-analysis in the P cohort. **Results:** In the P Cohort (n = 42), the overall RR was 38%. After a median follow-up of 18.5 months (mo), baseline SAA $\leq$ the ROC-derived cut-off (29.9 mg/L; n = 14/42, 33%) was significantly associated with higher RR (53.6 *versus* 7.1%; OR 15, 95%CI 1.72-130.7, *P*= 0.009), longer PFS (17.4 *versus* 2.1 mo; *P*< 0.0001) and OS (not reached *versus* 7.2 mo; *P*< 0.0001) compared with SAA > 29.9 mg/L. In multivariate analysis, low SAA positively affects PFS (*P*= 0.001) and OS (*P*= 0.048) irrespective of ECOG PS, number of metastatic sites and pleural effusion. SAA monitoring (n = 40) was also significantly associated with survival endpoints: median PFS 17.4 *versus* 2.1 mo and median OS not reached *versus* 7.2 mo when SAA remained low (n = 14) and high (n = 12), respectively. In the CT Cohort (n = 30), RR was not significantly affected by SAA level, while low SAA at baseline (n = 17) was associated with better PFS (HR = 0.42, 95%CI 0.16-1.10, *P*= 0.02) and OS (HR = 0.16, 95% CI 0.04-0.55, *P*= 0.0004). **Conclusions:** Low SAA predicts a higher likelihood of response to upfront pembrolizumab only and good survival outcomes irrespective of treatment in advanced NSCLC patients. Therefore, a simple blood test might be useful to identify patients likely to derive better outcomes from immunotherapy. A further study (FoRECATT-2) is ongoing to confirm the results in a larger validation cohort and to assess the potential effect of SAA on immune response in vitro assays. Research Sponsor: None.

9599 Poster Session (Board #365), Fri, 8:00 AM-11:00 AM

Outcomes in patients with metastatic non-small cell lung cancer (mNSCLC) with brain metastases treated with pembrolizumab-based therapy. *First Author: Lova Sun, UPHS, Philadelphia, PA*

Background: Patients (pts) with mNSCLC with active brain metastases (BM) are often excluded from clinical trials; data on efficacy and safety of immunotherapy in this population are limited. We compared outcomes of pts with mNSCLC with and without BM who received pembrolizumab-based therapy. **Methods:** We conducted a retrospective single-center study of pts with mNSCLC treated with pembrolizumab (P) with or without chemotherapy. Progression-free survival (PFS) and overall survival (OS) were determined by Kaplan-Meier methodology and compared using multivariable Cox regression and log rank testing. **Results:** We identified 587 consecutive pts with mNSCLC who began P-based therapy between 8/2013 and 12/2018: 306 (52%) female, median age 67 years (range 32-98), 437 (74%) adenocarcinoma, and 508 (87%) former/current smokers. 388 (66%) patients received P in first line therapy, and 334 (57%) received single-agent P. 131 pts (22%) had detectable BM at baseline (start of P-based therapy). Pts with BM were younger (median 65 y vs 68 y, p < 0.01) and more likely to have adenocarcinoma (86% vs. 71%, p < 0.01) and baseline steroid use (22% vs 1%, p < 0.01). Presence of BM did not differ by race, sex, line of therapy, treatment regimen, or PD-L1 status. Of the 131 patients with detectable BM on pre-treatment brain MRI, 55 (42%) had stable BM as a result of prior local therapy, while 76 (58%) had active (new or growing) BM on pre-treatment imaging. Most patients with active BM underwent radiation therapy (RT) in either the 30 days before (n = 46) or 30 days after (n = 17) P start; of the remaining 13 treated with P-based therapy alone, intracranial responses included 2 CR, 2 PR, 3 SD, and 4 PD. As of 1/1/2020, with 15-month median follow up, there was no difference in mPFS (9.2 vs 7.3 months, p = 0.41) or mOS (18.3 vs 18.0 mo, p = 0.67) between pts with and without BM in our P-treated cohort. On multivariable analysis, female sex, ECOG 0-1, adenocarcinoma histology, and P as first line therapy were associated with improved PFS and OS. Presence of BM, baseline steroid use, and timing of local RT (before vs. after P) were not associated with inferior survival. **Conclusions:** In our single-center experience of pts with mNSCLC treated with P, pts with and without BM had similar PFS and OS. We observed several intracranial responses to P-based therapy alone, but most pts with active BM underwent local RT. mNSCLC pts with BM should be considered for P-based therapy; BM may be treated with RT immediately before or even after P with similar survival outcomes. Research Sponsor: None.

9600 Poster Session (Board #366), Fri, 8:00 AM-11:00 AM

Physiologic colonic uptake of ^{18}F-FDG on PET/CT predicts immunotherapy response and gut microbiome diversity in patients with advanced non-small cell lung cancer (NSCLC). *First Author: Lena Cvetkovic, Centre de recherche du Centre hospitalier de l'Université de Montréal (CRCHUM), Montréal, QC, Canada*

Background: Immune checkpoint inhibitors (ICI) represent the backbone treatment of advanced non-small cell lung cancer (aNSCLC) patients. Emerging evidence suggests increased gut microbiome (GM) diversity is associated with favorable response. Conversely, antibiotic-induced dysbiosis may be associated with deleterious outcomes in patients receiving ICI in multiple retrospective studies and one prospective study. ^{18}F-FDG physiologic colonic uptake on PET/CT increases following treatment with antibiotics and could be a surrogate marker for GM diversity and therefore clinical response. The aim of this study was to determine if ^{18}F-FDG physiologic colonic uptake prior to ICI initiation correlates with outcomes and GM metagenomics in patients with advanced NSCLC. **Methods:** 71 patients with aNSCLC who underwent PET/CT prior to ICI were identified. For each patient, the colon was manually contoured, SUVmax was measured in each segment of the colon by a nuclear medicine specialist and average SUVmax was calculated for the whole colon. Patients were stratified in two groups according to median colon SUVmax (low vs high uptake). ^{18}F-FDG physiologic colonic uptake was then compared to overall survival (OS), objective response (ORR), and progression-free survival (PFS). For patients with available stool samples (n = 10), GM composition was defined using metagenomics sequencing. **Results:** 71 patients (54% men, median age: 68 years) with aNSCLC were included in the study and ICI was the first line of therapy in 38% of those patients. The mean colon SUV for the low and high uptake groups were 1.41 (CI 95% 1.35-1.47) and 2.18 (CI 95% 1.90-2.46) respectively. The high uptake group had a higher proportion of non-responders (p = 0.033) and significant shorter PFS (4.1 months vs 11.3 months, p = 0.005). In the caecum, high uptake also correlated with numerically shorter OS (10.82 vs 27.56 months, p = 0.058) compared to low uptake group. Despite the low number of samples, metagenomics sequencing revealed that PLS-DA (Partial Least Squares Discriminant Analysis) for diversity was lower in the high SUV group (p = 0.008). **Conclusions:** Higher colon SUVmax on pre-ICI FDG PET/CT is associated with worse clinical outcomes and lower baseline GM diversity in patients with advanced NSCLC. Here, we propose that ^{18}F-FDG physiologic colonic uptake on PET/CT could serve as a surrogate marker of GM diversity and predicts clinical outcomes. Research Sponsor: None.

9601 Poster Session (Board #367), Fri, 8:00 AM-11:00 AM

ctDNA resistance landscape of lazertinib, a third-generation EGFR tyrosine kinase inhibitor (TKI). *First Author: Ji-Youn Han, Center for Lung Cancer, Research Institute and Hospital, National Cancer Center, Goyang, South Korea*

Background: While *EGFR* mutant (*EGFRm*) non-small cell lung cancer (NSCLC) patients usually experience improved clinical benefit with EGFR TKIs, most eventually progress. Understanding mechanisms of resistance (MoR) may allow for more personalized treatment. Lazertinib is an irreversible third generation EGFR TKI for which MoR are unknown. Obtaining sufficient tumor tissue for genotyping at progression is often difficult. Therefore, we utilized plasma ctDNA from patients treated with lazertinib to explore MoR. **Methods:** Plasma samples from 47 NSCLC patients in the phase 2 trial of lazertinib (NCT03046992) were collected at screening and progressive disease (PD) and underwent ctDNA NGS of 74 genes using Guarant360. All patients were positive for an *EGFR* Ex19del or L858R (*EGFRm*) and T790M by tissue testing at screening. Acquired, nonsynonymous, characterized mutations detected in a PD sample but not in the screening sample from the respective patient were considered putative MoR, excluding aneuploidy. Patients with detectable plasma *EGFRm* and/or T790M at screening were evaluable. **Results:** ctDNA was detected in 47 (100%) screening samples and 43/45 (96%) PD samples (two failed sequencing). An *EGFRm* was detected in 85% of patients at screening (n = 40), 38 of which had PD ctDNA results and were included in analysis. T790M was detected in 30 patients at screening and subsequently not detected at PD in 21 of these patients, 55% of all 38 included patients. Among the ten patients with T790M detected at PD, on-target MoR were detected in 7 (18% of all included patients) including *EGFR* C797S (n = 3, 8%), *EGFR* amplification (n = 3, 8%), and *EGFR* T854A (n = 1, 3%). All C797S were in cis with T790M. No on-target MoR were detected in patients without T790M detected at PD. Off-target MoR were seen in 34% of patients (13/38) including mutations in *PIK3CA* (13%; 2 E545K, 2 E542K, 1 E81K), *ERBB2* (5%; 1 D769H, 1 V777L), *KRAS* (3%; 1 G12C), and *BRAF* (3%; 1 G469A). Gene amplifications were detected in *CCND1* (n = 1, 3%), *CCNE1* (n = 2, 5%), *ERBB2* (n = 1, 3%), *FGFR1* (n = 1, 3%), *MET* (n = 4, 11%), and *PIK3CA* (n = 1, 3%), with some patients having multiple MoR. **Conclusions:** The spectrum of MoR identified in this cohort of patients treated with lazertinib is similar to that reported in other third generation EGFR TKIs, but with some differences in frequencies. The most common resistance mechanisms are T790M loss and *PIK3CA* alterations which may address the mechanism of action. Our findings suggest putative MoR of lazertinib and show that ctDNA NGS is an effective way to identify MoR in patients progressing on targeted therapy. Clinical trial information: NCT03046992. Research Sponsor: Yuhan Corporation, Other Government Agency.

9602 Poster Session (Board #368), Fri, 8:00 AM-11:00 AM

Efficacy and safety of alflutinib (AST2818) in patients with T790M mutation-positive NSCLC: A phase IIb multicenter single-arm study. *First Author: Yuankai Shi, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing Key Laboratory of Clinical Study on Anticancer Molecular Targeted Drugs, Beijing, China*

Background: Alflutinib (AST2818) is a third generation EGFR-TKI. This phase IIb, multicenter, single arm study (ALSC003, NCT03452592) aimed to assess the efficacyand safety of Alflutinib in patients with EGFR T790M mutated non-small cell lung cancer (NSCLC). **Methods:** Patients with locally advanced or metastatic EGFR T790M mutated NSCLC who progressed after first/second-generation EGFR-TKIs therapy or primary EGFR T790M mutation positive received 80 mg Alflutinib orally once daily. Tumor tissue samples underwent central laboratory testing for EGFR T790M mutation. The primary endpoint was objective response rate (ORR). Secondary endpoints included disease control rate (DCR), duration of response (DoR), progression-free survival (PFS), overall survival (OS) and safety. Efficacy was assessed by independent radiological review committee per RECIST 1.1. Safety was assessed by NCI CTCAE version 4.03. **Results:** From Jun 4, 2018 to Dec 8, 2018, 220 patients were enrolled with a median age of 61.0 (range 29 to 80) years. According to the AJCC version 8 staging system, 212 (96.4%) cases were in stage IV, and 8 (3.6%) cases in stage III. All patients had EGFR T790M mutation. By April 12, 2019, the ORR was 73.6% (95% CI 67.3–79.3). The DCR estimated at 6 and 12 weeks were 87.3% (95%CI 82.1-91.4) and 82.3% (95%CI 76.6-87.1), respectively. The median PFS was 7.6 months (95% CI 7.0–NA). Median OS and DoR have not been reached. 209 (95.0%) patients had at least one adverse events (AEs), which were mostly grade 1 or 2 and well tolerable. The most common AEs were increased aspartate aminotransferase (33 [15.0%]), upper respiratory tract infection (33 [15.0%]), and cough (33 [15.0%]). Grade 3 to 5 AEs occurred in 42 (19.1%) patients. The most common one was elevated γ-glutamyltransferase (n = 4). There were 3 deaths patients, 2 of which possibly not be related to the study drug, and 1 could not be determined. No interstitial pneumonia was reported. **Conclusions:** Alflutinib has promising efficacy and acceptable safety profile for the treatment of EGFR T790M mutated NSCLC patients. Clinical trial information: NCT 03452592. Research Sponsor: Shanghai Allist Pharmaceuticals co. ltd., China National Major Project for New Drug Innovation (2017ZX09304015, 2018ZX09301014009 and 2019ZX09201-002) and CAMS Innovation Fund for Medical Sciences (CIFMS) (2016-I2M-1-001).

