Adjuvant chemotherapy for pathological stage I non-small cell lung cancer with high-risk factors for recurrence: A multicenter study.

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Background: The role of adjuvant chemotherapy for pathological stage I non-small cell lung cancer (NSCLC) is controversial. The purpose of this study was to investigate the effect of adjuvant chemotherapy for pathological stage I NSCLC with high-risk factors for recurrence. Methods: Prospectively collected data from 1,278 patients with pathological stage I (8th edition) NSCLC undergoing lobectomy were retrospectively analyzed. High-risk factors for recurrence were determined by multivariable Cox proportional hazards model for recurrence-free survival (RFS). RFS, overall survival (OS), and cancer-specific survival (CSS) were compared between patients who received adjuvant chemotherapy and those who did not. Results: In multivariable analysis, age ($\geq 70$ y; hazard ratio [HR], 2.14), invasive component size ($>2$ cm; HR, 1.60), visceral pleural invasion (HR, 1.81), lymphatic permeation (HR, 1.67), and vascular invasion (HR, 2.78) were identified as independent factors for RFS. In patients with high-risk factors for recurrence such as invasive component size of $>2$ cm, visceral pleural invasion, lymphatic permeation, or vascular invasion (high-risk group; $n = 641$), RFS was significantly different between patients who received adjuvant chemotherapy ($n = 222$; 5-y RFS, 81.4%) and those who did not ($n = 418$; 5-y RFS, 73.8%; $P = 0.023$). OS and CSS were also significantly better in patients who received adjuvant chemotherapy (5-y OS, 92.7%; 5-y CSS, 95.0%) than in those who did not (5-y OS, 81.7%; $P < 0.0001$; 5-y CSS, 89.5%; $P = 0.012$). In patients without any high-risk factors for recurrence (low-risk group; $n = 637$), RFS was not significantly different between patients who received adjuvant chemotherapy ($n = 83$; 5-y RFS, 98.1%) and those who did not ($n = 554$; 5-y RFS, 95.7%; $P = 0.30$). OS and CSS were also not significantly different between patients who received adjuvant chemotherapy (5-y OS, 98.0%; 5-y CSS, 100%) and those who did not (5-y OS, 95.6%; $P = 0.35$; 5-y CSS, 99.4%; $P = 0.52$). Conclusions: Adjuvant chemotherapy may improve survival in patients with pathological stage I NSCLC who have high-risk factors for recurrence such as invasive component size of $>2$ cm, visceral pleural invasion, lymphatic permeation, or vascular invasion.
Randomized phase III study of pemetrexed/cisplatin (Pem/Cis) versus vinorelbine/cisplatin (Vnr/Cis) for completely resected stage II-IIIA non-squamous non-small-cell lung cancer (Ns-NSCLC): The JIPANG study.

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Background: Although previous trials demonstrated the efficacy and safety of postoperative cisplatin-based adjuvant chemotherapy for resected NSCLC, no phase III study has so far evaluated Pem/Cis in this population. Methods: Patients with completely resected pathological stage II-IIIA Ns-NSCLC were randomized in a 1:1 ratio to receive either Pem (500 mg/m², day 1)/Cis (75 mg/m², day 1) or vinorelbine (Vnr) (25 mg/m², days 1 and 8)/Cis (80 mg/m², day 1), and stratified according to sex, age, pathologic stage, EGFR mutation status and institution. The primary endpoint was recurrence-free survival (RFS), and the planned sample size was 800 patients in total to detect the superiority of Pem/Cis over Vnr/Cis (Trial Identifier, UMIN000006737). Results: Between March 2012 and August 2016, 804 patients were randomized. Of 784 for the efficacy analysis (389 in Pem/Cis and 395 in Vnr/Cis), median age was 65/65 years; stage IIIA 52/52%; Adenocarcinoma, 96/96%; and EGFR mutation, 24/25%. With a median follow-up of 45.2 months (mo), median RFS was 38.9mo in Pem/Cis and 37.3mo in Vnr/Cis with a hazard ratio (HR) of 0.98 (95% CI, 0.81—1.20; log-rank test, P= 0.948), whereas HRs in patients with and without EGFR mutations were 1.38 (95% CI, 0.95—1.99) and 0.87 (95% CI, 0.69—1.09), respectively (Interaction, P= 0.046). Overall survival rate at 3 years was 83.5% versus 87.2% with a HR of 0.98 (95% CI, 0.71—1.35). Incidences of grade 3 or 4 febrile neutropenia (0.3/11.6%, P< 0.001), neutropenia (22.8/81.1%, P< 0.001), and anemia (2.8/9.3%, P< 0.001); any grade alopecia (12.8/30.1%, P< 0.001). One treatment-related death was observed in each arm. Rates of treatment completions were 87.9% (Pem/Cis) and 72.7% (Vnr/Cis), respectively (P < 0.001). Conclusions: Although this phase III study did not meet the primary endpoint, Pem/Cis had a similar efficacy to Vnr/Cis with a better tolerability as postoperative adjuvant chemotherapy for Ns-NSCLC patients. A significant interaction for RFS was found between treatment and EGFR mutation status. Clinical trial information: UMIN000006737.
Background: Metformin, a diabetes agent that inhibits mitochondria complex I, enhances radiotherapy and chemotherapy responses in pre-clinical models of NSCLC. NRG-LU001 examined whether metformin can improve outcomes of curative CRT in locally advanced (LA)-NSCLC. Methods: The primary endpoint of this trial was 1-year progression free survival (PFS). Unresected, non-diabetic, stage IIIA/B NSCLC patients were randomized (1:1) to either carboplatin-paclitaxel chemotherapy concurrent with chest RT (60Gy), followed by consolidation carboplatin-paclitaxel chemotherapy (Control Arm) or the same and oral metformin (2000mg daily) during cytotoxic therapy (Experimental Arm). PFS and overall survival (OS) were estimated with the Kaplan-Meier method; time to local-regional progression (TTLRP), time to distant metastasis (TTDM) were estimated using the cumulative incidence method. Adverse events (AEs) were graded with CTCAE v.4.0. Results: Between Aug.2014 and Dec.2016, 170 patients were accrued. Analysis was planned at 102 PFS events (Feb. 2019). There was no significant difference in rates or grade of toxicity between the two arms. 1- and 2-year PFS was 60.4% (95% CI: 48.5, 70.4) and 40.1% (95% CI: 29.0, 51.0) in Control vs 51.3% (95% CI: 39.8, 61.7) and 34.5% (95% CI: 24.2, 45.1) in the Metformin arm (multivariable Cox proportional HR=1.20 (95% CI: 0.81, 1.78), p=0.36). OS at 2 years was 65.4% (95% CI: 53.5, 75.0) for Control vs 64.9% (95% CI: 53.1, 74.5) for the Metformin arm (HR=1.03 (95% CI: 0.64, 1.68)), while deaths due to disease were 90% vs 71%, respectively. No significant differences were found for TTLRP or TTDM. Conclusions: NRG-LU001 center reported outcomes show that oral daily metformin was well-tolerated in combination with CRT treatment for LA-NSCLC. However, metformin did not improve PFS and OS and did not alter the rates of local-regional failure or distant metastasis. Acknowledgements: TT and HS are Co-Principal Investigators. This project was supported by National Cancer Institute (NCI) grants: U10CA180868 (NRG Oncology Operations), U10CA180822 (NRG SDMC), UG1CA189867 (NCORP), U24CA180803 (IROC). Clinical trial information: NCT02186847.
Neoadjuvant atezolizumab in resectable non-small cell lung cancer (NSCLC): Interim analysis and biomarker data from a multicenter study (LCMC3).

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Background: Small pilot studies (e.g., N Engl J Med. 2018;378:1976) have shown that preoperative immune checkpoint inhibitor therapy may be of benefit in early-stage NSCLC. This large multicenter trial assesses the benefit of neoadjuvant treatment with atezolizumab (atezo; NCT02927301). Methods: Patients (pts) with stages IB to selected IIIB resectable NSCLC receive 2 cycles of atezo 1200 mg (days 1, 22) then undergo resection (day 40 ± 10). Primary tumor +/- node biopsies and blood samples are obtained before atezo and at surgery for biomarker studies. The primary endpoint is major pathological response (MPR), defined as ≤ 10% viable tumor cells in the resection specimen. Secondary endpoints include safety and correlation of response with PD-L1 expression, tumor mutation burden (TMB) and gene expression signatures. Results: For this interim efficacy analysis (5 Sep 2018 data cut), we report on the first 101 of 180 planned pts: 47 males, median age, 64 y; all ECOG PS 0-1; 23 current and 68 former smokers; 66 non-squamous NSCLC; clinical stages IB/IIA/IIB/IIIA/IIIB n = 11/16/28/39/7. There were 2 treatment-unrelated Gr 5 AEs (cardiac death post surgical resection; death due to disease progression), 29 Gr 3-4 AEs (6 [6%] treatment related). 90 pts had surgery. Excluding 8 pts who had driver mutations (7 EGFR, 1 ALK, no MPR), MPR rate was 15/82 (18%, 95% CI 11%-28%), 4 pts had pathological complete response (pCR). By RECIST, 6/82 pts had PR, 72 had SD and 4 had PD. Two of 26 (8%) PD-L1+ (TC0 and IC0, clone SP142) and 10 of 35 (29%) PD-L1+ had MPR (P= 0.055). Five of 44 (11%) TPS < 50 (PD-L1 clone 22C3) and 7 of 20 (35%) TPS > 50 had MPR (P= 0.040). Exome sequencing data was available for 47/101 pts. Median TMB was 10.4 (range, 1.5-46.5) mutations per Mb and was not different in those with MPR compared with those without MPR. Further analysis of TMB, mutation signatures, and gene expression profiling is ongoing. Conclusions: Atezo in the neoadjuvant setting was well tolerated, and pCR and MPR rates are encouraging in this large multicenter trial. Efficacy interim analysis passed its futility boundary, and study enrollment continues. Safety, efficacy results and ongoing correlative analyses will be presented. Clinical trial information: NCT02927301.
Neoadjuvant nivolumab (N) or nivolumab plus ipilimumab (NI) for resectable non-small cell lung cancer (NSCLC): Clinical and correlative results from the NEOSTAR study.

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Background: Neoadjuvant immune checkpoint inhibitors (ICIs) induce major pathologic response (MPR) rates of 20 to 45% in resected NSCLCs. We report the results of NEOSTAR - a phase 2 trial of neoadjuvant N or NI for NSCLCs. Methods: Pts with stage I-IIIA (single N2) resectable NSCLC (AJCC 7th), PS 0-1, were randomized to N (3 mg/kg IV, D1, 15, 29) or N plus I (1 mg/kg IV, D1) followed by surgery (n = 44). Primary endpoint: MPR (≤10% viable tumor), hypothesized to be higher than MPR to induction chemotherapy historical controls. Tumor immune infiltrates and pre- & post-ICI tumor PD-L1 % were assessed by flow cytometry & IHC. Wilcoxon ranked sum test & Fisher's exact test were used for comparisons. Results: 44 pts were randomized, 23 N, 21 NI: mean age 66, 64% males, 18% never smokers, 59% adenocarcinomas, stages: IA 8 (18%), IB 15 (34%), IIA 7 (16%) IIB 5 (11%); IIIA 9 (20%). Only 3 pts received <3 doses due to TRAEs (7%). 34 pts had surgery post ICIs (7 not resected [7/41], 17%, [2 N, 5 NI, 3 pending]). There were 10 MPRs in 41 pts overall (24%, 4 N, 6 NI), of which 6 were path CRs (15%, 2 N [9%], 4 NI [21%]). Among 34 resected pts, MPR rate was 29% (N 20%, NI 43%). Median % of viable tumor was lower post NI vs N (20% vs 65%, p = .097). 34 pts had surgery post ICIs (7 not resected [7/41], 17%, [2 N, 5 NI, 3 pending]). There were 10 MPRs in 41 pts overall (24%, 4 N, 6 NI), of which 6 were path CRs (15%, 2 N [9%], 4 NI [21%]). Among 34 resected pts, MPR rate was 29% (N 20%, NI 43%). Median % of viable tumor was lower post NI vs N (20% vs 65%, p = .097). ORR (RECIST v1.1) was 22% (8 PRs [5 N, 3 NI], 1 CR [NI]); 15% of pts had PD (3 N, 3 NI). The proportion of CR+PR in MPR+ was higher than in MPR- (6 [60%] vs 2 [7%], p < .001). Surgical complications included 2 bronchopleural fistulas (BPFs) in N & 8 air leaks (5 N, 3 NI). G3-G5 TRAEs included a death due to BPF post steroid-treated pneumonitis (G5, N); G3 pneumonia, hypoxia, hypermagnesemia (1 each, all N), G3 diarrhea (1 NI). CD3⁺ & CD103⁺ tissue resident memory CD8⁺ TILs were higher in NI- vs N-treated tumors (CD3⁺ 81.2% vs 54.4%, p = .028; CD8⁺ 56.2% vs 38.3%, p = .069). Median pre-treatment tumor PD-L1 was higher in responders (MPR+, CR+PR) vs non-responders (80% vs 1%, p = .024), and the % of viable tumor was lower in tumors with PD-L1 > 1% vs PD-L1 ≤1% (median 20% vs 80%, p = .046). Conclusions: Overall a 24% MPR rate to neoadjuvant ICIs was observed. NI induced a higher % of non-viable tumor and of tissue resident memory TILs vs N. Antitumor activity was associated with higher pre-treatment PD-L1 levels. Clinical trial information: NCT03158129.
Effect of trilaciclib, a CDK 4/6 inhibitor, on myelosuppression in patients with previously treated extensive-stage small cell lung cancer receiving topotecan.