9603 Poster Session (Board #369), Fri, 8:00 AM-11:00 AM

Longitudinal monitoring by next generation sequencing of plasma cell-free DNA in ALK-rearranged non-small cell lung cancer (NSCLC) patients treated with ALK tyrosine kinase inhibitors. *First Author: Minsuk Kwon, Division of Hematology-Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea*

Background: Patients with anaplastic lymphoma kinase-rearranged (ALK+) NSCLC inevitably acquire resistance to ALK inhibitors. We hypothesized that longitudinal monitoring of cell-free plasma DNA (cfDNA) next generation sequencing (NGS) could predict the response and resistance of TKI therapy in ALK+NSCLC **Methods:** Patients with ALK+ advanced NSCLC determined by standard tissue testing and planned for TKI therapy were prospectively recruited. Plasma was collected before therapy (n = 92), two months post-therapy (n = 58), and at progression (n = 35). Plasma DNA NGS analysis was done retrospectively by Guardant360. **Results:** From April 2015 to July 2019, 92 patients enrolled; 81 (88.0%) received *ALK* TKI as first-line (crizotinib, n = 59; alectinib, n = 22), 10 (10.9%) received TKI as second-line (alectinib, n = 6; crizotinib, n = 2; ceritinib, n = 1; brigatinib, n = 1), and 1 (1.1%) was treated in third-line (lorlatinib). At the cut-off date of January 28, 2020, 56 of 92 patients had disease progression. Circulating tumor DNA (ctDNA) was detected in 69 baseline samples (75%); among these were 43 *ALK* fusions (62.3%) and 1 *ALK* G1202R without fusion (1.4%). Fusions included *EML4-ALK* v1 (n = 19), *EML4-ALK* v3 (n = 14), *CLTC-ALK* (n = 1), *TPM3-ALK* (n = 1), *GCC2-ALK/CLIP4-ALK* (n = 1), and other *EML4-ALK* fusions (n = 7). Eight patients developed *ALK* resistance mutations after crizotinib therapy: L1196M (n = 5), G1269A (n = 1), G1202R (n = 1), and co-occurring F1174L, G1202R, and G1269A (n = 1). Two patients developed *ALK* resistance mutations after ceritinib: G1202R (n = 1), and co-occurring G1202R and T1151R (n = 1). The absence of detectable ctDNA at baseline was associated with longer progression-free survival (PFS; median 36.1 vs 11.6 months, HR 0.432, p = 0.004) and overall survival (OS; median not reached vs 27.9 months, HR 0.418, p = 0.034). Patients with clearance of ctDNA at two months (n = 29) had significantly longer PFS (median 25.4 vs 13.9 months, HR 0.343, p = 0.030) and OS (median not reached vs 25.7 months, HR 0.173, p = 0.035) than those without clearance (n = 22). Patients with co-occurring *TP53* alterations and *ALK* fusions at baseline (n = 9) showed shorter PFS (median 7.0 vs 12.5 months, HR 3.596, p = 0.0154) than those without *TP53* alterations (n = 35). **Conclusions:** NGS of cell-free plasma DNA is useful not only for the detection of *ALK* fusions and resistance mutations but also for assessing prognosis and monitoring the dynamic changes of genomic alterations in *ALK*+ NSCLC treated with ALK TKI. Research Sponsor: Bio & Medical Technology Development Program of the National Research Foundation (NRF) funded by the Korean government (MSIT) (No.NRF-2017M3A9G5060259)Bio & Medical Technology Development Program of the National Research Foundation (NRF) funded by the Kor.

9604 Poster Session (Board #370), Fri, 8:00 AM-11:00 AM

Nintedanib + docetaxel in lung adenocarcinoma patients (pts) following treatment with immune checkpoint inhibitors (ICIs): Updated efficacy and safety results of the ongoing non-interventional study (NIS) VARGADO (NCT02392455). *First Author: Christian Grohé, Department of Pneumology, ELK Berlin, Berlin, Germany*

Background: Nintedanib (Vargatef) is an oral triple angiokinase inhibitor targeting VEGF-, PDGF- and FGF receptor pathways. It is approved in the EU and other countries in combination with docetaxel for treatment of locally advanced, metastatic or locally recurrent NSCLC of adenocarcinoma histology after 1st line chemotherapy. ICI +/- chemotherapy has changed the standard of care for 1st line treatment of metastatic non-mutated NSCLC. However, currently, only limited clinical data are available to help guide treatment decisions after prior ICI therapy in subsequent lines. **Methods:** This updated analysis is part of the ongoing NIS VARGADO (cohort B), a prospective non-interventional study of nintedanib + docetaxel after 1st line chemotherapy for adenocarcinoma NSCLC. The analysis includes 57 pts who had previously received both chemotherapy and ICI treatment. **Results:** Median age was 61 years (range: 45 – 80), 32/57 pts (56.1%) were men, and 41/57 pts (71.9%) were ECOG PS 0/1. 12/57 pts (21.1%) had brain metastases, and 46/57 pts (80.7 %) were current or former smokers. 1st line chemotherapy treatments included pemetrexed (36/57 pts, 63.2%), cisplatin (29/57 pts, 50.9%), carboplatin (33/57 pts, 57.9%), bevacizumab (14/57 pts, 24.6%), vinorelbine (13/57 pts, 22.8%), paclitaxel (8/57 pts, 14.0%), and docetaxel (1/57 pts, 1.8%). 2nd line treatments included nivolumab (34/57 pts, 59.7%), pembrolizumab (14/57 pts, 24.6%), and atezolizumab (7/57 pts, 12.3%). Under nintedanib and docetaxel, ORR was 50% (20/40 pts); DCR was 85.0% (34/40 pts). Median PFS was 6.5 months (95%CI 4.8 – 8.7), median OS was 12.4 months (95%CI 11.4 – 14.1). Treatment emergent adverse events (TEAEs) grade ≥3, serious TEAEs, and TEAEs leading to discontinuation were observed in 30/57 pts (52.6%), 30/57 pts (52.6%), and 17/57 pts (29.8%), respectively. **Conclusions:** This updated analysis of the VARGADO study continues to show the clinical benefit and manageable safety profile of nintedanib plus docetaxel in patients who had previously received both chemotherapy and ICI treatment. These data add to the real-world evidence that can inform clinical decision-making after prior ICI therapy. Clinical trial information: NCT02392455. Research Sponsor: Boehringer Ingelheim Pharma GmbH & Co. KG.

9605 Poster Session (Board #371), Fri, 8:00 AM-11:00 AM

Establishment of the first international large-scale, genomic screening platform to identify patients with rare oncogene drivers in non-small cell lung cancer (NSCLC) in East Asia. *First Author: Shingo Matsumoto, National Cancer Center Hospital East, Kashiwa, Japan*

Background: A rapidly increasing number of oncogenic drivers have been identified in non-small cell lung cancer (NSCLC), and most of them occur in less than 5% of patients. Large-scale genomic screening to identify patients with rare driver alterations is thus necessary to enable precision medicine and to support the development of novel targeted therapies and companion diagnostics (CDx). **Methods:** A lung cancer genomic screening project (LC-SCRUM-Asia) capturing clinical outcome was established in 2013 with 206 institutions in Japan and 5 in Taiwan currently participating. A separate genomic screening project with similar structure was established in China (LC-IRICA-China) in collaboration with LC-SCRUM-Asia in 2019 (3 institutions enrolling, 17 about to open, 63 undergoing review). Samples are analyzed by a multi-gene PCR panel and targeted next-generation sequencing. The target is to enroll 70000 NSCLC patients (20000 from LC-SCRUM-Asia and 50000 from LC-IRICA-China) by 2022. **Results:** From March 2013, a total of 9383 lung cancer patients were enrolled in LC-SCRUM-Asia, and from October 2019, 1649 pts were included in LC-IRICA-China (January 2020). The rates of genomic alterations in LC-SCRUM-Asia: *EGFR* (17%) of which ex20ins (2%), *KRAS* (13%) of which G12C (4%), *ALK* fusions (2%), *ROS1* fusions (2%), *RET* fusions (2%), *HER2* ex20ins (3%), *MET* ex14skip (2%), *BRAF* V600E (1%), *NRG1* fusions (0.2%) and *NTRK3* fusions (0.03%). Corresponding rates in the initial 243 pts in LC-IRICA China: *EGFR* (45%) of which ex20ins (2%), *KRAS* (8%), *ALK* (5%), *ROS1* (2%), *RET* (1%), *HER2* (2%), *MET* ex14skip (1%), *BRAF*V600E (1%). Through the screening, 266 patients from Japan and Taiwan were enrolled into genotype-matched clinical trials of unapproved targeted drugs. In Japan, ROS1-, BRAF- and TRK-targeted therapies were successfully approved based on these clinical trials, and a NGS-based multigene CDx for EGFR/ALK/ROS1/BRAF targeted-therapies was approved based a concordance study using archival samples from the project. **Conclusions:** An East Asian international genomic screening platform has been established to enable precision medicine for patients, accelerate drug and diagnostic development in patients with very rare alterations and to help provide a deeper understanding of the underlying biology of NSCLC in East Asian patients. The screening network will be further expanded to other countries in East Asia in the near future. Research Sponsor: Japan Agency for Medical Research and Development (AMED), Pharmaceutical/Biotech Company.

9606 Poster Session (Board #372), Fri, 8:00 AM-11:00 AM

Outcomes in patients with advanced non-small cell lung cancer (aNSCLC) and high PD-L1 expression treated with immune checkpoint inhibitor monotherapy: An FDA-pooled analysis. *First Author: Sujay Yogesh Shah, Food & Drug Administration, Silver Spring, MD*

Background: Higher PD-L1 score ≥ 50% predicts for greater benefit to immune checkpoint inhibitor (ICI) therapy in first line (1L) treatment of aNSCLC. It has recently been reported that PD-L1 score ≥ 90% predicts for even greater benefit to 1L ICI monotherapy (Aguilar et al., 2019). We examined pooled clinical trial databases to examine the relationship between high PD-L1 expression across multiple ICI monotherapies in 1L and second line (2L) treatment of aNSCLC. **Methods:** Data was pooled from trials (five 1L and five 2L) of ICI for the treatment of patients with aNSCLC. We defined PD-L1 score as the proportion of tumor cell stained by the assay (total of four assays identified) and included patients in the analysis with PD-L1 score ≥ 50%. Tumor-infiltrating immune cell staining was not considered. Progression-free survival (PFS) and overall survival (OS) by line of therapy for patients with PD-L1 score ≥ 90% and patients with PD-L1 score 50-89% was analyzed. **Results:** A total of 1320 patients treated with ICI monotherapy were identified, 873 in 1L and 447 in 2L. Median follow-up was 9.6 months in 2L patients and 13.3 months in 1L patients. Patients receiving 2L ICI therapy with PD-L1 score ≥ 90% (N = 208) had longer PFS and OS compared to patients with PD-L1 score 50-89% (N = 239), with mPFS 7.1 vs. 4.2 months (HR = 0.66 [95% CI: 0.52-0.83]) and mOS NR vs. 15.8 months (HR = 0.66 [95% CI: 0.49-0.89]). 1L ICI therapy analysis revealed similar trends, as patients with PD-L1 score ≥ 90% (N = 405) had longer PFS and OS compared to patients with a PD-L1 score 50-89% (N = 468), with mPFS 8.3 vs. 5.4 months (HR = 0.78 [95% CI: 0.66-0.92]) and mOS 22.9 vs. 16.4 months (HR = 0.74 [95% CI: 0.61-0.90]). **Conclusions:** This analysis showed the potential of an enhanced clinical benefit in patients with aNSCLC and PD-L1 score ≥90% across ICI monotherapies in both the 1L and 2L treatment setting. These data will be further analyzed in real world populations. Research Sponsor: Food & Drug Administration.