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Background: Multi-lineage myelosuppression is an acute toxicity of cytotoxic chemotherapy leading to hematologic adverse events and dose reductions and delays. Current therapies are lineage specific and administered after chemotherapy damage. Trilaciclib (T), a highly selective, reversible CDK4/6 inhibitor, is designed to preserve hematopoietic stem and progenitor cells and immune system function during chemotherapy (myelopreservation). We have shown that T mitigates myelosuppression in patients with newly diagnosed extensive-stage small cell lung cancer (ES-SCLC) receiving 1st-line chemotherapy.

Methods: In this blinded, placebo-controlled, multicenter Phase 2 study, patients with previously treated ES-SCLC were randomized to T (240 mg/m²) + 0.75 mg/m² topotecan, T (240 mg/m²) + 1.5 mg/m² topotecan, or placebo (P) + 1.5 mg/m² topotecan IV on days 1-5 of 21-day cycles. Patients had access to standard supportive care, except in cycle 1 where prophylactic growth factors were not allowed. Eligible patients had adequate organ function, measurable disease, ECOG PS 0-2, and disease progression during or after prior 1st/2nd-line chemotherapy. Objectives included safety, tolerability, measures of myelosuppression and tumor efficacy.

Results: 91 patients were randomized: 30 patients received T + 0.75 mg/m² topotecan, 32 patients received T + 1.5 mg/m² topotecan and 28 patients received P + 1.5 mg/m² topotecan. In patients receiving 1.5 mg/m² topotecan, T treatment reduced occurrence [40.6% (T) vs 75.6% (P), p = 0.016], and duration in cycle 1 [2 days (T) vs 8 days (P), p = 0.0001] of severe neutropenia. T-treated patients had fewer RBC transfusions on/after 5 weeks on study, GCSF administrations, and all-cause dose reductions. Chemotherapy efficacy was comparable in both arms (P and T) treated with 1.5 mg/m² topotecan (median PFS (T) 4.2 months vs (P) 4.2 months, HR = 0.83). OS data is immature.

Conclusions: T combined with topotecan mitigated chemotherapy-induced myelosuppression and improved tolerability of topotecan vs P. Results suggest the addition of T to cytotoxic chemotherapy for the treatment of ES-SCLC is clinically beneficial. Clinical trial information: NCT02514447.
**Efficacy and safety profile of lurbinectedin in second-line SCLC patients: Results from a phase II single-agent trial.**

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**Background:** Lurbinectedin (L) is a novel anticancer drug that inhibits activated transcription and induces DNA double-strand breaks, leading to apoptosis. **Methods:** A multicenter phase 2 basket trial assessed the efficacy and safety of L in several cancer types, including small cell lung cancer (SCLC). Primary endpoint was confirmed overall response rate (ORR) by RECIST v.1.1. In the SCLC cohort, a target ORR $\geq$30% was set. One-hundred and five patients (pts) with ECOG PS 0-2 who had received one prior chemotherapy line were treated with L 3.2 mg/m² as a 1-hour i.v. infusion on Day 1 q3wk. **Results:** Median age was 60 years (range, 40-83), 60% were male, ECOG PS 0/1/2 (32%/62%/6%), liver metastasis 41%, history of CNS involvement 3.8%, prior platinum 100%, median chemotherapy-free interval (CTFI): 3.5 (0-16.1) months; prior immunotherapy (IO): 7.6%. Pts received a median of 4 cycles (range, 1-24). **Conclusions:** L monotherapy is active in second-line SCLC in both resistant and sensitive disease. The acceptable and manageable safety profile is also associated to a convenient treatment administration (Day 1 q3wk). L as second-line treatment in SCLC emerges as a new promising drug for this unmet clinical need. Clinical trial information: NCT02454972.

<table>
<thead>
<tr>
<th>Overall (n=105)</th>
<th>CTFI&lt;90d (resistant disease) (n=47)</th>
<th>CTFI≥90d (sensitive disease) (n=58)</th>
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<tr>
<td>ORR, % (95% CI) (confirmed responses)</td>
<td>35.2 (26.2-45.2)*</td>
<td>21.3 (10.7-35.7)</td>
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<tr>
<td>Disease Control Rate (% at 8 wks)</td>
<td>64.8</td>
<td>46.8</td>
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<td>Median DOR (months) (95% CI)</td>
<td>5.3 (3.5-6.4)</td>
<td>4.7 (2.6-5.6)</td>
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<tr>
<td>DOR rate at 6 months (95% CI) %</td>
<td>40.3</td>
<td>11.7</td>
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<tr>
<td>Median OS (months) (95% CI) ^</td>
<td>10.8 (6.5-12.2)</td>
<td>5.1 (4.4-8.1)</td>
</tr>
</tbody>
</table>

* 5 of 8 pts who failed prior IO had confirmed response DOR: duration of response; ^ Preliminary Myelosuppression was the most common adverse event (AE): G3 (22%) and G4 (23.8%) neutropenia, G3/4 febrile neutropenia (3.8%) and G3/4 thrombocytopenia (6.6%). Secondary prophylaxis or therapeutic G-CSF was given in 15.2%. Most common non-hematological AEs were fatigue (G3: 4.8%), nausea and vomiting (all G1/2). Related serious AEs occurred in 10.5% pts, while treatment-related discontinuations in 3.8%. No treatment-related deaths were reported.
Randomized phase II study of adjuvant afatinib for three months versus two years in patients with resected stage I-III EGFR mutant NSCLC.

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Background: EGFR tyrosine kinase inhibitors are superior to chemotherapy in patients with advanced EGFR+ lung cancers. In the adjuvant setting, erlotinib for two years improves recurrence free survival (RFS) compared to historical controls. The optimal duration of adjuvant TKI is unknown. Methods: Patients with completely resected Stage I-III NSCLC with a sensitizing EGFR mutation were enrolled after standard adjuvant therapy. Pts were randomly assigned to 3 months (3m) or 2 years (2y) of adjuvant afatinib. Afatinib was started at 30 mg by mouth daily. Patients without toxicity after 28 days were allowed to escalate to 40 mg daily. Patients were imaged with CT every 6 months for 3 years and then annually or as clinically indicated. RFS was measured from the date of randomization. The primary study endpoint was recurrence rate at 2 years. 60 randomized patients would provide 82.5% power to detect a 26% difference in 2y-recurrence rate. Results: Patient characteristics are in the Table. The study was terminated for slow accrual after 46 of the planned 60 patients. Planned treatment was completed by 92% (22/24) pts in the 3m arm and 41% (9/22) of pt in the 2y arm. 22 patients required $1 dose modification due to toxicity including expected GI, mucosal, and skin AEs. With a median follow-up of $38 months there were 10 recurrences and 3 deaths in the 3m arm and there were 5 recurrences (2 on treatment) and 2 deaths in the 2y arm. Median RFS has not been reached in either arm, but recurrence was more common in the 3m arm at every landmark. 2y-recurrence rates were 29% for 3m and 15% for 2y. Conclusions: Recurrences at 2 years were 14% less common with 2y versus 3m of adjuvant afatinib. This difference did not meet the primary study endpoint. The RFS curves show a durable and clinically meaningful separation with substantial follow-up. Failure to meet significance was likely influenced by under-accrual and early drug discontinuation on the 2y arm. In the era of TKIs with improved tolerance, duration of adjuvant therapy remains an important question. Clinical trial information: NCT01746251.
The role of EGFR inhibitors as adjuvant therapy for EGFR mutation positive non-small cell lung cancer.

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Background: Cisplatin-based chemotherapy as adjuvant therapy for resected NSCLC has reached its plateau, and was limited by high risk of recurrence and significant toxicities. The clinical value of epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) in resected non-small cell lung cancer (NSCLC) harboring EGFR mutations remains controversial. In this study, we performed a meta-analysis to evaluate the role of EGFR inhibitors as adjuvant therapy for targeted patients.

Methods: Studies were identified via an electronic search on Pubmed, EMBASE, ISI Web of Science, ScienceDirect, SpringerLink, The Cochrane library and so on. Pooled odds ratio (OR) for disease-free survival (DFS) and overall survival (OS) were calculated for meta-analysis. Registration number: PROSPERO (CRD42018093144).

Results: There were 11 trials (1,152 resected NSCLC patients with EGFR sensitive mutations) in this meta-analysis. Results showed that adjuvant treatment with EGFR-TKIs can prolong both OS and DFS when compared to treatment without TKIs as adjuvant therapy (OS: OR, 0.63; 95% CI, 0.46 to 0.87, P = 0.004; heterogeneity I² = 61%, P = 0.008; DFS: OR, 0.56; 95% CI, 0.43 to 0.72, P < 0.00001; heterogeneity I² = 37%, P = 0.1). Results of predefined subgroup analyses in this meta-analysis suggested a greater DFS with EGFR-TKI mono compared with chemotherapy, whereas the OS benefit failed to show a similar difference between the two arms (p = 0.3). And we also find that treatment with EGFR-TKI plus chemotherapy was associated with significantly longer DFS as well as OS than chemotherapy mono in patients with completely resected EGFR-mutant NSCLC (DFS: OR, 0.48; 95% CI, 0.34-0.68; P < 0.00001; heterogeneity I² = 15%, P = 0.29; OS: OR, 0.50; 95% CI, 0.31-0.78; P = 0.003; heterogeneity I² = 57%, P = 0.05). And less grade 3 or higher AEs were observed in the TKIs group (OR, 0.22; 95% CI, 0.14 to 0.37, P < 0.00001; heterogeneity I² = 22%, P = 0.28).

Conclusions: Adjuvant EGFR-TKIs may be a potential treatment option compared to adjuvant chemotherapy in completed resected patients with EGFR mutation-positive NSCLC. This project was supported by the National Natural Science Foundation of China (Grant No. 81502667), Key Research and Development Plan of Shandong, China (Grant No. 2016GSF201167).

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Background: Patients with stage IIIA (N2 or T4N0) are potentially curable but median overall survival is only around 15 months and complete pathologic response with conventional chemotherapy (CT) is no more than 9%. Methods: A Phase II, single-arm, open-label multicenter study of resectable stage IIIA N2-NSCLC adult patients with CT plus IO as a neoadjuvant treatment: three cycles of Nivolumab (NV) 360mg IV Q3W + paclitaxel 200mg/m2 + carboplatin AUC 6 IV Q3W followed by adjuvant NV treatment for 1 year. After complete neoadjuvant therapy, tumor assessment is performed prior to surgery. Surgery is performed in the 3rd or 4th week after day 21 of the third cycle of neoadjuvant treatment. The study aims to recruit 46 pts. The primary endpoint is Progression-Free Survival (PFS) at 24 months. Efficacy is explored using objective pathologic response criteria. We present final data on all patients included in this study that underwent surgical assessment. Results: At the time of submission, 46 pts had been included and 41 had undergone surgery. CT-IO was well-tolerated and surgery was not delayed in any patient. None of the pts withdrew from the study preoperatively due to progression or toxicity. 41 surgeries had been performed and all tumors were deemed resectable, with R0 resection in all cases. 34 pts (83%) achieved major pathologic response (MPR) (CI 95% 71-95%), and 24 (71%) of them had a complete pathologic response (CPR) (CI 95% 54-87%). Downstaging was seen in 90% (CI 95% 81-100%) of cases. By RECIST, 29 pts (71%) (CI 95% 56-85%) had partial response and 3 (7%) (CI 95% 0-16%) complete response. Conclusions: This is the first multicentric study to CT-IO in the neoadjuvant setting in stage IIIA. Neoadjuvant CT-IO with nivolumab in resectable IIIA NSCLC yields a high complete pathologic response rate that has never been seen previously and unsuspected by RECIST criteria. Preliminary correlative analyses in blood samples are included in a separate abstract. EudraCT Number: 2016-003732-20. Clinical trial information: NCT 03081689.
Veliparib (Vel) in combination with chemoradiotherapy (CRT) of carboplatin/paclitaxel (C/P) plus radiation in patients (pts) with stage III non-small cell lung cancer (NSCLC) (M14-360/AFT-07).

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Background: CRT is standard treatment (Tx) for pts with unresectable stage III NSCLC. Vel, a potent oral PARP1/2 inhibitor, interferes with repair of chemotherapy- or radiation-induced DNA damage. In a phase 2 study, Vel showed favorable efficacy vs placebo when added to C/P in stage IV NSCLC. The reported phase 1 trial assessed the safety and efficacy of Vel + C/P-based CRT in Tx of stage III NSCLC (NCT02412371). Methods: Eligible pts (≥18 yr, unresectable stage III NSCLC, no prior NSCLC therapy) received Vel + CRT of weekly C area under the curve (AUC) 2 + P 45 mg/m² weekly + 60 Gy (2 Gy/day) RT over 6–9 weeks (wk). Vel was dose escalated from 60 mg twice daily (BID) to 240 mg BID followed by Vel 120 mg BID added to consolidation therapy (CON) once every 3 wk of C AUC 6 + P 200 mg/m² for 2 cycles (cohort 1–5). Cohort 6 received Vel 240 mg BID + CRT followed by Vel 240 mg BID + CON. Samples for pharmacokinetic (PK) analysis were collected on wk 4 day –3. The primary endpoint was to establish the recommended phase 2 dose (RP2D) of Vel + CRT/Vel + CON. Results: As of Sep 2018, 48 pts enrolled into cohorts 1–6 at Vel 60 mg/120 mg (n = 7), 80 mg/120 mg (n = 9), 120 mg/120 mg (n = 7), 200 mg/120 mg (n = 8), 240 mg/120 mg (n = 12), and 240 mg/240 mg (n = 5) added to CRT/CON; median age 65 yr (range, 48–81). Vel PK was dose proportional; 39 (81.3%) pts completed therapy. Grade 3 Tx-emergent adverse events (AEs) were reported in 37 (77.1%) pts; anemia and febrile neutropenia (10.4% each) were the most common. Serious AEs were observed in 19 (39.6%) pts. Dose-limiting toxicities occurred at 200 mg/120 mg (n = 1; influenza and pneumonia), 240 mg/120 mg (n = 1; insomnia), and 240 mg/240 mg (n = 2; febrile neutropenia, neutropenia, thrombocytopenia, esophagitis, suprapubic pain, sepsis); Vel 240 mg BID + CRT/Vel 120 mg + CON was chosen as the maximum tolerated dose/RP2D. Of 41 pts evaluable for tumor assessment, 26 (63.4%) had a confirmed response. Interim median progression-free survival was 24.1 mo (range, 8.9 – not reached); updated results will be reported. Conclusions: Vel 240 + CRT/Vel 120 mg BID + CON was well tolerated with promising antitumor activity in stage III NSCLC and was determined as RP2D. Clinical trial information: NCT02412371.
Prospective phase I multi-institutional trial of PD-1 blockade with pembrolizumab during concurrent chemoradiation for locally advanced, unresectable non-small cell lung cancer.

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Background: The PACIFIC study showed that consolidative Programmed Death Ligand 1 inhibition (PD-L1i) after chemoradiation therapy (CRT) improves PFS and OS in patients with Stage III NSCLC (Antonia et al. NEJM 2017, 2018). Limited data, however, exist regarding the incorporation of PD-L1i concurrently during CRT. We sought to assess the safety and toxicity of PD-1i using pembrolizumab (pembro) during definitive CRT for Stage III NSCLC. Methods: In this multi-center prospective Phase I clinical trial using a 3+3 design, we evaluated the timing and dosing of pembro combined with chemotherapy (carboplatin + paclitaxel weekly) and definitive RT (60 Gy in 2 Gy/day x 30 fractions) for unresectable, locally advanced Stage III NSCLC (AJCC 7thEd). Dose Cohorts (C) evaluated were--C1: full dose (FD) pembro (200 mg IV Q3 weeks) 2-6 weeks after CRT; C2: reduced dose (RD) pembro (100 mg IV Q3 weeks) starting Day 29 of CRT; C3: FD pembro starting Day 29 of CRT; C4: RD pembro starting on Day 1 of CRT; C5: FD pembro starting on Day 1 of CRT. For each cohort, pembro was continued Q3 weeks for up to 18 cycles (as monotherapy after CRT in either RD or FD based on initial dose assignment). Dose Limiting Toxicity (DLT) was defined as Grade 3-4 pneumonitis within 21 days of cycle 1 of pembro. Results: We enrolled 23 subjects from 8/2016-11/2018; median follow up (f/u) was 11.4 mo (range, 3.1 mo- 25.2 mo). Median age was 69 yrs (range 53-85); 52% were women. No DLTs were observed in any of the cohorts (C1 to C5). Grade 3 immune-related adverse events (irAE) occurred in 4 patients (18%). irAE’s included: Grade 5 (bilateral), 3, 2 pneumonitis (n=1, 1, 4, respectively (6 total)); Grade 3 hyperglycemia (n=1); Grade 3 interstitial nephritis (n=1); Grade 2 thyroiditis (n=1); Grade 2 myositis (n=1); Grade 1-2 transaminitis (n=3). Median PFS for patients who received ≥2 doses (n=18) of pembro was 20.3 mo. Conclusions: Combined treatment with PD-Li and CRT for stage III NSCLC was well tolerated with promising PFS to date but showed an increased risk for irAEs, particularly pneumonitis. Based on these encouraging results, further prospective study of PD-1i and CRT for Stage III NSCLC is warranted. Clinical trial information: NCT02621398.
Phase II trial combining atezolizumab concurrently with chemoradiation therapy in locally advanced non-small cell lung cancer.

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Background: Consolidation durvalumab after chemoradiation (CRT) is the new standard of care in locally advanced NSCLC (LA-NSCLC). We hypothesized that adding immunotherapy concurrently with CRT (cCRT) would increase efficacy without significant additive toxicity. To test this concept, we conducted a phase II trial called DETERRED combining atezolizumab (atezo) with cCRT followed by consolidation full dose carboplatin/paclitaxel (CP) with atezo (CP-atezo) for 2 cycles and then maintenance atezo for 1 year. The primary endpoint was safety/toxicity and feasibility. Methods: This study enrolled patients (pts) between February 2016 - April 2018 and was done in two parts: In part 1 (N=10), conventionally fractionated CRT (60-66 Gy in 30-33 fractions combined with weekly low dose CP) was followed by CP-atezo then maintenance atezo. Part 2 was cCRT (N=30) with atezo followed by CP-atezo then maintenance atezo. Atezo was given at 1200 mg IV Q3 weeks. Severe adverse events (SAEs) $\geq$ grade 3 were defined by CTCAE v5.0. Evaluable pts received at least one dose of atezo. PD-L1 staining utilizes the DAKO 22C3 platform. Kaplan Meier were analyzed for progression free survival (PFS) and overall survival (OS), and chi-square test for PD-L1 levels on any recurrence, with significance set at $p<0.05$.

Results: In Part 1, atezo related SAEs were seen in 4 pts (40%) (2 grade 3 arthralgia, 1 grade 3 dyspnea and 1 grade 5 TE fistula). Grade 2 radiation pneumonitis (RP) was seen in 1 pt. In Part 2, seven (23%) pts had atezo related SAEs (diarrhea, nephritis, dyspnea, fatigue and heart failure). RP was seen in 3 pts, 2 grade 2 and 1 grade 3, which led to atezo discontinuation. In Part 1, with an overall median follow up (f/u) time of 22.5 months and 27.4 months for survivors, the 1-year PFS is 50%, and OS is 79%. In Part 2, with a median f/u time of 11.8 months and 13.7 months for survivors, the 1-year PFS was 57%, and OS is 79%. Baseline tumor biopsy PD-L1 status was evaluable for 34 pts. There were no significant differences in cancer recurrence for PD-L1 $<1\%$ (7/16=44%) vs $\geq1\%$ (6/18=33%), or for the PD-L1 cutoff of $<50\%$ (11/26=42%) vs $\geq50\%$ (2/8=25%). Conclusions: Concurrent atezo with CRT followed by CP-atezo and maintenance atezo is safe without increased toxicities compared to CRT alone followed by CP-atezo and maintenance atezo. Updated efficacy results from DETERRED will be presented. Ultimately, the clinical benefit of immunotherapy with cCRT followed by consolidation chemo-immunotherapy will need to be compared to the PACIFIC regimen in a larger randomized trial. Clinical trial information: NCT02525757.
Phase II trial of carfilzomib and irinotecan in relapsed small cell lung cancer (NCT01941316).

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Background: Relapsed small cell lung cancer (SCLC) is incurable with limited therapeutic options. This phase II study evaluated efficacy and tolerability of carfilzomib + irinotecan in SCLC pts who progressed after prior platinum-based therapy, based on expected synergy of proteosome inhibitor carfilzomib and topoisomerase 1 inhibitor irinotecan. Methods: SCLC pts who progressed after one platinum-containing regimen (no maintenance therapy allowed) for recurrent/metastatic disease were eligible. Pts were stratified by response to platinum-based therapy: sensitive (progressive disease (PD) > 90 days after chemo) versus refractory (PD 30 to 90 days after chemo). Pts were treated with up to 6 cycles of carfilzomib (20/36 mg/m2 D1, 2, 8, 9, 15, 16 q28D) and irinotecan (125 mg/m2 D1, 8, 15 q28D), imaging was performed every 2 cycles. The primary efficacy endpoint was 6-month overall survival (OS). Results: 62 pts enrolled and were evaluable for efficacy and adverse events. The 6-month OS was 59% in the platinum sensitive stratum and 54% in the platinum refractory stratum. Overall response rate: sensitive stratum 21.6% (1.6% CR + 16.4% PR) and refractory stratum 12.5% (all PR). Disease control (SD+PR+CR) was 68% in platinum sensitive and 56% in refractory patients. Progression free survival and OS were 3.6 months (95% CI 2.6 - 4.6) and 6.9 months (95% CI 4.3 - 12.3) in the sensitive stratum, and 3.3 months (95% CI 1.8 – 3.9) and 6.8 months (95% CI 4.1-11) in the refractory stratum. Twenty-nine pts (47%) experienced at least one grade 3 AE and 8 subjects had grade 4 toxicities: decreased neutrophils, leukocytes, and lymphocytes, diarrhea, vomiting, sepsis, hypokalemia, hypocalcemia, and dehydration. There were three treatment related deaths: myocardial infarction (possible), lung infection (possible), sepsis (probable). Conclusions: In previously treated pts with relapsed SCLC, irinotecan and carfilzomib was effective in platinum-sensitive and, notably, platinum-refractory pts with similar toxicity profile. This combination is a viable option in relapsed SCLC, can be considered following progression on immunotherapy (IO) or in subjects who cannot receive IO, and should be further explored in a randomized phase III trial. Clinical trial information: NCT01941316.
Biomarker driven phase II umbrella trial study of AZD1775, AZD2014, AZD2811 monotherapy in relapsed small cell lung cancer.