9607 Poster Session (Board #373), Fri, 8:00 AM-11:00 AM

Phase II study of TAK228 in patients with advanced non-small cell lung cancer (NSCLC) harboring NFE2L2 and KEAP1 mutations. *First Author: Paul K. Paik, Thoracic Oncology Service, Memorial Sloan-Kettering Cancer Center, New York, NY*

Background: Despite past efforts, no targeted therapies exist for squamous cell lung cancer (LUSC) pts. We identified a heretofore untargeted oncogene (NFE2L2)/tumor suppressor (KEAP1) pair, each mutated in ~15% of LUSCs. NFE2L2 encodes NRF2, a transcription factor involved in the oxidative stress response and targeted for degradation by KEAP1. *NFE2L2* mutations (mut) occur only in an exon 2 hotspot (Neh2 domain), which is the binding site for KEAP1. Mutations in this region disrupt KEAP1 binding, leading to NRF2 nuclear translocation and increased mTOR signaling via RagD. We report translational studies and results from a phase 2 trial of the oral TORC1/2 inhibitor TAK228 in biomarker-selected pts. **Methods:** Cell line and xenograft experiments were performed using LK-2 LUSC (NFE2L2 E79K mut), A549 ADCL (KRAS G12S + KEAP1 loss), and SK-MES-1 LUSC cells (NFE2L2/KEAP1 WT) treated with TAK-228, everolimus, rapamycin, or deforolimus. Pts with stage IV LUSC harboring NFE2L2 or KEAP1 mut and ADCL harboring KRAS + KEAP1 co-mut were treated on an NCI CTEP phase 2 study of TAK228 3mg po qd (NCT02417701). Primary endpoint: ORR. Secondary endpoint: PFS. The study used a Simon 2-stage design for each cohort with H0 = 5% (N≥1/5 responses), HA = 40% (N≥2/10 responses). **Results:** TAK228 exhibited differential anti-tumor activity over TORC1 rapalogs in LK-2 and A549 cells. TAK228 alone was cytotoxic at sub-[μM] (IC50 68nM) in LK-2 cells; all other rapalogs had IC50s > 10μM. This was associated with marked decrease in TORC1/2 & MAPK signaling (decreased pS6, pAKT, pERK). Anti-tumor response was seen in LK-2 and A549 xenografts treated with TAK228. No anti-tumor/growth inhibitory responses were seen with any other rapalog. N = 21 evaluable pts have been treated (10 *NFE2L2*, 6 *KEAP1*, 5 *KRAS+NFE2L2/KEAP1*). Median age = 70; median prior lines tx = 2, smokers = 100%, median pack yrs = 39. Most common AEs included hyperglycemia (72%), fatigue (32%), diarrhea (32%), decreased appetite (32%). In *NFE2L2* mut LUSC pts, ORR = 20% (2/10 confirmed PR), DCR = 100% with median PFS = 8.9mos (95%CI 7-NR). In *KEAP1* mut LUSC pts, ORR = 17% (1/6 confirmed PR), DCR = 67% with PFS range = 1.8-8.6 mos. In *KRAS + NFE2L2/KEAP1* mut ADCL pts, ORR = 0% and DCR = 0%. **Conclusions:** TAK228 is tolerable with differential activity in *NFE2L2* (primary endpoint met) and *KEAP1* mutant LUSC. A randomized phase 2 trial of TAK228 + docetaxel vs. SoC chemotherapy in advanced LUSC pts with *NFE2L2/KEAP1* mut is in development (LungMAP S1900D) as is an NCI CTEP phase 1/1b trial of TAK228 + CB-839 in advanced NSCLC patients with *NFE2L2/KEAP1* mut (NCI #10327). Clinical trial information: NCT02417701. Research Sponsor: Druckenmiller Center for Lung Cancer Research Grant.

9609 Poster Session (Board #375), Fri, 8:00 AM-11:00 AM

Biomarker utilization in non-small cell lung cancer, are we treating after testing? *First Author: Elias Makhoul, Cedars-Sinai Medical Center, West Hollywood, CA*

Background: Targeted therapy in EGFR and ALK mutated non-small cell lung cancer (NSCLC) has been the standard of care for nearly a decade with subsequent FDA approvals for ROS1 and BRAF V600 mutated NSCLC occurring in 2016 and 2017. However, recent studies have shown suboptimal utilization of genomic profiling results in these patients. In 1 recent study of community oncologists, ~70% of EGFR/ALK+ patients received appropriate targeted therapy, while patients with other gene mutations (including BRAF and ROS1) only received targeted therapy ~30% of the time. Left unanswered was what patients were receiving instead and why. Additionally, it is unknown if this finding is generalizable to the academic setting. We aimed to investigate whether in our patient population, NSCLC patients with actionable mutations received associated FDA approved therapies and if not why. **Methods:** The pathology database was queried for all NSCLC with molecular testing (including qPCR, FISH and NGS) from 2009 to 2019. Patients with sensitizing EGFR, ALK, ROS1 or BRAF mutations that were detected after the first FDA approval for their respective targeted therapies were included for analysis with those lost to follow up subsequently excluded. Basic demographic and clinical variables were collected as well as treatment records. **Results:** 2160 NSCLC patients were evaluated (2160 EGFR, 1417 ALK, 810 ROS1, 589 BRAF). 468 patients were identified with targetable mutations (411 EGFR, 46 ALK, 5 ROS1, 6 BRAF). No patient had more than 1 targetable mutation. Of those patients, 248 were at an advanced stage and had clinical follow up (202 EGFR, 37 ALK, 4 ROS1, 5 BRAF). Of those patients 197/202 (97.5%), 33/37 (89.2%), 3/4 (75%) and 1/5 (20%) received EGFR, ALK, ROS1 or BRAF targeted therapy respectively. Across biomarkers 14/248 patients (5.6%) did not receive subsequent targeted therapy. 10 patients (5 EGFR, 3 ALK, 1 ROS1 and 1 BRAF) passed away before targeted therapy could be initiated. Physician choice and missed findings accounted for the remaining four cases. **Conclusions:** The vast majority of advanced NSCLC patients analyzed in this study received appropriate targeted therapy matched to genomic findings. The main reason (~4% of total cases) that patients did not receive therapy was due to rapidly progressive disease and death before it could be initiated. These findings are at odds with those published from the community setting. This may be due to multiple factors, including clinician education, ease of access to targeted therapies across patient populations and incomplete data in the previous study populations. Research Sponsor: None.

9610 Poster Session (Board #376), Fri, 8:00 AM-11:00 AM

Cabozantinib in combination with atezolizumab in non-small cell lung cancer (NSCLC) patients previously treated with an immune checkpoint inhibitor: Results from cohort 7 of the COSMIC-021 study. *First Author: Joel W. Neal, Stanford Cancer Institute, Stanford, CA*

Background: First-line immunotherapy with/without chemotherapy is standard of care for patients (pts) with advanced NSCLC; however, there is a need for effective treatment options after progression on a prior immune checkpoint inhibitor (ICI). Cabozantinib (C) may augment response to ICI by inhibiting kinases implicated in suppressing immune cell responses and has shown encouraging clinical activity in combination with ICI in other tumor types including RCC and HCC. COSMIC-021, a multicenter phase 1b study, is evaluating the combination of C with atezolizumab (A) in various solid tumors (NCT03170960). We report results from cohort 7 in NSCLC pts after prior ICI therapy. **Methods:** Eligible pts had ECOG performance status (PS) 0-1 and radiographic progression after one prior anti-PD-1/PD-L1 ICI given alone or in combination with chemotherapy for metastatic nonsquamous NSCLC. Up to 2 lines of prior systemic anticancer therapies were permitted. Pts received C 40 mg PO QD and A 1200 mg IV Q3W. CT/MRI scans were performed Q6W for the first year and Q12W thereafter. Primary endpoint is ORR per RECIST 1.1 by investigator. Other endpoints include safety, duration of response (DOR), progression-free survival, and overall survival. **Results:** Thirty pts with advanced NSCLC were enrolled. Median age was 67 yrs (range 41, 81), 43% were male, 57% had ECOG PS 1, and 23% had liver metastases. Median duration of prior ICI therapy was 4.8 months (mo; range 0.8, 29), and 15 (50%) pts were refractory to prior ICI (progressive disease as best response). As of December 20, 2019, the median follow-up was 8.9 mo (range 5, 20) with 9 (30%) pts continuing study treatment. The most common treatment related adverse events (TRAEs) of any grade were diarrhea (53%), fatigue (37%), nausea (23%), decreased appetite (20%), palmar-plantar erythrodysesthesia (20%) and vomiting (20%). Grade 3/4 TRAEs occurred in 14 (47%) pts, and 1 (3.3%) had grade 5 TRAEs of myocarditis and pneumonitis. Confirmed ORR per RECIST 1.1 was 23% (7 of 30 pts; all partial responses including 3 pts refractory to prior ICI). Time to response was 1.4 mo (range 1, 3), and median DOR was 5.6 mo (range 2.6, 6.9). DCR (CR+PR+SD) was 83%. **Conclusions:** The combination of C and A had an acceptable safety profile and showed encouraging clinical activity in pts with advanced NSCLC who had progressed after prior ICI therapy. The response rate was greater than previously observed with C monotherapy. Due to the promising data, enrollment in this cohort has been expanded and is ongoing. Clinical trial information: NCT03170960. Research Sponsor: Exelixis Inc.

9611 Poster Session (Board #377), Fri, 8:00 AM-11:00 AM

Resistance to lorlatinib in *ROS1* fusion-positive non-small cell lung cancer. *First Author: Jessica Jiyeong Lin, Massachusetts General Hospital, Boston, MA*

Background: Lorlatinib is a potent, brain-penetrant ROS1/ALK tyrosine kinase inhibitor (TKI), which has demonstrated efficacy in advanced *ROS1* fusion-positive (ROS1+) non-small cell lung cancer (NSCLC), including in patients (pts) previously treated with crizotinib. Despite initial benefit, however, most pts experience disease progression on lorlatinib. Mechanisms of resistance to lorlatinib in ROS1+ NSCLC are poorly understood. **Methods:** We analyzed repeat tumor biopsies derived from advanced ROS1+ lung cancer pts progressing on lorlatinib. Next-generation sequencing (NGS, n = 17) or whole exome sequencing (n = 1) was performed to detect mutations, indels, and copy number alterations. **Results:** Sixteen pts underwent a total of 18 repeat tumor biopsies after progression on lorlatinib. Fourteen had received prior crizotinib; two received prior crizotinib and entrectinib. Median duration of therapy on lorlatinib was 13.5 months (95% CI, 8.3-18.4). Among the 18 cases analyzed by sequencing, 7 (38.9%) harbored a *ROS1* resistance mutation, including G2032R (4/18, 22.2%), S1986F/L2000V (1/18, 5.6%), L2086F (1/18, 5.6%), and G2032R/S1986F/L2086F (1/18, 5.6%). Of note, ROS1 L2086F was a novel resistance mutation not previously reported in the literature, but analogous to ALK L1256F (a lorlatinib-resistant *ALK* mutation). Structural modeling studies showed that ROS1 L2086F causes steric interference with binding of lorlatinib, as well as crizotinib and entrectinib. In addition to ROS1 kinase domain mutations, NGS analyses also identified *MET* copy number gain in a lorlatinib-resistant case, validated by fluorescence in situ hybridization as high-level focal *MET* amplification (MET/CEP7 copy number ratio 6.3) without a concomitant *ROS1* resistance mutation. Duration of therapy on lorlatinib was significantly shorter in pts with a post-lorlatinib *ROS1* resistance mutation compared to those without (8.3 vs 18.1 months; p = 0.005). **Conclusions:** *ROS1* resistance mutations are observed in over one-third of cases progressing on lorlatinib, including the solvent front mutation G2032R and a novel L2086F mutation. These findings underscore the importance of developing next-generation ROS1 TKIs with activity against *ROS1* mutations, and the need to elucidate ROS1-independent resistance mechanisms. Research Sponsor: U.S. National Institutes of Health, Other Foundation.

9613 Poster Session (Board #379), Fri, 8:00 AM-11:00 AM

Clinical and genomic analysis of non-small cell lung cancer (NSCLC) patients with MET exon14 skipping (METex14) mutations and responses to anti-MET therapy. *First Author: Andrew McKenzie, Sarah Cannon Research Institute, Nashville, TN*

Background: *MET* is a validated oncogene for molecular targeted therapy in non-small-cell lung cancer (NSCLC), and METex14 mutations result in *MET* overexpression. Studies with MET-targeting therapies have demonstrated high objective response rates and prolonged disease control. There are few clinical and genomic analyses of patients with METex14-positive NSCLC in the community setting. We herein characterize key clinical and genomic findings for patients harboring METex14 mutations. **Methods:** Sarah Cannon provides clinical research to partnering medical oncology practices who order broad-based NGS, from both tissue and blood, as a part of standard of care. Genospace, a clinico-genomic software tool, was used for identification of patients for clinical trials and analysis of clinical and genomic data. **Results:** Of 6521 lung cancer patients with NGS results, 66 (1.01%) harbored METex14 mutations (45.5% from blood and 54.5% from in tissue). The mean age at diagnosis was 75.7 and 21.2% developed brain metastases. Of the 66 patients with METex14 mutations, 69.5% are current/former smokers. Nineteen percent of former/current smokers and 7.6% of never smokers had PD-L1 scores of $>50\%$, respectively. The majority of METex14-positive patients either received standard of care (66.7%) or were unable to take (19.7%) 1st-line therapy. Patients who received chemotherapy (Chemo), immunotherapy (IO), and Chemo/IO in the first and second line settings responded to SOC treatment, and patients receiving anti-MET therapy benefited from therapy even after front-line SOC (table). Genomic analysis revealed the most common co-occurring mutations to be *EGFR, MET, NF1, KRAS,* and *BRCA2* (Freq = 8.7%, 8.7%, 8.7%, and 7.6%, respectively). **Conclusions:** Genospace enables real-time patient identification of METex14-positive NSCLC cases and analysis of these cases indicates that anti-MET therapy may be effective at any line of treatment. Genospace's clinico-genomic database was used to analyze treatment history, clinical correlates, and co-occurring mutations that may reveal novel treatment combination strategies or resistance mechanisms. Research Sponsor: Sarah Cannon.