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Background: Recent progress in genomic profiling of small cell lung cancer (SCLC) has demonstrated that a high proportion of SCLC harbor mutations in cell cycle-related genes and RICTOR amplification. With the recent introduction of cell-cycle altering small molecules, AZD1775 (WEE1 inhibitor), AZD2811 (aurora kinase B inhibitor) and mTOR1/2 inhibitor (AZD2014), biomarker-driven umbrella study is being conducted in relapsed SCLC. Methods: This is a phase II umbrella trial study with multiple monotherapy arms in resistant SCLC who has failed prior platinum-based chemotherapy and known genomic profile from pre-designed screening study of SUKSES-S (Small cell lung cancer Umbrella Korea StudiES, NCT02688894). Patients with MYC family amplification or co-alteration in CDKN2A and TP53 were allocated to SUKSES-C (AZD1775 arm, NCT02593019); RICTOR amplification to SUKSES-D (AZD2014 arm, NCT03106155). Otherwise, patients were randomly assigned to non-biomarker specific arms, SUKSES-N1 (AZD1775 arm, NCT02593019) or SUKSES-N3 (AZD2811 arm, NCT03366675). Each cohort was designed as Simon 2-stage scheme. Results: Patients allocated to SUKSES-C (n = 7) & N1 (n = 24) showed no objective response rate and stable disease was observed in 3 patients (42.9%) and 6 patients (25.0%), respectively. The median progression-free survival (PFS) was 1.28 months (95% confidence interval [CI] 1.18–not available [NA]) and 1.21 months (95%CI 1.15-2.33), respectively. SUKSES-D (n = 4) showed no objective response as well as no stable disease with PFS of 1.25 months (95% CI 0.98-NA). SUKSES-N3 (n = 15) showed no objective response with 5 stable disease (33.3%) and PFS of 1.61 months (95%CI 1.18-NA). For the safety record, adverse events (AEs) grade $\geq 3$ were observed as follows: SUKSES-C & -N1 (n = 1, 3.2%), -D (n = 3, 75.0%), -N3 (n = 9, 60%). Notably, neutropenia (grade $\geq 3$) was frequently observed (n = 8, 53.3%) in AZD2811 arm including a case of septic shock. Conclusions: SUKSES is the first biomarker-driven umbrella study with the largest cohort of genomic profile pre-screened in resistant SCLC patients (n = 275). However, it does not support further development of the current regimens of AZD1775, AZD2811, AZD2014. Altered administration schedule or combination regimen is under development. Clinical trial information: NCT02593019, NCT03106155, NCT03366675.
A randomized phase II study of tremelimumab and durvalumab with or without radiation for patients with relapsed small cell lung cancer (SCLC).

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**Background:** The combination of PD-1 and CTLA-4 inhibition has demonstrated activity in the second line therapy setting for SCLC. Radiotherapy enhanced the effectiveness of immunotherapy in NSCLC. We conducted this signal finding study to assess the efficacy of combined ICI with or without radiation in relapsed SCLC. **Methods:** Patients with relapsed SCLC who have received not more than 2 lines of therapy were enrolled and randomized to either Arm A: [Tremelimumab (T) 1500mg/durvalumab (D) 75mg i.v. every 4 weeks without SBRT] or Arm B: T/D with immune sensitizing SBRT to one selected tumor site (9 Gy x 3 fractions). Treatment continued until progression or maximum of 2 years. Paired tumor biopsies and serial samples of peripheral blood were employed for correlative endpoints (changes in intratumoral and circulating lymphocyte repertoire and immune cytokines). The study was designed to show a promising efficacy signal in either Arm with a hypothesized median PFS of 7 months (10 patients give 87% power at 1-sided alpha of 0.1). **Results:** Study randomized 17 patients to Arm A (8 patients) or B (9 patients); median age of 70 yrs; females 41.2%; White, 70%, Black 17.6%. Best response in 14 overall evaluable patients was PD in 9 (64.3%), PR in 2 (14%) and SD in 3 (21.4%); median PFS of 2.76 months and OS of 4.47 months. There was no significant difference in efficacy between Arms A and B but a trend of improved PFS and OS with T/D plus SBRT (see table): Median PFS of 2.1 vs. 3.3 months [HR: 2.44 (0.75-7.93); p = 0.122] and median OS of 2.6 vs. 5.7 months [HR: 1.50 (0.45-4.99); p = 0.5068]. Observed grade ≥ 3 adverse events were: Cytopenia (4), Dyspnea (1), and endocrine disorders (3) in Arm A; diarrhea (3) and cytopenias (1) in Arm B. There was an increase in circulating CD8(+) lymphocytes on treatment versus baseline in patients with objective tumor response. **Conclusions:** The study did not show sufficient signal of efficacy for ICI with or without SBRT in relapsed SCLC. Detailed result of the biomarker analysis will be available at the meeting. Clinical trial information: NCT02701400.
Ph1/2 study of Rova-T in combination with nivolumab (Nivo) ± ipilimumab (Ipi) for patients (pts) with 2L+ extensive-stage (ED) SCLC.

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Background: Rovalpituzumab tesirine (Rova-T™) is an antibody-drug conjugate targeting DLL3, a Notch ligand expressed in SCLC but not normal tissue. Nivo ± Ipi has activity in 2L+ SCLC. Preliminary data suggest Rova-T may result in immunogenic cell death, complementing effects of Nivo ± Ipi. Methods: Eligibility: DLL3 expression (DLT phase only), progression after ≥1 line of therapy including a platinum-based regimen; ECOG 0-1; no prior immunotherapy. All pts received 0.3 mg/kg Rova-T IV on Day 1 of two 6-wk cycles. Cohort 1 (C1) also received two 3-wk cycles of 360 mg Nivo beginning on wk 4. Cohort 2 (C2) received four 3-wk cycles of 1 mg/kg Nivo and 1 mg/kg Ipi beginning on wk 4. Both cohorts then received 480 mg Nivo q4wks until PD. Primary objective: safety. Secondary: antitumor activity by RECISTv1.1, OS. Exploratory: PK. Results: As of Sep 7, 2018, 30 pts were dosed in C1 and 12 in C2. 55% were DLL3 high (>75% DLL3 expression). 28 (67%) completed 2 planned cycles of Rova-T. 4 pts (1 in C1, 3 in C2) experienced DLTs including rash (3), pneumonitis (1) and colitis (1). C1 completed recruitment, and C2 enrollment was stopped after DLT evaluation phase. Preliminary PK showed Nivo ± Ipi had no substantial effect on Rova-T exposure. Clinical trial information: NCT03026166. Conclusions: Despite activity in 2L+ ED-SCLC, Rova-T with Nivo/Ipi is not appropriate due to DLTs. Rova-T/Nivo demonstrated some durable responses; however, the safety data suggest that optimization of dose and schedule is warranted. NCT03026166.

Randomized phase 2 study of maintenance pemetrexed (Pem) versus observation (Obs) for patients (pts) with malignant pleural mesothelioma (MPM) without progression after first-line chemotherapy: Cancer and Leukemia Group B (CALGB) 30901 (Alliance).

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Background: Standard front-line chemotherapy for advanced MPM is (Pem and a platinum; optimal treatment duration is unknown. We performed a randomized phase 2 trial (NCT01085630) to determine if continuation of single-agent Pem after 4-6 cycles of Pem-platinum would improve progression-free survival (PFS).

Methods: Eligible pts had histologically confirmed unresectable MPM, and performance status (PS) 0-1. Pts with at least stable disease following 4-6 cycles of Pem-platinum were stratified by first-line regimen (cis- or carboplatin) and histology (epithelioid versus other) and randomized 1:1 to Obs or continuation of Pem until progression. The primary endpoint was PFS. We assumed that Obs produced a median (m) PFS of 3 months (mo) and Pem would yield a 100% improvement in mPFS to 6 mo; 60 eligible pts (30 per arm) were to be randomized. Results: 72 pts from 30 sites registered 12/10-6/16. The study closed early due to slow accrual once 53 pts were randomized; 49 eligible pts (22 Obs, 27 Pem) are included in the efficacy analysis. Pt characteristics (Obs/Pem): age; median (range) 70 (39-85)/70 (52-87); male 68%/78%; PS 0 27%/33%; epithelioid histology 77%/70%; first-line cisplatin 27%/26%. A median of 4 cycles of Pem (range 1-33) was delivered; 22% of pts required dose modification. mPFS was 3 mo on Obs and 3.4 mo on Pem (hazard ratio (HR) 0.99; 95% CI: 0.51-1.90; p=0.9733). Median overall survival (mOS) was 11.8 mo for Obs, and 16.3 mo for Pem (HR 0.86; 95% CI 0.44-1.71; p=0.6737). Toxicities ≥ grade 3 on Pem included anemia 8%, lymphopenia 8%, neutropenia 4%, and fatigue 4%; there were no grade 5 toxicities. A higher baseline level of serum mesothelin related peptide (SMRP) was associated with worse PFS (HR 1.861, p=0.049). Baseline osteopontin did not significantly affect PFS (p=0.3630). Conclusions: Although it was well tolerated, maintenance Pem following initial Pem/platinum doublet chemotherapy does not improve PFS in MPM patients. High baseline SMRP was associated with shorter PFS. Support: U10CA180821, U10CA180882; https://acknowledgments.alliancefound.org. Clinical trial information: NCT01085630.
A feasibility study of induction pemetrexed plus cisplatin followed by pleurectomy/decortication for malignant pleural mesothelioma (Japan Mesothelioma Interest Group 1101 Trial).

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Background: Although pleurectomy/decortication (P/D) has become a preferred surgical technique for malignant pleural mesothelioma (MPM), only a few prospective, multi-center clinical trials have been conducted. Here we present final results of a nationwide, prospective, multi-institutional study to evaluate the feasibility of induction chemotherapy followed by P/D.

Methods: Eligibility criteria: a histologically confirmed diagnosis of MPM; clinical T1–3, N0–2, M0 disease; no prior treatment for the disease; age between 20 and 75 years; ECOG performance status of 0 or 1; and written informed consent. Treatment methods: Induction chemotherapy of pemetrexed 500 mg/m² plus cisplatin 75 mg/m² for 3 cycles, followed by P/D. Intraoperative conversion from P/D to extrapleural pneumonectomy (EPP) was permitted. Pulmonary function tests were performed at 3, 6, 12, 24, and 36 months after surgery. Primary endpoint was macroscopic complete resection (MCR) rate regardless of the surgical technique.

Results: Of 24 patients enrolled, 20 patients were eligible: median age 66 (48–74); M/F: 17/3, Clinical stage I/II/III: 8/9/3; Histology epi/sar/bi: 19/1/0. Two discontinued protocol before surgery due to deteriorated FEV1 or adverse effect (AE) of chemotherapy, and the remaining 18 patients completed surgery with MCR: P/D in 15 patients and EPP in 3. The trial met the primary endpoint with MCR rate of 90% (18/20). There was no treatment-related 30- and 90-day mortality. There were two cases of chemotherapy-related grade 4 AEs, but no surgery-related grade 4 AE occurred. The overall survival rates at 1 and 2 years and median survival time (MST) after registration were 95.0% (95% CI, 69.5 to 99.3), 70.0% (45.1 to 85.3), and 41.4 months (19.7 to NA), respectively. The progression-free survival rates at 1 and 2 years and MST after registration were 84.7% (60.0 to 94.8), 42.4% (20.5 to 62.7), and 22.9 months (12.7 to 28.4), respectively. Recurrence occurred in 17 patients, and initial relapse sites were local in 17 (100%) and distal in 6 (35.3%). The best values of FVC and FEV1 during postoperative period were 78.0% and 82.5% of preoperative values, respectively. Conclusions: Induction chemotherapy plus P/D yielded a MST over 40 months with acceptable risks. Postoperative pulmonary function was approximately 80% of preoperative value. Clinical trial information: UMIN000009092.
Refining the role of adjuvant chemotherapy in stage IB and IIA NSCLC.