	1st line		2nd Line		3rd Line		4th Line	
	# of patients	median TTF (days)	# of patients	median TTF (days)	# of patients	median TTF (days)	# of patients	median TTF (days)
Chemo	10	49	6	118.5	4	79	0	N/A
Chemo/IO	15	168	0	N/A	0	N/A	0	N/A
Chemo/radiation			8	44	1	50	1	876
IO	N/A							
EGFRi	1	227	3	70	1	78	0	N/A
METi	10	70	12	188	3	363	2	42.5
No tx	8	84	5	83	4	99.5	3	149
WEE1i	13	N/A	39	N/A	53	N/A	60	N/A
	1	47					1	36

9614 Poster Session (Board #380), Fri, 8:00 AM-11:00 AM

Effect of genomic and transcriptional alterations in first-line chemotherapy on subsequent immunotherapy in non-small cell lung cancer (NSCLC) patients. *First Author: Yayi He, Division of Medical Oncology, Department of Medicine, University of Colorado Anschutz Medical Campus, Aurora, CO*

Background: Recent studies have demonstrated that first-line immunotherapy has better therapeutic response than second-line immunotherapy in NSCLC patients. However, the mechanism behind this observation has not been elucidated. The aim of this study is to investigate the mechanism of unfavorable influence that the first-line chemotherapy exerts on subsequent immunotherapy. **Methods:** 29 NSCLC patients without tyrosine kinase inhibitor (TKI)-related driver gene (EGFR, ALK, ROS1, RET, BRAF, C-MET) mutations were enrolled in this study. Paired cancer tissues before and after chemotherapy were collected, and NGS-based WES and mRNA sequencing were performed. Sequencing data were analyzed with R packages and statistics analysis was performed with SPSS 20 software. $P \leq 0.05$ was regarded as statistically significant. **Results:** We found that the total number of SNV/INDEL mutations and the tumor mutational burden (TMB) decreased significantly following chemotherapy. The decrease of mutation burden correlated well with therapeutic response: patients with partial response (PR) exhibited significant decrease while patients with stable disease (SD) or progression of disease (PD) did not. Meanwhile, a sharp decrease in common mutations before and after chemotherapy was observed in PR and PD patients, but not SD patients, suggesting that mutational change reflected the therapeutic response. The change in copy number variations (CNVs) exhibited similar trends and correlation with therapeutic response. Subsequent analysis on mRNA levels revealed a sharp decrease in the expression levels of genes related to antigen processing and presentation as well as other factors relevant to immunotherapy response. Pathway enrichment analysis showed that the genes with decreased expression mainly represented immune-related signaling pathways or biological processes. **Conclusions:** Our study revealed a possible mechanism underlying unsatisfactory multiple-line immunotherapy following chemotherapy, and indicated that first-line chemotherapy may influence the tumor microenvironment to exert unfavorable influence on subsequent immunotherapy. Research Sponsor: Development and Reform ommission of Shenzhen Municipality (grant number XMHT20190104006), the Science and Technology Project of Shenzhen (grant number KQTD20161129103502213).

9615 Poster Session (Board #381), Fri, 8:00 AM-11:00 AM

Lorlatinib for advanced ALK and ROS1+ non-small cell lung cancer (NSCLC): Efficacy and treatment sequences in the IFCT-1803 LORLATU expanded access program (EAP) cohort. *First Author: Simon Baldacci, Thoracic Oncology Department, Lille University Hospital, Lille, France*

Background: Lorlatinib, a third-generation tyrosine kinase inhibitor targeting ALK and ROS1, has been made available in France starting October 2015 through an EAP for advanced, refractory, ALK+ NSCLC after the failure of chemotherapy and TKIs. Besides the landmark, multi-cohort phase II trial that assessed lorlatinib in ALK+ NSCLC, real-life evidence regarding the efficacy and safety, as well as treatment sequences including lorlatinib, is lacking. **Methods:** We report the cohort of consecutive patients with advanced, refractory, ALK or ROS1+ NSCLC enrolled in the French EAP of lorlatinib from October 2015 to October 2019. Data were collected from medical records by French Cooperative Thoracic Intergroup (IFCT) research study assistants on site. Primary endpoint was progression-free survival. **Results:** 200 patients were included: 143 (71.5%) ALK+, 57 (28.5%) ROS1+, 87 (44%) men, 127 (66%) never-smokers, and 167 (85%) stage IV disease. Mean age was 59 years. At the time of initiation of lorlatinib, 146 (74%) patients had Central Nervous System (CNS) disease (78 % for ALK+, 63% for ROS1+), 131 (76%) were PS 0/1. Lorlatinib was delivered as 2nd/3rd/4th/5th+ line in 3%/17%/27%/53%of ALK+ patients and in 30%/30%/16%/24%of ROS1+ patients, respectively. 150 (75%), 185 (93%), 138 (69%), and 80 (40%) patients had received prior chemotherapy, crizotinib, 2nd generation TKIs, and brain radiotherapy, respectively. Median PFS and OS from the initiation of lorlatinib were 11.8 (95% CI 7.3-14.6) months and NR (95% CI 18.6-NR) months, respectively for ALK+ patients and 7.6 (95% CI 6.2-10.2) months and 20.9 (95% CI 10.0-NR) months, respectively for ROS1+ patients. ORR and DCR were 46.2% (95% CI 37.6-54.7) and 86.2% (95% CI 80.2-92.1), respectively for ALK+ patients and 47.1% (95% CI 33.4-60.8) and 88.2% (95% CI 79.4-97.1), respectively for ROS1+ patients. CNS ORR was 41.7% (95% CI 33.3-50.1) and 37.7% (95% CI 24.7-50.8), respectively. With a median follow-up of 15.6 (95% CI 14.0-17.6) months, progression under lorlatinib treatment was observed in 71 (50%) ALK+ patients and 35 (61%) ROS1+ patients, and CNS progression in 24 (34%) and 8 (23%) patients, respectively. The safety profile of lorlatinib was consistent with published data. **Conclusions:** These real-life results confirmed lorlatinib as a major treatment option for patients with advanced refractory ALK or ROS1+ NSCLC. Research Sponsor: IFCT, Pharmaceutical/Biotech Company.

9616 Poster Session (Board #382), Fri, 8:00 AM-11:00 AM

Randomized phase I trial to evaluate *C*oncurrent *or S*equential *I*pilimumab, *N*ivolumab, and stereotactic body *R*adiotherapy in patients with stage IV non-small cell lung cancer (*COSINR Study*). *First Author: Jyoti D. Patel, Lurie Cancer Center, Northwestern University Feinberg School of Medicine, Chicago, IL*

Background: Stereotactic body radiotherapy (SBRT) provides high rates of treated metastasis control, stimulates innate and adaptive immune pathways, and is safe in patients treated with anti-PD1 monotherapy following SBRT. We hypothesize that SBRT may improve outcomes for patients receiving immunotherapy through both direct cytoreduction and increased immunogenicity. Within this context, we conducted a phase 1 trial designed to evaluate the safety of combination immune checkpoint blockade with nivolumab and ipilimumab(N/Ip) plus sequential (Seq) or concurrent (Con) multisite SBRT (mSBRT) in patients with stage IV NSCLC. **Methods:** Treatment naïve patients (EGFR/ALK WT) with advanced NSCLC received SBRT to 1 to 4 metastases. Not all metastases were targeted, and metastases >65 mL were partially irradiated. Brain metastases were allowed on protocol, and those >3mm were treated prior to enrollment. SBRT dose varied by anatomic site and ranged from 45 to 50 Gy in 3 to 5 fractions with predefined dose de-escalation if excess dose-limiting toxicities were observed. Patients on Seq arm received N/Ip between 1-7 days after completion of SBRT. Patients in Con arm received N/Ip prior to completion of SBRT. N/Ip continued until progression, development of toxicity, or up to 2 years. Patients underwent pre- and post-treatment biopsy of one irradiated lesion. **Results:** A total of 35 patients (Seq/Con 19/16) were enrolled and evaluable for toxicity analysis (SBRT and at least 1 cycle N/Ip). Brain metastases were present in 27%. PD-L1 expression: 0% (16), 1-49% (10), >50% (9). Median number of metastases treated with SBRT was 3.2. 6 patients experienced DLT (4 pneumonitis), resulting in dose reduction in central lung Seq cohort of the organs at risk (OAR) by 20%. Median PFS by RECIST (total/Seq/Con) was 5.9 mo, 95% CI: 4.9-13.1/ 6.2 mo, 95% CI: 3.5-12.6/ 5.9 mo, 95% CI: 3.1-18.0. RECIST best response was 11% CR, 57% PR, 6% SD, and 26% PD. Treatment past first progression was allowed, and time to second line therapy (chemotherapy) by arm (Seq/Con) was NR/17.5 months. Median OS has not been reached with median follow up of 15mo. PDL1 status did not impact PFS ($p = 0.64$) nor OS ($p = 0.77$). **Conclusions:** Multisite SBRT and concurrent N/Ip was well tolerated. Responses appear durable as median OS was not reached. Multimodality therapy with mSBRT and dual checkpoint inhibitor therapy resulted in impressive tumor control and clinical benefit with promising efficacy. Clinical trial information: NCT03223155. Research Sponsor: BMS.

9618 Poster Session (Board #384), Fri, 8:00 AM-11:00 AM

FLT3 ligand (CDX-301) and stereotactic radiotherapy for advanced non-small cell lung cancer. *First Author: Nitin Ohri, Albert Einstein College of Medicine and Montefiore Medical Center, Bronx, NY*

Background: In a murine non-small cell lung cancer (NSCLC) model, we demonstrated synergy between localized radiotherapy and the dendritic cell growth factor fms-like tyrosine kinase 3 (FLT3) ligand. We now present results from a phase II study testing this combination in patients with advanced and treatment-refractory NSCLC. **Methods:** Advanced NSCLC patients with multi-focal active disease after at least one line of systemic therapy and ECOG performance status 0-2 received 5 daily subcutaneous injections of CDX-301 (75 μg/kg) concurrent with stereotactic body radiotherapy (SBRT, 30-54 Gy in 1-5 fractions based on target size and location) directed at a single site of disease. Additional "cycles" of SBRT and CDX-301 could be administered at least four months after the initial study treatment, at the discretion of the treating physicians. The primary endpoint was progression-free survival four months after treatment initiation (PFS4), with a hypothesis that the PFS4 rate would exceed 40%. Secondary endpoints included overall survival (OS) duration, responses on PET (PERCIST criteria) and CT (RECIST criteria), and dose-limiting toxicities (grade $\geq$3 adverse events within 30 days). Lesions targeted with SBRT were excluded from response assessments. The intended sample size was 29 subjects. Blood samples were obtained for flow cytometry and other analyses of immune activation. **Results:** Twenty-nine subjects received study therapy between October 2016 and January 2020. Subjects received a median of 3 lines (range: 1-5) of systemic therapy prior to study enrollment, including immune checkpoint inhibitors targeting the PD-1/PD-L1 axis in 26 subjects (90%). At the time of this analysis, the actuarial PFS4 rate is 60%, which exceeds our pre-specified efficacy objective. With a median follow-up duration for living patients of 12 months, the actuarial 12-month OS rate is 55%. Partial response of lesions not targeted with SBRT ("abscopal effect") was observed in 9 subjects (31%) using PET criteria and in 4 subjects (14%) using CT criteria. Seven subjects (24%) received a second course of SBRT and CDX-301 after initial study therapy. No dose-limiting toxicities have been observed. Only six subjects (21%) have received additional chemotherapy or immunotherapy after study treatment. **Conclusions:** The combination of CDX-301 and SBRT is well-tolerated and has activity as systemic therapy for advanced NSCLC. Additional studies to maximize the efficacy of this *in situ* vaccination approach with the addition of an agonist anti-CD40 antibody (CDX-1140) are planned. Clinical trial information: NCT02839265. Research Sponsor: U.S. National Institutes of Health.