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Background: The role of adjuvant chemotherapy (AC) in stage IB (pT2aN0) and IIA (pT2bN0) non-small cell lung cancer (NSCLC) is currently unclear. Existing guideline recommendations are inconsistent, ranging from all tumors >4 cm, to any patient with “high-risk features” (visceral pleural invasion (VPI), lymphovascular invasion (LVI), high grade, or sublobar resection). We used the National Cancer Data Base (NCDB) to clarify the role of AC in pT2N0 patients. Methods: The NCDB was queried for treatment-naïve, post-R0 resection, pT2N0 (AJCC 8th edition) NSCLC patients between 2010 & 2014. Patients treated with single-agent AC were excluded. Survival was calculated from 30 days after surgery to minimize immortal time bias. Multivariable Cox proportional hazards regression was used to estimate the association between AC and survival across tumor sizes (T2a: 3-4 cm and T2b: 4-5 cm to reflect guideline stratifications) and risk features. Results: Of the 10,127 patients identified, 1,856 (18%) received multi-agent AC. AC patients tended to be younger (median age 64 vs 70 yrs, p<0.001), privately insured (40% vs 24%, p<0.001), treated at a non-academic center (71% vs 66%, p<0.001), and comorbidities-free (53% vs 48%, p<0.001). In T2a patients (N=6,699), AC was not significantly associated with a mortality reduction, regardless of the presence of any high-risk features. In T2b patients (N=3,428), AC (N=931, 27%) was associated with a lower mortality (HR 0.77, 95% CI 0.65-0.9, p=0.001). However, in the absence of any high-risk features (N=1414, 41% of the 4-5 cm cohort), AC was not significantly associated with survival benefit (Table). Conclusions: The presence of high-risk features does not appear to support the guideline recommendations regarding the use of AC in stage IB patients with 3-4 cm tumors. On the other hand, the benefit of AC for 4-5 cm tumors may be limited to patients with at least one high-risk feature.

<table>
<thead>
<tr>
<th>Feature</th>
<th>Total N</th>
<th>AC N (%)</th>
<th>Mortality Hazard</th>
<th>P</th>
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<td>0.57</td>
<td>0.38-0.86</td>
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<td>128 (32)</td>
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<td>0.25-0.68</td>
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<td>High grade</td>
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<td>0.61</td>
<td>0.48-0.77</td>
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<tr>
<td>Sublobar surgery</td>
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<td>0.69</td>
<td>0.33-1.45</td>
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<tr>
<td>0/4 features</td>
<td>1414</td>
<td>313 (22)</td>
<td>1.12</td>
<td>0.85-1.49</td>
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Phase II, prospective single-arm study of adjuvant pembrolizumab in N2 positive non-small cell lung cancer (NSCLC) treated with neoadjuvant concurrent chemoradiotherapy followed by curative resection: Preliminary results.

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Background: The standard treatment option for stage IIIA-N2 subgroup is still under discussion with controversies. We hypothesize that immune checkpoint inhibitor consolidation therapy could have an additional role in prolongation of the disease-free survival (DFS) for stage IIIA-N2 NSCLC treated with trilodalities therapy. Methods: This is a phase 2 study evaluating the clinical efficacy of pembrolizumab treatment after CCRT with curative resection in stage IIIA-N2 NSCLC pts. Pathologically confirmed pts were treated with five cycles of CCRT, weekly paclitaxel (50mg/m²) and cisplatin (25mg/m²) combined with radiotherapy (total of 44Gy over 22 fractions) followed by curative resection. Adjuvant Pembrolizumab (200mg fixed dose) is applied every three weeks up to 2 years or until disease recurrence. The primary objective is disease-free survival of more than 20 months. The first patient was recruited in October 2017, and the data for this abstract was locked at 20th of January, 2019. Results: Total of 40 pts were screened, and 37 pts received treatment. Median age was 64 years (range 39-74), and twenty-three pts were male (62.2%). As a curative surgery, pts received lobectomy (n=34), bi-lobectomy (n=2), or pneumonectomy (n=1). Adenocarcinoma was predominant (n=27, 73.0%). After the neoadjuvant CCRT, down-staging were observed in nine pts (24.3%). The median follow-up duration was 10.6 months (range 3.1-17.2), and pts received a median of 11 cycles (range 1-22) of adjuvant pembrolizumab. DFS is not reached. Fourteen patients discontinued treatment due to disease progression (n=9), adverse events (n=4) and withdraw consent (n=1). There was a case of grade 4 pneumonitis and a case of grade 3 autoimmune hepatitis which lead to discontinuation of the treatment. Otherwise, grade 1-2 hypothyroidism (n=6), pneumonitis (n=5), skin rash (n=3) were observed. Patients with sever immune-related adverse event showed a significantly high percentage of Ki-67+ cells among CD8 T-cells in peripheral blood. Conclusions: This study is the first study to demonstrate the feasibility of adjuvant pembrolizumab monotherapy in stage IIIA-N2 patients. Updated and detail clinical and exploratory biomarker outcome will be presented at the annual meeting. Clinical trial information: NCT03053856.

The tumor microenvironment in EGFR-driven loco-regional lung adenocarcinoma can predict higher risk of recurrence.

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Background: The role of EGFR tyrosine kinase inhibitors (TKIs) as adjuvant therapy in EGFR-mutated NSCLC is still controversial. Identifying biomarkers associated with increased risk of recurrence may help stratify pts & guide adjuvant therapy. We hypothesized that tumor immune microenvironment (TME) alterations could predict disease-free survival (DFS) in these pts. Methods: The Cancer Genome Atlas (TCGA) lung Adenocarcinoma (LUAD) data at Genomic Data Common (GDC) was accessed for pt phenotype, updated outcome & normalized gene expression profile (RNA seq). Immune landscape data was obtained from PANCAN. We chose to focus on 54 key TME genes, identified from a commercially available immune report card from OmniSeq (Inc.). Pts were divided via K-mean clustering. Group comparison was done via Likelihood Ratio (LR, categorical), Mann Whitney (continuous), log-rank (survival) & Cox regression (outcome). Bonferroni correction was used to correct for multiple comparisons. Results: 877 pts with LUAD were identified, 32 of whom had EGFR mutations and were at stages I to III. The mutations were mostly in the TK domain, involving exons 18 (12%), 19 (27%), 20 (6%), & 21 (33%). Only 3% harbored the T790M mutation. None of the pts received adjuvant TKI. Analysis of the impact of individual genes on DFS yielded a group of 8 genes whose high expression was associated with improved DFS: IL10 (HR 0.58, p 0.029), BTLA (HR 0.66, p 0.07), CD8A (HR 0.6252, p 0.099), CD39 (HR 0.454, p 0.037), CCR2 (HR 0.729, p 0.039), CSF1R (HR 0.70, p 0.087), ICOS (HR 0.66, p 0.062), & CD4 (HR 0.67, p 0.059). K-mean clustering of the pts using these genes demonstrated 2 groups with distinct immune profiles. Group 1 was characterized by higher leukocyte and stromal fractions, lymphocyte infiltration score, macrophage regulation, TGF-β response, & T cell richness with less proliferation, pointing towards a more “inflamed” phenotype. Significant difference between the two groups in the immune subtypes was found (LR 10, p = 0.039). 90% of pts in the inflamed group had tumors with IFN-γ dominant, inflammatory, and TGF-β dominant subtypes, while 45% of the “non-inflamed” group had lymphocyte depleted & wound healing signatures. DFS was significantly longer in the inflamed group (median DFS 1480 vs 772 days, p = 0.002). Conclusions: In pts with resected EGFR-mutated LUAD, an inflamed TME is associated with prolonged DFS. Identifying these pts may help select those who would benefit from adjuvant therapy.
Ultrasensitive DNA hypermethylation detection using plasma for early detection of NSCLC: A validation study in Chinese patients.

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Background: Our previous study revealed that high diagnostic accuracy for early stage lung cancer could be obtained in plasma samples with ultrasensitive DNA hypermethylation detection methods called MOB-qMSP. In this study, we sought to validate and also improve the diagnostic accuracy of lung cancer screening with modified MOB-qMSP approach in Chinese patients. We also develop a lung cancer specific gene panel for Chinese patients. Methods: We included patients with small lung nodules (less than 3cm in diameter) on CT scan screening and conducted a case-control study. Cases (n=138) had pathological confirmation of Non-Small Cell Lung Cancer (NSCLC) lesions staged IA or IB. Controls (n=65) had pathological confirmation of non-cancerous lesions. Plasma samples were obtained pre-operatively. Promoter methylation of eight lung cancer-specific genes (CDO1, TAC1, SOX17, HOXA7, HOXA9, GATA4, GATA5 and PAX5B) was detected using nanoparticle-based DNA extraction (MOB) followed by qMSP. Results: DNA methylation was detected in plasma more frequently in cases compared to controls (p<0.001) for 5 out of 8 genes. The sensitivity and specificity for lung cancer diagnosis using the best individual gene was 64-85% and 55-79% respectively. A three-gene combination of the best individual genes has sensitivity and specificity of 92% and 78%. Area under the Receiver Operating Curve (AUC) for this panel was 0.90, 95% CI (0.86-0.96). Cross validation combining gene methylation with clinical information correctly predicted lung cancer in 86% of subjects using plasma detection. Furthermore, we analyzed the sensitivity and specificity of the same three-gene combination in cases subgroups regarding the tumor size and the results are as follow: in subgroup with tumor size of 2-3cm, the sensitivity and specificity were 94% and 87%, and the AUC was 0.96, 95% CI (0.91-0.99); in subgroup with tumor size of 1-2 cm, the sensitivity and specificity were 92% and 80%, and the AUC was 0.90, 95% CI (0.84-0.96); in subgroup with tumor size less than 1cm, the sensitivity and specificity decreased to 66% and 87%, and the AUC was 0.77, 95% CI (0.64-0.88). Conclusions: This study validates our previous study but in Chinese patients that it is possible to obtain high diagnostic accuracy for early stage NSCLC using a panel of methylated promoter genes in plasma samples with ultrasensitive MOB-qMSP, especially in patients with tumor of larger size. These epigenetic biomarkers could potentially be used to identify patients with high risk of lung cancer development.

S1206: A dose-finding study followed by a phase II randomized placebo-controlled trial of chemoradiotherapy (CRT) with or without veliparib in stage III non-small cell lung cancer (NSCLC).

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Background: Veliparib (V), a PARP inhibitor, may potentiate the antitumor effect of CRT in NSCLC. Methods: Eligibility included newly diagnosed unresectable stage III NSCLC. Patients were randomized to receive concurrent CRT with weekly carboplatin (AUC 2) and paclitaxel (45 mg/m²) with V at 120 mg or placebo (P) twice daily during CRT followed by 2 cycles (every 21 days) of consolidation carboplatin (AUC 6), paclitaxel (200 mg/m²) with V at 80 mg or P (per randomized arm) orally on days 1-7 of each cycle. Progression-free survival (PFS) was the primary endpoint. The accrual goal was 132 patients. Results: The dose-finding study results were previously presented (ASCO 2016;A8537). V 120 mg twice daily was the recommended phase II dose. A total of 31 eligible and evaluable patients were enrolled in the phase II randomized trial: 17 on V and 13 on P (1 patient in the V arm withdrew prior to starting any treatment, thus was not evaluable). The study was closed to accrual early due to the positive results from the PACIFIC trial that changed standard practice. Median follow-up among alive patients was 16 months. During CRT, the following grade (G) 3-4 adverse events (AE) were seen with V vs P: any G3 AE (6 vs 6), any G4 AE (2 vs 3), G3 pneumonitis (0 vs 1), G3 esophagitis (1 vs 1), G3 oral mucositis (1 vs 0), G3 anorexia (1 vs 1), G3 hyponatremia (0 vs 3), G3 anemia (1 vs 0), G3 neutropenia (3 vs 1), G3 thrombocytopenia (1 vs 0), G4 hypoglycemia (0 vs 1). Also, 2 patients per arm had G4 lymphopenia. During consolidation (11 evaluable patients with V; 10 with P), G3 anemia (1 vs 0), G3 anorexia (1 vs 0), G3 weight loss (0 vs 1), G3 dehydration (1 vs 0), G3 dysphagia (2 vs 0), G3 fatigue (1 vs 0), G3 hypomagnesemia (0 vs 1), G3 nausea (1 vs 0), G4 hyperglycemia (0 vs 1), G3-4 neutropenia (3 vs 0), G3 thrombocytopenia (1 vs 0), G3-4 lymphopenia (2 vs 1); a G5 pneumonitis occurred in the P arm. Response rates were 56% (95% CI, 31-78%) and 69% (95% CI, 38-91%) on the V and P arms, respectively. PFS at 1 year was 47% (95% CI, 23-68%) with V and 46% (95% CI, 19-70%) with P. Overall survival (OS) at 1 year was 89% (95% CI, 61%-97%) with V and 54% (95% CI, 25%-76%) with P. Adding the 6 patients treated at 120 mg in the phase I part, 1-year with V was 91% (95% CI, 69%-98%). Conclusions: V in combination with CRT was tolerable with expected toxicities that relate to the backbone regimen. In the small number of randomized patients there was a suggestion of promising survival with V that may provide rationale for future trials of PARP inhibitors with CRT. Clinical trial information: NCT01386385.
Neoadjuvant nivolumab in resectable non-small cell lung cancer: Extended follow-up and molecular markers of response.