9619 Poster Session (Board #385), Fri, 8:00 AM-11:00 AM

Dose escalation and expansion from the phase I study of DS-1062, a trophoblast cell-surface antigen 2 (TROP2) antibody drug conjugate (ADC), in patients (pts) with advanced non-small cell lung cancer (NSCLC). *First Author: Aaron Elliott Lisberg, Department of Medicine, Division of Hematology/Oncology, UCLA, Los Angeles, CA*

Background: TROP2 is an intracellular calcium signaling transducer overexpressed in NSCLC, portending poor survival. DS-1062 is a TROP2-targeting ADC with a novel topoisomerase 1 inhibitor (exatecan derivative, DXd) and promising preclinical antitumor activity. Updated results inclusive of 24 additional dose escalation pts and 32 dose expansion pts from an ongoing phase 1 study of DS-1062 in advanced/metastatic NSCLC are reported (NCT03401385/J101). **Methods:** Pts aged $\geq$18 (US) or $\geq$20 (Japan) with unresectable NSCLC refractory to/relapsed from standard treatment with measurable disease (RECIST v1.1) and available tumor for retrospective TROP2 evaluation were eligible. Primary objectives include maximum tolerated dose (MTD) identification, safety, and tolerability and secondary objectives include efficacy, pharmacokinetics, and incidence of anti-drug antibodies against DS-1062. Pts were eligible regardless of TROP2 level. **Results:** As of November 16, 2019, 95 pts were treated with $\geq$1 dose of DS-1062. 63 pts were treated during escalation at 0.27 (n = 4), 0.5 (n = 5), 1.0 (n = 7), 2.0 (n = 6), 4.0 (n = 6), 6.0 (n = 19), 8.0 (n = 8), and 10.0 (n = 8) mg/kg and 32 pts were treated in expansion at the MTD of DS-1062, 8 mg/kg. 59 pts (62%) discontinued (25 [42%] due to progressive disease per RECIST v1.1). Pts were exposed to a median of 3 treatment cycles (range, 1-19). In 88 response-evaluable pts, 22 had partial response (1 PR/6 pts at 2.0 mg/kg, 2 PR/6 pts at 4.0 mg/kg, 5 PR/18 pts at 6.0 mg/kg, 13 PR/34 pts at 8.0 mg/kg, and 1 PR/8 pts at 10.0 mg/kg; 14 PRs were confirmed and 8 PRs are awaiting confirmation). Treatment emergent adverse events (TEAEs) regardless of causality were reported in 91 of 95 pts (96%; 44 pts [46%] experienced $\geq$grade 3, 30 pts [32%] had serious events). Treatment-related TEAES were reported in 76 of 95 pts (80%; 17 pts [18%] experienced $\geq$grade 3, 8 pts [8%]) had serious events). Potential interstitial lung disease (ILD) occurred in 8 pts (8%; 2 at 6.0 mg/kg and 6 at 8.0 mg/kg); 6/8 with potential ILDs adjudicated as treatment-related (1 at 6.0 mg/kg [grade 2] and 5 at 8.0 mg/kg [1 grade 1, 2 grade 2, 1 grade 3, and 1 grade 5]). 14 escalation pts and 22 expansion pts remain on trial. Updated trial details/results will be presented. **Conclusions:** In this first-in-human study of DS-1062, treatment was well tolerated up to 8 mg/kg, and a dose effect on antitumor activity was observed over 2.0-10.0 mg/kg in heavily pretreated pts with prior progression on standard treatment. Clinical trial information: NCT03401385. Research Sponsor: Daiichi Sankyo.

9620 Poster Session (Board #386), Fri, 8:00 AM-11:00 AM

Genomic characterization and outcome evaluation of kinome fusions in a large non-small cell lung cancer population. *First Author: Fengying Wu, Shanghai Pulmonary Hospital, Shanghai, China*

Background: Lung cancer is the leading cause of cancer death worldwide. Kinase fusion represents an important type of somatic alterations which promote oncogenesis and serve as a diagnostic marker in lung cancer. This study aims to identify the landscape of kinase fusions in lung cancer and expand our understanding of druggable fusions, together providing valuable information for therapeutics decision making. **Methods:** We performed genomic profiling of tumor/plasma biopsies of a total of 18,839 Chinese lung cancer patients using next generation sequencing (NGS) by targeting 425 cancer-relevant genes. Patients' clinical characteristics and treatment history were retrospectively studied. **Results:** A total of 1,048 patients (5.56%, 1,048/18,839) were identified with kinase fusions, including 815 adenocarcinomas (ADCs) and 34 squamous cell carcinomas (SCCs). Briefly, a total of 198 unique gene fusion events have been observed, including 37 recurrent fusions and 114 novel fusions which have previously not been documented. ADC patients with kinase fusions were relatively younger than SCC patients (median: 53 vs 61 years old, $p< 0.01$). The most frequently observed fusion was *EML4-ALK* for both ADCs (50.0%) and SCCs (32.4%), followed by *FGFR3-TACC3* (29.4%) in SCCs and *KIF5B-RET* (11.8%), *CD74-ROS1* (9.2%), *CCDC6-RET* (3.9%) and *SLC34A2-ROS1* (2.3%) in ADCs, retrospectively. A total of 14 recurrent fusions including *FN1-ALK*, *MEMO1-ALK, CUX1-ALK*, *KIF13A-RET* and *PHF20-NTRK1* were also identified at low frequencies. Of note, *EML4-* or *STRN-ALK* fusion events mainly rearranged in the intron 19 of *ALK*, but the breakpoints of *VCL-ALK* were mostly located upstream of *ALK* exon 18. Meanwhile, *CD74-*, *SLC34A2-* and *TPM3- ROS1* rearrangement mainly occurred in the *ROS1* introns 31, 33 and 34. In addition, among patients with novel fusions, *RORB-ALK* and *AFF2-RET* may potentially function as oncogenic drivers in lung cancer and have demonstrated clinical benefit from crizotinib treatment. **Conclusions:** Our data have depicted a comprehensive overview of the landscape of kinase fusions in lung cancer, which helps recognize potentially druggable fusions and translate into therapeutic applications. Research Sponsor: None.

9621 Poster Session (Board #387), Fri, 8:00 AM-11:00 AM

Acquired resistance to PD-1 blockade in NSCLC. *First Author: Adam Jacob Schoenfeld, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Although durability is the trademark characteristic of response to PD-1 blockade, acquired resistance can occur. The frequency, patterns, and survival outcomes of patients with acquired resistance to PD-1 blockade are unknown. **Methods:** All patients with NSCLC treated with PD-1 blockade at MSKCC were examined. Acquired resistance was defined as initial CR/PR (by RECIST) followed by progression/death. Oligo vs systemic patterns of acquired resistance were defined as progression in ≤ 2 sites of disease or ≥ 3 sites of disease, respectively. **Results:** Of 1201 patients treated with PD-1 blockade, 243 (20%) achieved initial response and 189 (78%, 95% CI 72-83%) eventually developed acquired resistance (AR). Onset of AR was variable and decreased with longer duration of response (53% within 1 year, 37% 1-2 years, 10% $>$ 2 years). Patients with PD-L1 expression $<$ 50% and TMB $<$ 8mut/Mb were more likely to develop resistance compared those with PD-L1 expression $\geq$50% and TMB $\geq$8mut/Mb (OR 5.5, p = 0.02). Unlike organ sites of primary refractory disease, AR commonly occurred in lymph nodes (41%) and infrequently in the liver (6%). Patterns of AR were most commonly oligo rather than systemic (79/141 [56%], 39/141 [28%]); some patients died without radiographic progression (23/141 [16%]). Oligo-AR occurred later (median onset 13 vs 5.6 mo) and associated with improved post-progression survival (median OS 55.2 vs 9.2 mo, HR 6.0, p $<$ 0.001) compared to systemic-AR. Post-progression survival was highest in patients with AR compared to those with initial SD or PD to PD-1 blockade (median 18.9 vs 12.5 vs 4.4, p $<$ 0.001). Of 49 patients treated initially with locally-directed therapy for AR, 28 (57%) remain alive and systemic therapy-free. **Conclusions:** Acquired resistance to PD-1 blockade is common in NSCLC. Risk of acquired resistance is lower in biomarker-enriched patients and with increased duration of response. Patterns of acquired resistance is commonly oligo in nature, which is amenable to locally-directed therapy and can be associated with improved survival. Differences in organ-site distribution and post-progression survival suggest distinct biology associated with acquired resistance vs primary refractory disease. Research Sponsor: U.S. National Institutes of Health, Other Foundation.

9622 Poster Session (Board #388), Fri, 8:00 AM-11:00 AM

Progression-free survival estimates in non-small cell lung cancer when RECIST is unavailable: Project GENIE's integration of genomic, therapeutic and phenomic data. *First Author: Jessica A. Lavery, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Molecular tumor profiling has become an integral component of oncology practice but linked genomic-phenomic data remain scarce. Recurrence, treatment response and progression are not structured consistently in medical records and this deficit has been a roadblock to discovery of biomarkers that are associated with favorable outcomes. **Methods:** The Genomics Evidence Neoplasia Information Exchange (GENIE) consortium is an AACR sponsored project to link and share genomic and phenomic data to promote discovery in precision medicine. 3 cancer centers that routinely perform somatic tumor profiling for advanced cancers agreed to curate anti-neoplastic treatment exposures and outcomes including recurrence, progression, response and survival using a standard method. 6 cancer types (lung, colorectal, breast, prostate, pancreas and bladder) were selected and a REDCAP database captures anti-neoplastic treatments, and specific elements from pathology, radiology and oncology reports. Curators abstract data using data fields that rely on the PRISSMM standard. "Real world" progression free survival (PFS) was identified based on curation of: 1) the text of radiologists' reports for CT, PET/CT, PET and MRI scans (PFS_I) and 2) medical oncologists' notes (PFS_M). PFS_I and PFS_M were estimated from the start of 1st line anti-neoplastic systemic therapy until progression or death for all patients with molecularly characterized non-small cell lung cancer (NSCLC). **Results:** Genomic sequencing was performed between 2015 and 2017 for 748 patients with NSCLC treated at three major cancer centers. Median age at diagnosis was 66 years (interquartile range 58, 73) and 43% were male. As shown in the table, when RECIST assessments are unavailable, estimates of PFS vary based on whether they are derived from radiologists' or oncologists' interpretations. **Conclusions:** Radiologists' reports and oncologists' reports provide different PFS estimates. Cohort studies should specify the method used to define "real world" endpoints. Project GENIE will have 1800 NSCLC patients with curated endpoints by the ASCO meeting. Research Sponsor: American Association for Cancer Research.

"Real World" PFS from 1st line treatment for NSCLC: estimates based on radiologists' reports (PFS_I) and oncologists' notes (PFS_M).

Regimen	N	PFS_I (months; 95% CI)	PFS_M (months; 95% CI)
Any therapy	468	7.6 (6.4, 9.2)	10.7 (9.9, 12.4)
Immunotherapy	45	3.7 (1.5, 6.0)	7.0 (4.4, 10.1)
Cytotoxic therapy	370	9.0 (7.4, 10.5)	11.5 (9.9, 14.0)
Targeted therapy	53	7.3 (4.9, 14.1)	11.1 (8.9, 24.4)

9623 Poster Session (Board #389), Fri, 8:00 AM-11:00 AM

SWOG S1400F (NCT03373760): A phase II study of durvalumab plus tremelimumab for previously treated patients with acquired resistance to PD-1 checkpoint inhibitor therapy and stage IV squamous cell lung cancer (Lung-MAP Sub-study). *First Author: Natasha B. Leighl, Princess Margaret Cancer Centre, Toronto, ON, Canada*

Background: The Lung Cancer Master Protocol (Lung-MAP) is designed to evaluate novel targeted therapies in patients with advanced squamous lung carcinoma. In the S1400F sub-study (non-match), we tested whether combined CTLA-4 and PD-1 inhibition with durvalumab plus tremelimumab (D+T) could overcome primary or acquired resistance to anti-PD-(L)1 therapy. Response, progression-free (PFS) and overall survival, and safety in the acquired resistance cohort are reported herein. **Methods:** Patients with previously treated squamous lung carcinoma, performance status (PS) 0-1, and adequate organ function that developed disease progression after $\geq$24 weeks of anti-PD-(L)1 monotherapy were eligible. Prior severe immune-related toxicities, intervening systemic therapy and combination chemo-immunotherapy were not permitted. Patients received D1500 mg + T75 mg IV q28 days for 4 cycles then D maintenance until disease progression. The primary endpoint was best objective response (RECIST 1.1). Interim analysis for futility was planned after 20 patients evaluable for response were enrolled. If no responses were observed, the cohort would stop enrolment. **Results:** 30 eligible patients were accrued to the acquired resistance cohort. Median age was 68 years, 60% of patients were male, 33% PS 0 and had received a median of 2 prior lines of therapy (maximum 4). Best response to prior anti-PD-(L)1 therapy was CR/PR/SD in 3/7/20 patients, with a median duration of anti-PD-(L)1 therapy of 8.6 months (5.2-30.4). No objective responses were seen with D+T; 47% had SD as best response. Median PFS was 2.0 months (95% CI 1.6-2.9) and survival 7.5 months (95% CI 5.3-8.7). Among the 14 patients with SD as best response, the median PFS calculated from first disease assessment is 2.8 months (95% CI: 1.4-3.9). Grade$\geq$3 adverse events at least possibly related to protocol therapy were seen in 10/30 patients. These include 1 treatment-related death due to pneumonitis and 1 death not otherwise specified. Other adverse events include grade 3 confusion (1), dehydration (2), diarrhea (3), encephalopathy (1), weakness (1), hyperglycemia (1), hypoxia (1), lymphopenia (1), nausea, (1), neutropenia (1), thrombocytopenia (1), rash (1), vomiting (1), grade 4 dyspnea (1), leucopenia (1) and lymphopenia (1). **Conclusions:** D+T did not demonstrate activity in patients with acquired resistance to PD-1 checkpoint inhibitors and pretreated advanced squamous lung carcinoma. Clinical trial information: NCT03373760. Research Sponsor: U.S. National Institutes of Health, Lung-MAP trial supported in part by NIH/NCI grants CA180888, CA180819, CA180820, CA180821, CA180863, CA180868, and by AbbVie Inc., Amgen, AstraZeneca, Bristol-Myers Squibb Company, Genentech and Pfizer through the Foundation for the National Institutes of Health, in partnership with Friends of Cancer Research.