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Background: Improved therapy is needed for patients (pts) with early-stage non-small cell lung cancer (NSCLC), as the majority relapse after curative resection. Our group reported the first trial of neoadjuvant PD-1 blockade in resectable NSCLC, finding therapy to be safe and feasible. Here we report extended clinical follow-up and long-term molecular response data from this trial.

Methods: IV nivolumab 3 mg/kg was given every 2 weeks for 2 doses prior to surgery in 20 pts with resectable NSCLC at Johns Hopkins and MSKCC. Blood for correlative studies was taken prior to each dose of nivolumab, prior to surgery, 2-4 weeks post-surgery, and during long-term follow up. In a subgroup of pts, longitudinal molecular data was assessed in peripheral blood for circulating tumor DNA (ctDNA) and dynamics of tumor-infiltrating T-cell clonotypes.

Results: At median follow up of 30 months (m), 15 of 20 pts are disease-free and alive. Two pts have died (one from relapsed disease). Median recurrence free survival (RFS) has not been reached. The 24m RFS rate is 69% (95% CI: 51-93). Thus far, presence of ctDNA at diagnosis and major pathologic response (MPR - ≥10% viable tumor in resected specimen) do not associate with RFS. One long-term immune-related adverse event has occurred (skin, G3). All pts who on pathologic review had ≥30% reduction in viable tumor in response to nivolumab demonstrated clearance of detectable ctDNA from blood prior to surgery. Pts with MPR experienced expansion of neoantigen-specific T-cells in peripheral blood. In one patient with ongoing disease free status, expansion of tumor-associated T-cells has persisted in peripheral blood beyond 15m from surgery. By contrast, in a patient who had detectable peri-operative ctDNA and 75% residual disease at surgery, minimal T-cell expansion was observed in peripheral blood, with a decreasing frequency of expanded T-cell clones over time that correlated with eventual cancer relapse. Conclusions: Long-term follow up reinforces the safety of neoadjuvant nivolumab in resectable NSCLC. Analysis of ctDNA and peripheral T-cell expansion in responders compared with non-responders suggests potential biomarkers for response and surveillance. While RFS data is encouraging, phase 3 trials are ongoing to evaluate efficacy of PD-(L)1 blockade in early-stage NSCLC. Clinical trial information: NCT02259621.
Oncologic outcomes of segmentectomy versus lobectomy for radiologically aggressive small-sized lung cancer.

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**Background:** Despite increasing evidence of favorable outcomes after segmentectomy for indolent lung cancer, such as ground glass opacity-dominant tumors, the adaptation of segmentectomy for radiologically aggressive lung cancer remains controversial. We attempted to elucidate oncologic outcomes after segmentectomy for radiologically aggressive lung cancer. **Methods:** Data from a multicenter database of 1353 patients with completely resected clinical Stage IA1–IA2 lung cancer at three institutions were retrospectively analyzed to identify radiologically aggressive lung cancer and compare outcomes of segmentectomy versus lobectomy in patients with radiologically aggressive lung cancer using propensity score matching. **Results:** Multivariable analysis showed that consolidation to maximum tumor (C/T) ratio on preoperative high-resolution computed tomography ($P = 0.037$) and maximum standardized uptake value (SUVmax) on 18-fluorodeoxyglucose positron emission tomography/computed tomography ($P = 0.029$) were independent predictors of recurrence-free survival (RFS). The criteria for radiologically aggressive lung cancer were determined as C/T ratio $\geq 0.8$ or SUVmax $\geq 2.5$, for which 522 patients were identified. RFS and overall survival (OS) were significantly worse in patients with aggressive lung cancer (5-year RFS, 83.3%; 5-year OS, 89.4%) than in those without the same (5-year RFS, 97.0%; $P < 0.0001$; 5-year OS, 97.3%; $P < 0.0001$). Among patients with aggressive lung cancer, no significant difference in RFS and OS was found between those undergoing lobectomy (n = 392) (5-year RFS, 81.3%; 5-year OS, 88.3%) and segmentectomy (n = 130) (5-year RFS, 90.0%; $P = 0.33$; 5-year OS, 92.3%; $P = 0.76$). Among the 111 pairs propensity matched for age, sex, smoking history, solid tumor size, C/T ratio, SUVmax, tumor location, clinical stage, and histology, similar RFS and OS were found between those undergoing lobectomy (5-year RFS, 83.3%; 5-year OS, 88.3%) and segmentectomy (5-year RFS, 90.9%; $P = 0.92$; 5-year OS, 94.5%). **Conclusions:** For radiologically aggressive small-sized lung cancer, oncologic outcomes of segmentectomy were equivalent to those of lobectomy.
Three-year overall survival update from the PACIFIC trial.

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Background: In the phase 3 PACIFIC study of patients with unresectable, Stage III NSCLC without progression after chemoradiotherapy (CRT), durvalumab demonstrated significant improvements versus placebo in the primary endpoints of progression-free survival (HR, 0.52; 95% CI, 0.42–0.65; P = 0.0001) and overall survival (OS; HR, 0.68; 95% CI, 0.53–0.87; P = 0.00251). Safety was similar and durvalumab had no detrimental effect on patient-reported outcomes. Here, we report 3-year OS rates for all patients randomized in the PACIFIC study. Methods: Patients with WHO PS 0/1 (any tumor PD-L1 status) who received 2 cycles of platinum-based CRT were randomized (2:1), 1–42 days following CRT, to receive durvalumab 10 mg/kg intravenously every 2 weeks or placebo, up to 12 months, and stratified by age, sex, and smoking history. OS was analyzed using a stratified log-rank test in the ITT population. Medians and OS rates at 12, 24 and 36 months were estimated by Kaplan-Meier method. In total, 713 patients were randomized of whom 709 received treatment (durvalumab, n = 473; placebo, n = 236). The last patient had completed the protocol-defined 12 months of study treatment in May 2017. As of January 31, 2019 (data cutoff), 48.2% of patients had died (44.1% and 56.5% in the durvalumab and placebo groups, respectively). The median duration of follow-up was 33.3 months (range, 0.2–51.3). Updated OS remained consistent with that previously reported (stratified HR 0.69, 95% CI, 0.55–0.86), with the median not reached in the durvalumab group and 29.1 months (95% CI, 22.1–35.1) with placebo. The 12-, 24- and 36-month OS rates with durvalumab and placebo were 83.1% versus 74.6%, 66.3% versus 55.3%, and 57.0% versus 43.5%, respectively. After discontinuation, 43.3% and 57.8% in the durvalumab and placebo groups, respectively, received subsequent anticancer therapy (9.7% and 26.6% subsequently received immunotherapy). OS subgroup results will be presented. Conclusions: Updated OS data from PACIFIC, including 3-year survival rates, underscore the long-term clinical benefit with durvalumab following CRT and further establish the PACIFIC regimen as the standard of care in this population. Clinical trial information: NCT02125461.
Randomized phase II trial of uracil/tegafur and cisplatin versus pemetrexed and cisplatin with concurrent thoracic radiotherapy for locally advanced unresectable stage III non-squamous non-small-cell lung cancer: NJLCG1001.

Kana Watanabe, Yukihiro Toi, Atsushi Nakamura, Tatsuro Fukushima, Ryosuke Chiba, Masachika Akiyama, Jun Sakakibara-Konishi, Hisashi Tanaka, Naruo Yoshimura, Eisaku Miyachi, Taku Nakagawa, Ryotaro Igsu, Hiroyuki Minemura, Yoshiaki Mori, Keisuke Fujimoto, Haruo Matsushita, Fumiaki Takahashi, Akira Inoue, Shunichi Sugawara, Makoto Maenomoe, Department of Respiratory Medicine, Miyagi Cancer Center, Natori, Japan; Department of Pulmonary Medicine, Sendai Kousei Hospital, Sendai, Japan; Iwate Medical University, Morioka, Iwate, Japan; Iwate Medical University Division of Pulmonary Medicine, Allergy, and Rheumatology, Morioka, Japan; Hokkaido University Hospital, Sapporo, Japan; Department of Respiratory Medicine, Hiroshi University Graduate School of Medicine, Hirosaki, Japan; Department of Respiratory Medicine, Tohoku Medical and Pharmaceutical University, Sendai, Japan; Tohoku University, Sendai, Japan; Department of Thoracic Surgery, Omagari Kosei Medical Center, Daisen, Japan; Osaki Citizen Hospital, Osaki, Japan; Department of Pulmonary Medicine, Fukushima Medical University, Fukushima, Japan; Iwate Prefectural Central Hospital, Morioka, Japan; Miyagi Cancer Center, Natori, Japan; Department of Radiation Oncology, Tohoku University Graduate School of Medicine, Sendai, Japan; Department of Information Science, Iwate Medical University, Iwate, Japan; Department of Palliative Medicine, Tohoku University School of Medicine, Sendai, Japan; Iwate Medical University, Morioka, Japan

Background: It is unknown which regimen is the best in concurrent chemoradiotherapy (CCRT) of locally advanced non-squamous non-small cell lung cancer (NSCLC). Our previous randomized phase II study, NJLCG0601, showed that chemoradiotherapy with uracil/tegafur (UFT) and cisplatin achieved promising efficacy with acceptable toxicities. In this trial, this regimen was compared to a regimen with pemetrexed and cisplatin for stage III non-squamous NSCLC. Methods: Patients with inoperable stage III non-squamous NSCLC were randomized to UFT 400 mg/m² on days 1–14 and 29–42, and cisplatin 80 mg/m² on days 8 and 36 (UP), or pemetrexed 500 mg/m² and cisplatin 75 mg/m² on days 1, 22, and 43 (PP). Involved-field radiotherapy (IFRT) was administered from day 1 to a total dose of 66 Gy radiotherapy in 33 fractions. Consolidation chemotherapy after CCRT was not planned for this study. The primary endpoint was 2-year overall survival (OS), with expected rates of 55% and a lower limit of 35% (alpha 0.05, beta 0.2). Secondary endpoints were the objective response rate (ORR), progression-free survival (PFS), OS, and toxicity profile. Results: From November 2010 to June 2017, 86 patients were enrolled from 11 institutions. Of the 85 eligible patients, the rate of 2-year OS was 78.6% (95% CI: 62.8–88.3%) in the UP arm and 85.5% (95% CI: 70.5–93.2%) in the PP arm. The ORR was 76.7% in the UP arm and 81.0% in the PP arm. With a median follow-up of 54 months, median PFS and OS were 12.3 and 64.2 months in the UP arm, and 26.2 months and not reached in the PP arm, respectively. Grade 3/4 febrile neutropenia was more frequent in the UP arm than in the PP arm (14.0%, 2.0%, respectively). Grade 3/4 pneumonitis occurred in 7.0% and 4.8% of patients in UP and PP arms, respectively. Conclusions: Both regimens with IFRT achieved the expected 2-year survival rate. PP had more favorable results than UP in terms of OS and PFS. We selected the PP arm for the next step.
Identifying actionable somatic mutations in lung cancer using cell-free DNA from bronchial washing fluid.

Xin Zhang, Xinyu Zhang, Weiran Wang, Jian'An Huang, Min Zhou, Chun Li, Maosong Ye, Yancheng Zhao, Yuhua Gong, Yaping Xu, Qin Hu, Yanfang Guan, Ling Yang, Xuefeng Xia, Hua Zhang, Tao Ren, Qian Shen, Kai Wang, YY Hou, Xin Yi; Zhongshan Hospital Fudan University, Shanghai, China; Zhongshan Hospital, Fudan University, Shanghai, China; Geneplus-Beijing institute, Xi'an Jiaotong University, Beijing, China; The First Affiliated Hospital of Soochow University, Suzhou, China; Shanghai Jiaotong University, Shanghai, China; Department of Pulmonary Medicine, Zhongshan Hospital, Fudan University, Shanghai, China; Geneplus-Beijing Institute, Beijing, China; Department of Pathology, Zhongshan Hospital Fudan University, Shanghai, China; Geneplus-Beijing, Beijing, China; Zhengzhou Central Hospital, Zhengzhou University, Zhengzhou, China; Shanghai Sixth People's Hospital, Shanghai, China; First Affiliated Hospital of Zhejiang University, Hangzhou, China; Second Affiliated Hospital of Zhejiang University, Hangzhou, China

Background: Bronchial washing is the most common technique for sampling the components of the alveolar space. Here, we evaluated the potential use of bronchial washing fluid (BWF) in liquid biopsy in lung cancer. Methods: This study enrolled 65 lung cancer patients. BWF (separated supernatant and precipitate) samples, peripheral blood lymphocytes (PBL) and formalin-fixed paraffin-embedded tissues were obtained and subjected to next-generation sequencing using a 1021-gene panel. Results: Mutations were identified in 58 (89.2%) of BWF precipitate (BWFp) samples and 64 (98.5%) of BWF supernatant (BWFs) samples, comparing with 61 (93.8%) of tumor tissues. In total, 461 somatic mutations were identified in tissues, of which 331 (71.8%) and 381 (82.6%) were detected in the matched BWFp and BWFs samples. In addition, there were 44.6% of patients carrying actionable variants identified in tissue DNA, including EGFR, ALK, ROS1, RET, etc. (Table). Similarly, there were 40.0% of BWFp samples and 44.6% of BWFs samples identified actionable variants. Moreover, tumor mutation burden (TMB) was also calculated. Nearly 9% of BWFp samples and 23% of BWFs samples were TMB-H (more than 9 mutations per megabase), compared with 20% of tissues. Significantly, the combined results of three types of samples showed that, 49.2% of patients carrying actionable variants and 24.6% of patients with TMB-H, which suggested more patients benefit from targeted therapy or immunotherapy. Conclusions: In summary, liquid biopsy using BWF showed high potential to identify actionable mutations and to calculate TMB grade of patients with lung cancer, which might be implemented and standardized into clinical use.

<table>
<thead>
<tr>
<th>Somatic Mutations</th>
<th>Actionable Variants</th>
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<tr>
<td>counts MEAN±SD</td>
<td>Total EGFR BRAF ROSI ALK RET fusion fusion counts</td>
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<tr>
<td>Tissue</td>
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<tr>
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<td>Combined</td>
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Updated survival date of phase I/II study of carboplatin plus nab-paclitaxel and concurrent radiotherapy for patients with locally advanced non-small cell lung cancer.

Atsushi Horiike, Yuko Kawano, Tomonari Sasaki, Hiroyuki Yamaguchi, Katsuya Hirano, Miyako Satouchi, Shinobu Hosokawa, Ryotaro Morinaga, Kazutoshi Komiya, Koji Inonue, Yuka Fujita, Ryo Toyozawa, Tomoki Kimura, Kosuke Takahashi, Kazuo Nishikawa, Junji Kishimoto, Yoichi Nakamishi, Isamu Okamoto; Department of Thoracic Medical Oncology, The Cancer Institute Hospital of Japanese Foundation for Cancer Research, Tokyo, Japan; Research Institute for Diseases of the Chest, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan; Department of Clinical Radiology, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan; Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan; Department of Respiratory Medicine, Hyogo Prefectural Amagasaki General Medical Center, Amagasaki, Japan; Hyogo Prefectural Hospital, Oita, Japan; Division of Hematology, Respiratory Medicine and Oncology, Department of Internal Medicine, Faculty of Medicine, Saga University, Saga, Japan; Department of Respiratory Medicine, Kitakyushu Municipal Medical Center, Kitakyushu, Japan; Department of Respiratory Medicine, National Hospital Organization Asahikawa Medical Center, Asahikawa, Japan; Department of Thoracic Oncology, National Kyushu Cancer Center, Fukuoka, Japan; Tosei General Hospital, Seto, Japan; Aichi Cancer Center Aichi Hospital, Okazaki, Japan; Oita University Hospital, Oita-Shi, Japan; Department of Research and Development of Next Generation Medicine, Kyushu University, Fukuoka, Japan

Background: Chemoradiation regimens of greater efficacy are needed for patients with locally advanced non–small cell lung cancer (NSCLC). Methods: Patients between 20 and 74 years of age with unresectable NSCLC of stage IIIA or IIIB and a performance status of 0 or 1 were eligible for the study. In the phase II part of the study, patients received weekly nab-paclitaxel at 50 mg/m² together with weekly carboplatin at an area under the curve (AUC) of 2 mg mL⁻¹ min and concurrent radiotherapy with 60 Gy in 30 fractions. This concurrent phase was followed by a consolidation phase consisting of two 3-week cycles of nab-paclitaxel plus carboplatin. The primary end point of the phase II part of the study was progression-free survival (PFS). Results: Between October 2014 and November 2016, 58 patients were enrolled at 14 institutions in Japan, with 56 of these individuals being evaluable for treatment efficacy and safety. At the median follow-up time of 26.0 months (range, 4.0 to 49.6 months), the median overall survival (OS) was not reached (95% confidence interval [CI], 25.3 months to not reached) and the 2-year OS rate was 66.1% (95% CI, 52.1% to 76.8%). The median PFS was 11.8 months (60% CI, 10.6 to 16.8 months; 95% CI, 8.2 to 21.0 months). The overall response rate was 76.8% (95% CI, 64.2% to 85.9%), and the disease control rate was 94.6% (95% CI, 85.4% to 98.2%). Subgroup analysis according to histology or age revealed no significant differences in median PFS or OS. Common toxicities of grade 3 or 4 in the concurrent phase included leukopenia (60.7%) and neutropenia (28.6%). Pneumonitis of grade 3 was observed in two patients during the study period. No treatment-related deaths occurred. Conclusions: Our results reveal encouraging feasibility and activity for concurrent chemoradiation with nab-paclitaxel at 50 mg/m² and carboplatin at an AUC of 2 mg mL⁻¹ min in patients with locally advanced NSCLC. Clinical trial information: UMIN000012719.
Alteration in tumor immune microenvironment after chemo-radiotherapy for locally advanced non-small cell lung cancer.

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Background: The consolidation treatment with durvalumab, an anti-PD-L1 antibody, after concurrent chemo-radiotherapy (CCRT) has become a new standard of care for locally advanced non-small cell lung cancer (LA-NSCLC). The rationale of the addition of anti-PD-L1 antibody is based on preclinical evidence suggesting that chemotherapy and radiotherapy may up-regulate PD-L1 expression on tumor cells. However, there has been reported no clinical evidence showing up-regulation of PD-L1 expression after CCRT.

Methods: LA-NSCLC patients with paired sufficient histologic specimens for immune-histochemical analysis of tumoral PD-L1 expression (tumor proportion score, TPS) and stromal CD8-positive tumor-infiltrating lymphocyte density (CD8+ density) before and after pre-operative treatment were eligible in this study. Twenty-three patients who underwent CCRT were reviewed in comparison with 18 patients who underwent chemotherapy.

Results: PD-L1 expression was significantly enhanced after CCRT (median TPS, 48 from 1; P<0.01), but not after chemotherapy (median TPS, 7.5 from 1; P=0.62). No significant correlation between baseline TPS and TPS after CCRT (P=0.119). Stromal CD8+ density was significantly increased after CCRT (median, 39 from 11; P<0.01) and after chemotherapy (median, 23 from 12; P<0.01). No significant correlation between baseline TPS and TPS after CCRT (P=0.378). Among CCRT cases, stromal CD8+ density after treatment was significantly higher in cases with higher pathologic response to CCRT (median, 55 versus 27; P<0.01), and higher stromal CD8+ density was a significant factor to predict a favorable survival after surgery (P=0.03 for recurrence-free survival; P=0.02 for overall survival).

Conclusions: PD-L1 expression was significantly upregulated after CCRT regardless of baseline PD-L1 status, which may provide a pathologic rationale for the use of anti-PD-L1 agent after CCRT to improve the prognosis. Stromal CD8+ density also increased after CCRT, which was correlated with pathologic response to CCRT and provided a significant prognostic impact.
Efficacy and safety of neoadjuvant PD-1 blockade with sintilimab in resectable squamous non-small cell lung cancer (sqNSCLC).

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Background: NSCLC patients who have potentially resectable disease often subsequently relapse after surgery. New therapy that prevents relapse after surgery is desperately needed. In this study, we tested the efficacy and safety of neoadjuvant sintilimab, an anti-PD-1 antibody, for patients with resectable sqNSCLC in China.

Methods: All patients had treatment-naive resectable sqNSCLC (stage IB-IIIA) that was confirmed by histopathology. Patients received two cycles of sintilimab (200 mg IV) on Day 1 and 22. Surgery was performed between Day 29-43. An enhanced PET/CT was obtained at baseline and seven days prior to surgery. Preliminary analysis of safety profile and efficacy was planned after at least 20 patients had received operation.

Results: As of Jan. 28, 2019, 22 patients (20 males and 2 females) with sqNSCLC received two doses of sintilimab followed by radical resection. The median age was 61.5 yr (range, 48 to 70). Six (27.3%) and four (18.2%) patients experienced neoadjuvant treatment emergent adverse events (TEAEs) and neoadjuvant treatment-related AEs (TRAEs), respectively. Most of the TEAEs and TRAEs were grade 1 or 2. Three patients achieved radiological partial response: an ORR of 13.6% based on RECIST 1.1. Ten patients (45.5%) achieved a major pathologic response (MPR, ≥10% viable tumor cells), including four (18.2%) had complete pathologic response (no viable tumor cell). There was a direct correlation between pathological response and decrease in the standardized uptake values (SUV) in the primary tumor. Among nine patients with > 30% decrease of SUV, eight had MPR, compared with no MRP response in the 11 patients with ≤30% decrease of SUV.

Conclusions: Neoadjuvant sintilimab for sqNSCLC patients was tolerable and the 45.5% MRP rate is encouraging. A decrease in SUV may be predictive of pathologic response after PD-1 therapy in sqNSCLC. Clinical trial information: ChiCTR-OIC-17013726.
T cell repertoire analysis of non-small cell lung cancer patients treated with neoadjuvant nivolumab alone or in combination with ipilimumab (NEOSTAR trial).

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Background: Neoadjuvant immune checkpoint inhibitors (ICIs) are being explored in resectable non-small cell lung cancer (NSCLC). Here, we studied the composition and changes in the T cell repertoire in a cohort of NSCLC patients (n = 44) treated with neoadjuvant nivolumab (N) alone or in combination with ipilimumab (NI) followed by surgery (NEOSTAR trial).