9624 Poster Session (Board #390), Fri, 8:00 AM-11:00 AM

BRIGHTSTAR: A pilot trial of local consolidative therapy (LCT) with brigatinib in tyrosine kinase inhibitor (TKI)-naïve ALK-rearranged advanced NSCLC. *First Author: Yasir Elamin, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Approximately, 95% of patients who have an initial response to ALK-TKIs exhibit an incomplete response resulting in residual disease that enables the emergence of acquired resistance. Eliminating residual disease using LCT may delay resistance emergence and improve clinical outcomes. **Methods:** This is a single center investigator-initiated trial that assesses the safety, feasibility and efficacy of brigatinib with LCT. Eligible patients have TKI-naïve ALK rearranged advanced NSCLC with any number of metastases. Patients treated with brigatinib for an induction period of 8 weeks followed by LCT with radiation and/or surgery. **Results:** Between 12/2018 and 01/2020, 17 out of 24 planned patients were enrolled. Median age 55 (range 33-73). At study entry, 15 patients had polymetastatic disease ($>$ 3 sites) while 2 had oligometastatic disease. As of February 1, 2020, 16 patients were evaluated for response and completed LCT while 1 patient remained on induction brigatinib. The disease control rate was 100% with an objective response rate of 94% (n = 15). Median follow up was 8 months (range 3-13) with no patients with disease progression to date. LCT used was radiation (n = 11), surgery (n = 3), surgery and radiation (n = 2). Among 5 patients who had surgery, 4 had lobectomy and mediastinal lymph node dissection (MLND), 1 had wedge resection with MLND, and 1 had adrenalectomy. Of these, 2 had complete pathological response and 1 had complete pathological response at the primary tumor. There were no grade $\geq$2 adverse events (AEs) related to LCT, including in 7 patients treated with concurrent brigatinib and radiation, and 6 patients treated with radiation while brigatinib was held. All patients continued brigatinib after LCT. Brigatinib-related severe AEs included grade 3: increased blood levels of creatine kinase, lipase, alanine aminotransferase, amylase (n = 1 each) and nausea (n = 1). One patient had grade 2 pneumonitis after 2 weeks of starting brigatinib, this resolved with steroids and brigatinib was resumed at a lower dose. **Conclusions:** Brigatinib with LCT is safe and feasible in patients with ALK-rearranged advanced NSCLC irrespective of number of metastatic sites. Brigatinib and LCT may be an effective therapeutic strategy in this subset of NSCLC patients. Clinical trial information: NCT03707938. Research Sponsor: Takeda.

TPS9625 **Poster Session (Board #391), Fri, 8:00 AM-11:00 AM**

Phase III trial comparing antibody-drug conjugate (ADC) SAR408701 with docetaxel in patients with metastatic non-squamous non-small cell lung cancer (NSQ NSCLC) failing chemotherapy and immunotherapy. *First Author: Melissa Lynne Johnson, Sarah Cannon Research Institute, Nashville, TN*

Background: Despite recent advances in the treatment of NSQ NSCLC, including the integration of immune checkpoint inhibitors (ICI) into first-line treatment of all patients, novel therapies are necessary at disease progression. Carcinoembryonic antigen-related cell adhesion molecule 5 (CEACAM5), a cell-surface glycoprotein, is overexpressed in several tumor types, including NSQ NSCLC; ~20% of patients express high CEACAM5 levels. SAR408701 is an ADC combining a humanized antibody targeting CEACAM5 with the potent cytotoxic maytansinoid derivative DM4 and is expected to selectively deliver DM4 to CEACAM5-expressing cancer cells. In an interim analysis of a first-in-human study (NCT02187848) in patients with NSQ NSCLC and CEACAM5 expression in ≥50% of tumor cells, SAR408701 administered 100 mg/m^2 every 2 weeks showed an objective response rate (ORR) of 23% and a favorable safety profile (Gazzah A et al *J Clin Oncol*. 2019;37:15, 9072). **Methods:** In this randomized, open-label, phase 3 trial, patients receive either SAR408701 100 mg/m^2 IV every 2 weeks or the standard of care treatment docetaxel 75 mg/m^2 IV every 3 weeks. Randomization is stratified on ECOG performance status (PS), previous ICI treatment (sequential vs combination), and geographical region. Patients are ≥18 years with metastatic NSQ NSCLC after platinum-based chemotherapy and ICI treatment (anti-PD-1/PD-L1 monoclonal antibody), express CEACAM5 in ≥50% of tumor cells at ≥2+ intensity (central testing), and have ECOG PS 0–1. Exclusion criteria include untreated brain metastases, history of corneal disorders, and prior treatment with docetaxel, maytansinoid derivatives, or CEACAM5-targeting drugs. Tumor imaging occurs at baseline and every 8 weeks until disease progression. Primary endpoints are progression-free survival (PFS; RECIST v1.1 by independent blinded review committee) and overall survival (OS), both analyzed by Kaplan-Meier method, stratified log-rank test, and stratified Cox proportional hazard model. Study success is defined either on PFS or OS, with a strong type-I error control for multiple hypotheses. Secondary endpoints are ORR and duration of response (RECIST v1.1), health related quality of life (EORTC QLQ-C30 and EORTC QLQ-LC13), and safety (adverse events graded by NCI CTCAE v5). Approximately 554 randomized patients (277 per arm) is adequate to reach both PFS and OS events. The study opened in Nov 2019, and as of Feb 7, 2020, 20 sites in 8 countries are activated. Clinical trial information: NCT04154956. Research Sponsor: Sanofi.

TPS9626 **Poster Session (Board #392), Fri, 8:00 AM-11:00 AM**

Randomized phase II study of canakinumab (CAN) or pembrolizumab (PEM) as monotherapy or in combination as neoadjuvant therapy in patients (Pts) with surgically resected (Stage IB-IIIA) non-small cell lung cancer (NSCLC): CANOPY-N. *First Author: Tony S. K. Mok, The Chinese University of Hong Kong, Hong Kong, China*

Background: Complete surgical resection is the standard treatment (tx) for pts with stage I-IIIA NSCLC. 5-year survival rates range from 19-50%, with most pts dying from distant recurrence. Neoadjuvant or adjuvant chemotherapy improves overall survival (OS) by only 5% in pts with NSCLC, and new tx options are needed. Preliminary data with PD-1 or PD-L1 inhibitors as neoadjuvant therapy has shown major pathologic responses (MPR) or pathologic complete responses (pCR) in pts with early stage NSCLC. CANTOS study demonstrated reduced incidence of NSCLC and decreased lung cancer-related mortality with CAN (IL-1β inhibitor) versus placebo, in a dose-dependent manner for pts with atherosclerosis. In pre-clinical NSCLC humanized models, tx with CAN±anti PD-1 inhibitor could lead to anti-tumor activity. Combination of CAN and PEM is expected to enhance the efficacy of PD-1 inhibition by inhibiting dysregulated inflammation in tumor microenvironment. Based on available evidence, CANOPY-N study was designed to evaluate effect of CAN and PEM as monotherapy or in combination as neoadjuvant tx for pts with resectable NSCLC. **Methods:** CANOPY-N (NCT03968419) is a phase II, randomized, open-label study evaluating effect of CAN or PEM monotherapy or in combination as neoadjuvant tx in resectable NSCLC pts. Histologically confirmed stage IB-IIIA, tx-naive, ECOG PS 0-1 NSCLC pts eligible for surgery and with a planned surgical resection in approximately 4-6 weeks (after 1st dose of study tx), are eligible to participate. An archival (if obtained up to 6 months before 1st day of tx) or new biopsy is required. Approximately 110 pts will be randomized in 2:2:1 ratio (stratified by histology [squamous/non-squamous]) to one of the tx arms to receive a total of 2 doses (200 mg Q3w) of CAN alone (n = 44) or in combination with PEM (n = 44) or PEM (n = 22) with safety follow-up up to 130 days from last study drug dose. Primary endpoint is to determine MPR rate (≤10% of residual viable tumor cells at time of surgery), secondary endpoints include determination of ORR, MPR rate based on local review, surgical feasibility rates, anti-drug antibodies incidence and PK parameters. Clinical trial information: NCT03968419. Research Sponsor: Novartis Pharmaceuticals Corporation.

TPS9627 **Poster Session (Board #393), Fri, 8:00 AM-11:00 AM**

A phase II randomized study of telaglenastat, a glutaminase (GLS) inhibitor, versus placebo, in combination with pembrolizumab (Pembro) and chemotherapy as first-line treatment for KEAP1/NRF2-mutated non-squamous metastatic non-small cell lung cancer (mNSCLC). *First Author: Ferdinandos Skoulidis, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Mutational activation of the KEAP1/NRF2 pathway occurs in >20% of NSCLC patients (pts). KEAP1/NRF2 activation protects tumor cells from diverse forms of oxidative stress and promotes tumor growth and survival. In pts w/ advanced NSCLC, mutation of the KEAP1/NRF2 pathway is associated w/ dramatically reduced survival and poor outcomes following standard-of-care therapy. These tumors have increased dependence on GLS-mediated conversion of glutamine to glutamate due to upregulation of NRF2 target genes involved in glutamine metabolism. Telaglenastat (CB-839), an investigational, first-in-class, potent, oral GLS inhibitor, has demonstrated preclinical activity in KEAP1/NRF2-mutated NSCLC cell lines and xenograft models. This study will evaluate the safety and efficacy of telaglenastat + standard-of-care pembro and chemotherapy as 1L therapy for KEAP1/NRF2-mutated non-squamous mNSCLC (NCT04265534). **Methods:** This phase II, randomized, multicenter, double-blind study will enroll ~120 pts with histologically or cytologically documented stage IV non-squamous NSCLC w/ KEAP1 or NRF2 mutation, no prior systemic therapy for mNSCLC, measurable disease (RECIST v1.1), ECOG PS 0-1, and no EGFR, ALK, ROS, or other actionable mutation w/ available approved therapy in 1L setting. KEAP1 or NRF2 mutations will be determined by next generation sequencing (NGS), and study-provided liquid biopsy NGS will be available. Pts will be randomized 1:1 to receive telaglenastat (800 mg BID PO) or placebo, in combination with pembro, carboplatin, and pemetrexed at standard doses on day 1 of each 21-day cycle. Pts will be stratified by STK11/LKB1 mutational status and M stage of cancer (M1a-b vs M1c). The study will include an initial safety run-in period (n=12; 1 cycle). Co-primary endpoints are safety and investigator-assessed progression-free survival (RECIST v1.1). Secondary endpoints include overall response rate, duration of response, overall survival, and efficacy analysis in the subgroup of pts w/ biochemical confirmation of KEAP1/NRF2 pathway activation. Findings of this novel NGS biomarker-selected study will inform the efficacy and safety profile of telaglenastat + standard-of-care chemoimmunotherapy for 1L treatment of KEAP1/NRF2-mutated, non-squamous mNSCLC. Clinical trial information: NCT04265534. Research Sponsor: Calithera Biosciences, Inc.

TPS9628 **Poster Session (Board #394), Fri, 8:00 AM-11:00 AM**

A phase I/II study of REGN5093, a MET x MET bispecific antibody, in patients with MET-altered advanced non-small cell lung cancer (NSCLC). *First Author: Tracey Rowlands, Regeneron Pharmaceuticals, Inc., Tarrytown, NY*

Background: Mesenchymal-epithelial transition (MET) factor is a transmembrane tyrosine kinase receptor activated by hepatocyte growth factor (HGF). Aberrant activation of MET via gene amplification or gene mutations, as well as MET protein overexpression, has been reported in NSCLC and other cancer types and can promote tumorigenesis. REGN5093 is a human bispecific antibody that binds to two distinct epitopes of MET, blocking HGF binding and inducing internalization and degradation of MET. REGN5093 prevents MET-mediated signaling and inhibits growth of MET-driven tumor cells without inducing MET-driven biological responses (DaSilva et al, *CCR*, 2019; PMID: 31848185). **Methods:** This Phase I/II, first-in-human, multicenter study is investigating the safety, tolerability, pharmacokinetics (PK), and efficacy of REGN5093 in patients with MET-altered advanced NSCLC who have received all available approved therapies (NCT04077099). Key eligibility criteria include age ≥18 years, Eastern Cooperative Oncology Group performance status of ≤1, and documented presence of either *MET* exon 14 gene mutation and/or *MET* gene amplification and/or elevated MET protein expression. Patients are required to provide a biopsy during screening for assessment of MET biomarkers. Key exclusion criteria include prior MET-targeted biologic therapy (expansion cohorts only). Prior therapy with tyrosine kinase inhibitors are not exclusionary in any part of the study. For each patient, the study comprises a screening period of up to 28 days, followed by 3-week cycles of REGN5093 monotherapy. Study treatment will continue until confirmed disease progression or other protocol-defined reason for discontinuation. The study has two parts: dose escalation and dose expansion. Dose escalation will proceed via 4+3 design until a maximum-tolerated dose is reached or a recommended Phase II dose selected. The primary objective of the dose escalation part is to assess safety (incidence and severity of adverse events and Grade ≥3 laboratory abnormalities), tolerability (incidence of dose-limiting toxicities), and PK of REGN5093. During the expansion phase, patients will be allocated to cohorts according to the type(s) of documented biomarkers of MET-altered disease. Anti-tumor activity based on objective response rate per Response Evaluation Criteria in Solid Tumors version 1.1, determined by CT or MRI, will be the primary endpoint in the expansion cohorts. The study is currently open for enrollment. Clinical trial information: NCT04077099. Research Sponsor: Regeneron Pharmaceutical, Inc.

TPS9629 **Poster Session (Board #395), Fri, 8:00 AM-11:00 AM**

Phase II randomized trial of carboplatin + pemetrexed + bevacizumab, +/- atezolizumab in stage IV non-squamous non-small lung cancer (NSCLC) patients who harbor a sensitizing EGFR mutation or have never smoked. *First Author: Joseph Nicholas Bodor, Fox Chase Cancer Center, Philadelphia, PA*

Background: Stage IV NSCLC patients who are never-smokers or with EGFR-mutated tumors generally do not benefit from single-agent immunotherapy. Retrospective subgroup analyses from recent phase III trials suggest that immunotherapy-chemotherapy +/- VEGF inhibition may overcome resistance to PD-L1 inhibitors in these patients, however prospective research on this is needed. This trial will examine a patient population with stage IV non-squamous disease who either have tumors that possess an EGFR exon 19 or 21 mutation or who are never-smoker wild-types, to determine whether the PD-L1 inhibitor atezolizumab in combination with pemetrexed, carboplatin, and bevacizumab can improve outcomes. **Methods:** This is a randomized, phase II, multi-center, open-label trial to assess pemetrexed/carboplatin and bevacizumab +/- atezolizumab in 117 subjects with stage IV non-squamous NSCLC. Randomization will be 2:1 favoring the + atezolizumab arm. Patients are stratified by EGFR mutation status (i.e. EGFR exon 19 or 21 vs. never-smoker wild-type). Never-smoker wild-type is defined as smoking $<$ 100 cigarettes in a lifetime and without any EGFR mutation or ALK or ROS1 rearrangement. Patients with EGFR exon 19 or 21 mutated tumors must have progression of disease or intolerance of treatment with one or more prior TKIs. Primary endpoint is progression-free survival (PFS). Secondary endpoints include overall survival (OS), overall response rate, duration of response, and time to response. Primary objective is to compare PFS between arms. Secondary objectives include a safety analysis in all treated subjects, and comparisons of PFS and OS between arms for the patient subset with EGFR-mutated tumors. Correlative studies include interrogating flow cytometry-based peripheral blood biomarkers, examining the role of desmoplasia in local tumor immunosuppression, and assessing the contribution of estrogen metabolites to tumorigenesis. This study opened in August 2019 with 2 patients enrolled at the time of submission. Twenty U.S. sites through the NCCN are participating. This study was approved and funded by the National Comprehensive Cancer Network (NCCN) Oncology Research Program from general research support provided by Genentech, Inc. Clinical trial information: NCT03786692. Research Sponsor: F. Hoffmann-La Roche Ltd./Genentech.

TPS9630 **Poster Session (Board #396), Fri, 8:00 AM-11:00 AM**

Phase IIa study of marrow infiltrating lymphocytes (MILs), an adoptive T cell therapy, alone or in combination with nivolumab in non-small cell lung cancer (NSCLC). *First Author: Martin Edelman, Fox Chase Cancer Center, Philadelphia, PA*

Background: Primary or secondary resistance to anti-PD-1 may be due to loss of T cell function. Persistent antigen stimulation can lead to impaired CD8+ T cell function, which often results in acquired resistance to PD-1 inhibition. It is unclear whether reinvigoration of tumor infiltrating cells or recruitment of novel T cells impart the activity of anti-PD-1 therapy. The bone marrow is a reservoir for antigen experienced memory T cells. We have previously shown that MILs can be generated for patients with hematologic malignancies and solid tumors including patients with NSCLC. MILs are the product of the activation and expansion of bone marrow T cells with a polyantigenic memory phenotype that recognize tumor antigens, are cytotoxic to autologous tumor and are able to persist over a long period of time. In a pre-clinical study of NSCLC, MILs were able to be expanded in all patients tested. Furthermore, all of the NSCLC products tested showed specificity to shared NSCLC antigens. The combination of adoptive cell therapy (ACT) with checkpoint inhibitors (CPIs) has distinctive positive effects on CD8 and CD4 T cell subsets, with the possibility for complete tumor control. We hypothesize that patients with NSCLC who have relapsed on anti-PD-1 treatment could benefit from an infusion of non-exhausted, central memory-enhanced, antigen specific T cells i.e. MILs which can delay the induction of tumor-associated anergy and augment the overall effectiveness of immunotherapy. **Methods:** Patients with advanced NSCLC who have progressed following prior anti-PD-1 therapy, with sufficient bone marrow reserve and an ECOG 0-1 are eligible. In eligible patients, bone marrow (200 mL) will be harvested and processed. Patients will undergo lymphodepletion (fludarabine 300 mg/m^2/day and cyclophosphamide 30 mg/m^2/day on days -5,-4,-3) followed by infusion of MILs on day 0. In Part 1, up to 6 patients will be administered MILs alone on day 0. In Part 2, approximately 20 subjects will be administered MILs on day 0 followed by NIVO 480 mg Q4W starting on day 1. The objectives of the study are to assess safety of MILs alone and in combination with NIVO, as well as efficacy. The first patient was treated in December 2019. Clinical trial information: NCT04069936. Research Sponsor: None.

TPS9631 **Poster Session (Board #397), Fri, 8:00 AM-11:00 AM**

A phase II trial of durvalumab (MEDI4736) and tremelimumab with chemotherapy in metastatic EGFR mutant non-squamous non-small cell lung cancer (NSCLC) following progression on EGFR tyrosine kinase inhibitors (TKIs) (ILLUMINATE). *First Author: Chee Khoon Lee, St George Hospital, Kogarah, Australia*

Background: Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) have proven remarkably effective in the treatment of advanced EGFR mutant non-small cell lung cancer (NSCLC). However, drug resistance is inevitable and outcomes with subsequent platinum-pemetrexed chemotherapy are poor. The role of immune-checkpoint inhibitor monotherapy in EGFR mutant NSCLC remains uncertain with trials demonstrating inferior survival outcomes compared to chemotherapy. However, a recent randomised study with combination checkpoint inhibitor-chemotherapy demonstrated improved survival over chemotherapy alone in this patient population. This study aims to evaluate the efficacy and tolerability of combination dual immune-checkpoint blockade, durvalumab and tremelimumab, with platinum-pemetrexed chemotherapy in metastatic EGFR mutant NSCLC following progression on EGFR-TKIs. **Methods:** This international phase II cohort study will recruit 100 participants from Australia and Taiwan with advanced EGFR mutant NSCLC following disease progression with EGFR-TKIs [Cohort 1 (n=50): T790M mutation negative on tissue and plasma; Cohort 2 (n=50): T790M mutation positive on tissue and/or plasma, and progression on3rd generation TKIs]. Participants will receive 4 cycles of induction durvalumab 1500mg and tremelimumab 75mg with platinum-pemetrexed chemotherapy every 3 weeks, followed by maintenance durvalumab 1500mg and pemetrexed 500mg/m2 every 4 weeks until disease progression. Response will be assessed at 6 and 12 weeks, then 8-weekly during the first year, and 12-weekly thereafter. Major endpoints include objective tumour response rate (OTRR; RECIST1.1; primary), disease control rate, OTRR (iRECIST), progression-free survival, overall survival, and adverse events. Correlative studies include biomarker assessment as potential predictive/prognostic factors. ILLUMINATE is a collaboration between the Australasian Lung Cancer Trials Group, National Health Research Institutes (Taiwan) and the NHMRC Clinical Trials Centre, University of Sydney. As of 6/2/2020, 11 of planned 100 participants have been recruited. Clinical trial information: NCT03994393. Research Sponsor: AstraZeneca.

TPS9632 **Poster Session (Board #398), Fri, 8:00 AM-11:00 AM**

Randomized phase III study of first-line pembrolizumab plus pemetrexed/platinum followed by pembrolizumab and maintenance olaparib versus pemetrexed in patients with metastatic nonsquamous non-small cell lung cancer (NSCLC): KEYLYNK-006. *First Author: Jhanelle Elaine Gray, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL*

Background: First-line treatment with pembrolizumab + pemetrexed/platinum improved clinical outcomes in patients with advanced non-squamous NSCLC in KEYNOTE-021 and KEYNOTE-189. Poly(ADP-ribose) polymerase inhibitors (PARPi), including olaparib, have been shown to upregulate PD-L1 expression in preclinical studies, and preliminary evidence suggests potential therapeutic benefit and acceptable safety with PARPi plus anti–PD-(L)1 therapy. KEYLYNK-006 (NCT03976323) evaluates first-line pembrolizumab + pemetrexed/platinum followed by pembrolizumab + olaparib vs pembrolizumab + pemetrexed in patients with metastatic nonsquamous NSCLC. **Methods:** This phase III, randomized, open-label trial enrolls patients aged $\geq$18 years with histologically/cytologically confirmed treatment-naive, metastatic, nonsquamous NSCLC. Patients (target n = 792) receive induction pembrolizumab 200 mg + pemetrexed 500 mg/m^2 + carboplatin AUC 5 mg/mL/min or cisplatin 75 mg/m^2 Q3W for 4 cycles. Patients with PR/CR or SD are randomized (target n = 618) 1:1 to pembrolizumab 200 mg Q3W (31 cycles) + maintenance olaparib 300 mg twice daily or pembrolizumab + pemetrexed 500 mg/m^2 Q3W stratified by ECOG PS (0 vs 1), PD-L1 tumor proportion score ($<$50% vs $\geq$50%), and response (CR/PR vs SD). Tumor imaging per RECIST version 1.1 ($\leq$5 per organ; maximum 10 total lesions) by central review (BICR) is performed at baseline and Q6W until 60 weeks after randomization, then Q9W until disease progression, start of new cancer therapy, study withdrawal, or death. Primary endpoints are PFS (RECIST 1.1 by BICR) and OS estimated by the Kaplan-Meier method, stratified log-rank test, and Cox proportional hazard model with Efron's method of tie handling. Secondary endpoints are safety and quality of life; ORR and duration of response are exploratory endpoints. AEs are monitored throughout the study until 30 days after the last dose of treatment (90 days for serious AEs) and graded using NCI CTCAE, version 4.0. The study began enrolling in June 2019. Clinical trial information: NCT03976323. Research Sponsor: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

TPS9633 Poster Session (Board #399), Fri, 8:00 AM-11:00 AM

AcceleRET Lung: A phase III study of first-line pralsetinib in patients (pts) with RET-fusion+ advanced/metastatic non-small cell lung cancer (NSCLC). *First Author: Benjamin Besse, Gustave Roussy Université Paris Sud, Villejuif, France*

Background: RET gene fusions have been identified as oncogenic drivers in multiple tumor types, including 1-2% of NSCLC, but no selective RET inhibitors are approved for use. The investigational RET inhibitor, pralsetinib, potently and selectively targets oncogenic RET alterations, including those that confer resistance to multikinase inhibitors. In the registration-enabling phase 1/2 study (ARROW; NCT03037385), pts with RET-fusion+ NSCLC treated with 400 mg once daily (QD) of pralsetinib (N = 80) after platinum-based chemotherapy achieved an overall response rate (ORR) of 61% (95% CI 50, 72; 2 responses pending confirmation) per independent central review. In addition, a promising ORR of 73% (all centrally confirmed responses) was attained in the treatment naïve cohort (N = 26). Most treatment-related adverse events were grade 1-2 across the entire safety population treated at 400 mg QD (N = 354). AcceleRET Lung, an international, open-label, randomized, phase 3 study, will evaluate the efficacy and safety of pralsetinib versus standard of care (SOC) for first-line treatment of advanced/metastatic RET fusion+ NSCLC (NCT04222972). **Methods:** Approximately 250 pts with metastatic RET-fusion+ NSCLC will be randomized 1:1 to oral pralsetinib (400 mg QD) or SOC (non-squamous histology: platinum/pemetrexed ± pembrolizumab followed by maintenance pemetrexed ± pembrolizumab; squamous histology: platinum/gemcitabine). Stratification factors include intended use of pembrolizumab, history of brain metastases, and ECOG PS. Key eligibility criteria include no prior systemic treatment for metastatic disease; RET-fusion+ tumor by local or central assessment; no additional actionable oncogenic drivers; no prior selective RET inhibitor; measurable disease per RECIST v1.1. Pts randomized to SOC will be permitted to cross-over to receive pralsetinib upon disease progression. The primary endpoint is progression-free survival (blinded independent central review; RECIST v1.1). Secondary endpoints include ORR, overall survival, duration of response, disease control rate, clinical benefit rate, time to intracranial progression, intracranial ORR, safety/tolerability and quality of life evaluations. Recruitment has begun with sites (active or planned) in North America, Europe and Asia. Clinical trial information: NCT04222972. Research Sponsor: Blueprint Medicines.

TPS9635 Poster Session (Board #401), Fri, 8:00 AM-11:00 AM

Phase III trial of sitravatinib plus nivolumab vs. docetaxel for treatment of NSCLC after platinum-based chemotherapy and immunotherapy (SAPPHIRE). *First Author: Ivor John Percent, Florida Cancer Specialists South/Sarah Cannon Research Institute, Port Charlotte, FL*

Background: Sitravatinib is an oral spectrum-selective tyrosine kinase inhibitor that targets the TAM (TYRO3/AXL/MERTK) and split (VEGFR2/KIT) family receptor tyrosine kinases (RTKs), as well as MET. Inhibition of TAM RTKs may promote the depletion of myeloid-derived suppressor cells (MDSCs) in the tumor microenvironment (TME) and repolarize tumor associated macrophages towards the pro-inflammatory M1 phenotype. Inhibition of the split RTKs may reduce immunosuppressive regulatory T cells in addition to MDSCs within the TME. Given these pleiotropic immune-stimulating effects, sitravatinib may reverse resistance to checkpoint inhibitor therapy (CIT) and augment the antitumor immune response of nivolumab in patients (pts) with non-small cell lung cancer (NSCLC). An ongoing Phase 2 study (MRTX-500) demonstrates clinical activity of this combination in pts with metastatic non-squamous NSCLC after progression on or after CIT. **Methods:** Global, randomized, open-label, Phase 3 study of sitravatinib in combination with nivolumab vs docetaxel in pts with advanced non-squamous NSCLC who have progressed on or after CIT. Pts must have also received platinum-based chemotherapy either in combination with CIT or prior to CIT. Pts are randomized (1:1) to receive oral sitravatinib 120 mg once daily in continuous 28-day cycles combined with nivolumab IV 240 mg every 2 weeks or 480 mg every 4 weeks vs treatment with docetaxel 75 mg/m^2 IV every 3 weeks. Patients are stratified based on number of prior treatment regimens in the advanced setting, ECOG performance status, and presence of brain metastases. Key eligibility criteria include duration of treatment of CIT of at least 4 months, discontinuation of prior treatment with CIT $<$ 90 days prior to the date of randomization, and absence of symptomatic or uncontrolled brain metastases. The primary endpoint is overall survival (OS). Key secondary endpoints include safety and tolerability, ORR, PFS, PROs, and PK. OS will be analyzed using Kaplan-Meier methods and the stratified log-rank test to estimate and compare the median OS between the two treatment arms with 95% CI. An IDMC will review safety at regular intervals and efficacy at a planned interim analysis based on OS. Enrollment is ongoing. Clinical trial information: NCT03906071. Research Sponsor: Mirati Therapeutics, Inc.

TPS9636 Poster Session (Board #402), Fri, 8:00 AM-11:00 AM

A phase III, open-label, randomized study of atezolizumab in combination with carboplatin + paclitaxel + bevacizumab compared with pemetrexed + cisplatin or carboplatin with stage IV non-squamous non-small cell lung cancer (NSCLC) with activating EGFR mutation or ALK translocation (ATLAS Trial). *First Author: Sehhoon Park, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea*

Background: In patients with activating EGFR mutations and ALK fusion, target specific tyrosine kinase inhibitor (TKI) showed significant survival improvement compared to the cytotoxic chemotherapy. However, the questions remain which combination strategy will be the best option for the patients who have failed from TKI. Especially, the role of an immune checkpoint inhibitor (ICI) in this population is still unclear. This study is designed and conducted based on the recent subgroup analyses from the IMpower 150 study which showed the positive clinical outcomes of atezolizumab combined with VEGF inhibitor and conventional cytotoxic chemotherapy in EGFR mutation and ALK translocation. **Methods:** This study is the phase III, open-label, multicenter study of atezolizumab in combination with bevacizumab + carboplatin + paclitaxel (ABCP, Arm A) compared with pemetrexed + cisplatin or carboplatin (Arm B). The study population will be randomized to either Arm A (n = 152) or Arm B (n = 72) based on two stratification factors, EGFR vs. ALK and presence of brain metastases. In Arm A, patients will be treated with 4 or 6 cycles of ABCP followed by maintenance atezolizumab and bevacizumab every three weeks. In Arm B, pemetrexed maintenance therapy will be applied every three weeks after 4 or 6 cycles of pemetrexed + cisplatin or carboplatin. As key inclusion criteria, the patients must be diagnosed with stage IV non-squamous non-small cell lung cancer with either activating EGFR mutation or ALK translocation. All the patients need to be cytotoxic chemotherapy naïve and must have experienced disease progression to treatment with at least one EGFR or ALK TKI. If the patients have T790M mutation after 1st or 2nd generation EGFR TKI, second line 3rd generation EGFR TKI treatment is mandatory. The number of T790M positive patients is restricted to under 30% of the entire study population. The primary endpoint is progression-free survival and the major secondary endpoints are overall survival, objective response rate and duration of response. A total of 228 subjects will be enrolled to detect a hazard ratio of 0.67. The first subject received treatment in Aug. 2019 and 19 patients receive the treatment. This study is opened in 3 sites and expected to be opened at 18 sites in South Korea. The time point for the primary analyses is Q3. 2022. Clinical trial information: NCT03991403. Research Sponsor: Roche/Genentech.

TPS9637 Poster Session (Board #403), Fri, 8:00 AM-11:00 AM

TRIDENT-1: A global, multicenter, open-label Phase II study investigating the activity of repotrectinib in advanced solid tumors harboring *ROS1* or *NTRK1-3* rearrangements. *First Author: Robert Charles Doebele, University of Colorado, Aurora, CO*

Background: Repotrectinib is a next-generation ROS1/TRK inhibitor with $>$ 90-fold greater potency than crizotinib against ROS1 and $>$ 100-fold greater potency than larotrectinib against TRK. Preclinical studies demonstrated inhibitory activity of repotrectinib against ROS1 resistance mutations, including the solvent-front mutation (SFM) G2032R. In the phase 1 portion of the study, repotrectinib was found to be well tolerated with encouraging antitumor activity including a 91% confirmed overall response (cORR) in TKI-naïve *ROS1+* NSCLC pts. In *ROS1+* NSCLC pts who received 1 prior chemo and 1 prior TKI, the cORR was 57% at the clinical dose of 160 mg QD or above. Intra-cranial (IC) activity was observed in *ROS1+* NSCLC pts with measurable CNS disease (100% IC-ORR in TKI-naïve and 75% IC-ORR in patients with 1 prior TKI). Encouraging antitumor activity was observed in pts with NTRK+ solid tumors. **Methods:** A global phase 2 study was initiated and is actively enrolling. The primary endpoint for the Phase 2 study is cORR assessed by BICR (Blinded Independent Central Review) using RECIST v1.1, in each expansion cohort in pts with advanced solid tumors that harbor a ROS1 or NTRK1/2/3 gene fusion. Secondary endpoints include duration of response (DOR), progression-free survival (PFS), overall survival (OS), IC-ORR, IC-PFS, and quality of life assessments. All pts need to have RECIST 1.1 measurable disease confirmed by BICR and ECOG performance score $\leq$1. Repotrectinib is administered at 160 mg QD for 14 days and, if tolerated, the dose can be increased to 160 mg BID. Approximately 320 pts ($\geq$12 years old) will be enrolled into 6 defined expansion cohorts, depending on the status of previous treatment with TKIs and cancer types (see table below). Clinical trial information: NCT03093116. Research Sponsor: Turning Point Therapeutics Inc.

Cohort #	Tumor Type	Prior Treatment	Sample Size (pts)
1	*ROS1*+NSCLC	*ROS1* TKI-naive	55
2		1 Prior *ROS1* TKI AND 1 Platinum-based Chemo	100
3		2 Prior *ROS1* TKIs AND 1 Platinum-based Chemo	40
4		1 Prior *ROS1* TKI and NO Prior Chemo OR Immunotherapy	Up to 30
5	*NTRK*+solid tumors	*TRK* TKI-naïve	55
6		*TRK* TKI-pretreated (up to 2 prior TKIs)	40

TPS9638 Poster Session (Board #404), Fri, 8:00 AM-11:00 AM

A phase II study of atezolizumab and cobimetinib in PD-1/PD-L1 inhibitor resistant or refractory non-small cell lung cancer: ETCTN #10166. *First Author: Stephen V. Liu, Georgetown University, Washington, DC*

Background: Use of checkpoint inhibitors, alone or with chemotherapy, has emerged as the preferred standard treatment for patients with advanced, driver-negative non-small cell lung cancer (NSCLC). While outcomes are superior to chemotherapy alone, only a subset of patients achieve durable response and long term survival. One potential mechanism of primary resistance to checkpoint inhibitors is the lack of tumor-infiltrating lymphocytes. Inhibition of mitogen-activated protein kinase (MAPK) kinase (MEK) increases the number of CD8+ T-cell within a tumor and has shown synergy with anti-programmed death-ligand 1 (PD-L1) antibodies. The combination of the MEK inhibitor cobimetinib and the PD-L1 antibody atezolizumab has led to limited responses in colorectal cancer, a tumor typically non-responsive to checkpoint inhibition. This phase II trial explores the combination of cobimetinib and atezolizumab in patients with PD(L)1-refractory NSCLC. **Methods:** This phase II study is being conducted through the Experimental Therapeutics Clinical Trials Network (ETCTN #10166). Eligible patients have advanced NSCLC with primary resistance to anti-PD(L)1 therapy (defined as progression noted within 6 months of initiating therapy) and tumor amenable to serial core biopsy. Patients will receive atezolizumab 840mg intravenously every 2 weeks and cobimetinib 60mg orally for 21 days in 28-day cycles. Two cohorts will enroll in parallel, defined by presence or absence of a KRAS mutation. Each cohort will employ a Simon two-stage design to test a null rate of 5% vs. 25% (power = 0.90, □ = 0.10). If > 1 of 9 patients in stage 1 achieve a partial response, an additional 15 patients are enrolled and if > 3 patients achieve a durable response, the combination will be worthy of further investigation. The primary endpoint is durable (> 6 months) response rate. Secondary endpoints are overall response rate, progression free survival, overall survival, duration of response and adverse events. Biopsies performed at baseline and after 3 weeks of therapy will assess the change in the density of tumoral CD8+ T-cells. Whole exome sequencing and immune cell profiling will also be performed on serial samples. Enrollment was initially limited to KRAS-mutant NSCLC. Prespecified activity goal for the first stage of accrual has been met; second stage accrual began in September 2019. Enrollment to the KRAS wild-type cohort will commence. Clinical trial information: NCT03600701. Research Sponsor: U.S. National Institutes of Health.