Methods: Sequencing of the variable CDR3β chain of the T cell receptor (TCR) involved in antigen binding was performed in pre-treatment and surgical tumors, matched adjacent uninvolved lung specimens, as well as paired longitudinal blood at baseline, prior to each dose of therapy, prior to surgery, and within 8 weeks post-surgery. T cell repertoire density, diversity, and clonality (reactivity) were evaluated in addition to tumor PD-L1 expression pre- and post-neoadjuvant treatment. Results: Median T cell diversity in the blood post-therapy was 3.3-fold higher in NI- compared to N-treated patients (40,993 [NI, n = 3] vs 12,177 [N, n = 4] unique TCR rearrangements, n.s.). However, median T cell clonality in the blood was 3.5-fold higher in N- than NI-treated patients post-therapy (0.093 [N, n = 4] vs 0.026 [NI, n = 3], n.s.). Median clonality was 3.8-fold higher in the tumor post-therapy in patients receiving NI than in those receiving N (0.076 [NI, n = 7] vs 0.020 [N, n = 5], n.s.). Interestingly, diversity in the blood at baseline and in the tumor post-therapy were positively correlated ([n = 7], r = 0.82; p = 0.023), which may reflect an influx of cells from the periphery following ICIs. Importantly, higher baseline T cell clonality in the blood was associated with a lower % of viable tumor at time of surgery in both treatment arms ([n = 7], r = -0.77; p = 0.04).

Conclusions: Our study is the first to assess the TCR repertoire in NSCLC patients treated with combination neoadjuvant NI and highlights potential mechanistic differences compared to N alone. Neoadjuvant NI is associated with higher clonality in tumors and lower clonality in blood post-therapy, suggesting increased T cell trafficking into the tumor. Finally, lower pre-treatment clonality in the periphery was correlated with higher % viable tumor post-neoadjuvant ICIs. Clinical trial information: NCT03158129.
Neutrophil-to-lymphocyte ratio and subsequent recurrence of non-small cell lung cancer patients in remission.

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Background: Baseline neutrophil-lymphocyte ratio (NLR), a surrogate marker for systemic inflammation and immunosuppression, is a well-established prognostic marker in non-small cell lung cancer (NSCLC). This study tests if interim NLR is prognostic in NSCLC patients in remission. Methods: This single-center, retrospective cohort study analyzed 131 NSCLC patients treated from 2010-2015 who achieved complete remission. Patient data included demographics, histologic subtypes, stage, and treatment type. NLR was calculated at baseline and from the first available blood sample during remission. Kaplan-Meier estimates of overall survival (OS) and time to recurrence were compared using the log-rank test for trend. Multivariable analysis was conducted using the Cox proportional hazards model. Results: Of 131 cases, 63 had subsequently recurred at the last follow up. Mean age was 64 ± 10 years. Histology: adenocarcinoma (60%), squamous cell (33%), and unspecified (7%). Ninety percent were smokers. Thirty-five percent had stage I, 24% had stage II, and 41% had stage III disease. Treatment modalities varied from surgery (28%), chemotherapy (2%), or radiation therapy (10%) alone, or combined (50%). The time from end of treatment, median (range), to the interim NLR was 9.2 months (2.2, 66.7). The baseline and interim median NLR were 2.6 (0.6, 34.0) and 3.1 (0.5, 20.5), respectively. The median follow-up duration was 44 months (5.9, 101). For the univariate analysis interim NLR was binned into tertiles. In multivariable analysis remission NLR remained strongly prognostic for OS (P = 0.001) as did patient’s age (P = 0.002), but not stage, race, sex, and baseline NLR. Conclusions: Our study found that interim NLR, obtained in remission, was strongly prognostic for OS and recurrence. The results may indicate that even subclinical disease promotes immunosuppression or alternatively that immunosuppression increases recurrence risk. NLR during remission may help identify NSCLC patients at high risk of recurrence and may thus be of value in surveillance of lung cancer survivors.

<table>
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<th>Interim NLR</th>
<th>2-year overall survival ± 1 SEE (%)</th>
<th>2-year progression free ± 1 SEE (%)</th>
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<tr>
<td>&lt;2</td>
<td>97.4 ± 2.5</td>
<td>78.9 ± 6.6</td>
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<tr>
<td>2-4.08</td>
<td>84.7 ± 5.7</td>
<td>55.0 ± 7.9</td>
</tr>
<tr>
<td>&gt;4.08</td>
<td>58.8 ± 8.3</td>
<td>50.5 ± 9.0</td>
</tr>
<tr>
<td>P for trend</td>
<td>0.0004</td>
<td>0.032</td>
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Neoadjuvant pembrolizumab (Pembro) for early stage non-small cell lung cancer (NSCLC): Updated report of a phase I study, MK3475-223.

Jair Bar, Damien Urban, Efrat Ofek, Aliza Ackerstein, Ilanit Redinsky, Nir Golan, Iris Kamer, David Simansky, Amir Onn, Stephen Raskin, Tiberiu Shulimzon, Michael Peled, Nona Zeitlin, Sharon Halparin, Menucha Jurkowitz, Ramez Abukhalil, Marina Perelman, Alon Ben-Nun; Institute of Oncology, Sheba Medical Center, Ramat Gan, Israel; Department of Pathology, Sheba Medical Center, Ramat Gan, Israel; Chaim Sheba Medical Center, Ramat Gan, Israel; Sheba Medical Center, Ramat Gan, Israel; Thoracic Surgery, Sheba Medical Center, Ramat Gan, Israel; Institute of Pulmonology, Sheba Medical Center, Ramat Gan, Israel; Pulmonology Institute, Sheba Medical Center, Ramat Gan, Israel; Pulmonology Institute, Sheba Medical Center, Ramat Gan, Israel; Department of Thoracic Surgery, Chaim Sheba Medical Center, Ramat-Gan, Israel

Background: Resected NSCLC clinical stage I or II harbor a 5 year survival of only 30-50%. Immunotherapy might be more effective in low-burden disease. We hypothesized that neo-adjuvant immunotherapy is a feasible, safe and effective treatment (Tx) for early stage NSCLC. Methods: MK3475-223 is an ongoing phase I study of neoadjuvant pembrolizumab in stage I-II NSCLC. All Pembro Txs are 200mg q 3 weeks (wks). Objectives: determine safety; recommended phase 2 dose/schedule; pathological & radiological response. Doses-schedule limiting toxicities (DLT) were defined as significant surgical complications (bleeding, delayed wound healing, ARDS, prolonged air-leak) or a significant delay of surgery. The doses-schedule escalation cohorts were (i) single pembro dose 3 wk prior to surgery; (ii) 2 pembro doses, 2 wks later surgery; (iii) 2 pembro doses, 1 wk later surgery. Expansion cohort received the doses-schedule of cohort (iii). Percentages of remaining viable tumor in the post-Tx were assessed, 10% or less was considered a major pathological response (MPR). IHC for pre-Tx PDL1 was done. Efficacy was evaluated for the patients who had received 2 doses of pembrolizumab. Results: No DLT occurred in the dose-schedule escalation cohorts. 10 patients received 2 cycles of neo-adjuvant pembrolizumab, 4 patients achieved a MPR (4/10 who received 2 cycles of pembro; 40%; 95% C.I. 16.7-68.8%). No correlation is seen between the levels of PDL1 pre-Tx and the pathologic response. Size of the tumor and N status was also not in any apparent correlation with MPR (data not shown). Interestingly, all of the MPR cases had a relatively long interval from 1st Tx till surgery. Clinical trial information: NCT02938624. Conclusions: Neo-adjuvant pembro is safe and feasible. A promising sign of efficacy is seen. Achieving MPR might require a longer 1st-Tx-surgery interval. Predictive biomarkers for response might be different from those in advanced disease. Recruitment and correlative studies are ongoing.

<table>
<thead>
<tr>
<th>MPR</th>
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<tbody>
<tr>
<td>Male (n)</td>
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</tr>
<tr>
<td>Female (n)</td>
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</tr>
<tr>
<td>Age median (yr)</td>
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<td>Interval 1st Tx-Surgery (range, days)</td>
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<tr>
<td>PDL1 IHC (n)*</td>
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<tr>
<td>1-49%</td>
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<td>50% or more</td>
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*PDL1 IHC is pending for one patient
Interim safety analysis of consolidation nivolumab and ipilimumab versus nivolumab alone following concurrent chemoradiation for unresectable stage IIIA/IIIB NSCLC: Big Ten Cancer Research Consortium LUN 16-081.

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Background: Consolidation PD-1 inhibition after chemoradiation (chemoRT) for unresectable stage IIIA/IIIB NSCLC improves overall survival. The efficacy and safety of combining a CTLA-4 inhibitor with a PD-1 inhibitor in this setting are unknown but may further improve efficacy in this patient population. Methods: In this randomized, multi-center, phase II study, 105 pts with unresectable stage IIIA/IIIB NSCLC will receive chemoRT, then randomize 1:1 to either nivolumab 480mg IV q4 wks (nivo) or nivolumab 3mg/kg IV q2 wks + ipilimumab 1mg/kg IV q6 wks (nivo/ipi), for up to 24 wks. In this interim analysis, we assess the safety of the first 20 patients treated. Results: From 9/2017 to 11/2018, 20 patients were accrued. Characteristics of those treated on the nivo arm (n = 10) were: median age 62 years, stage IIIA/B 7/3; non-squamous/squamous 7/3; and the nivo/ipi arm (n = 10): median age 61 years; stage IIIA/B 6/4; non-squamous/squamous 7/3. Most toxicities were grade 1 or 2 and the most frequently noted grade 2 AEs included fatigue (25%), pneumonia (25%), extremity pain (20%). Adverse events reported in the Nivo only arm included 81 total events with only four grade 3 events and a single grade 4 thromboembolic event. The Nivo/ipi arm reported 101 total AEs, with only 3 grade 3 events and a single grade 4 toxicity (amylase elevation). With respect to immune-related adverse events (irAEs), in the nivo arm there were two cases of grade 2 pneumonitis and no grade 3/4 events. In the nivo/ipi arm, there was one grade 2 pneumonitis, three grade 3 irAEs (pneumonitis, colitis, pancreatitis), and one asymptomatic grade 4 amylase elevation. No treatment-related deaths were observed in either arm. Conclusions: There were no unexpected safety signals in the first 20 patients treated on BIG10CRC LUN 16-081. The incidence of grade 3 or higher irAEs was higher in the nivo/ipi arm, as expected, but this was manageable with the use of established guidelines. The study currently remains open to accrual (32 of 105 have been randomized as of 2/8/19). Clinical trial information: NCT03285321.
10-year patient journey of stage III non-small cell lung cancer patients: A single-center, observational, retrospective study in Korea real-time automatically updated data warehouse in health care (UNIVERSE - ROOT study).

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Background: The current standard of care (SoC) for locally advanced stage III NSCLC is concurrent chemoradiotherapy (CCRT) but the outcomes are poor and unsatisfactory. The purpose of this study is to analyze the clinical features of patients with locally advanced lung cancer for 10 years in order to help develop future treatment strategy. Methods: This study through big data analysis retrospectively collected de-identified patient data from clinical data warehouse (CDW) using an unique algorithm with Standard Query Language (SQL). This new algorithm was developed by the close interactive collaboration between senior data scientists and medical oncologists. These algorithms include clinical natural language processing (NLP) systems that generate structured information from unstructured free text and structured data capture (SDC). We performed pre-processing work and data quality management (DQM) operation using over 700 clinical variables from 23,735 patients with NSCLC. Through data extraction, transformation, cleansing, and organization, we have developed a systematic and optimized program for lung cancer cohorts, including clinical features and molecular study and outcomes. It is also automatically updated every 24 hours in real time. Results: In the past 10 years, 23,735 patients were diagnosed with NSCLC and complete clinical data were available in 22,718 patients (95.7%). Out of total 22,718 patients 4,138 (18.2%) were diagnosed with stage III NSCLC. Among them, 2,676 patients (64.7%) received any type(s) of anti-cancer treatments or regular follow up at our institute. Of these 2,676 patients, 1,275 (47.6%) received curative surgery (+/- neo- and/or adjuvant CCRT); 685 (25.6%) patients definitive CCRT; 220 (8.2%) patients palliative thoracic RT; 76 (2.8%) patients best supportive care. Median OS was 48.0 months for neoadjuvant CCRT followed by curative surgery, 51.8 months for curative surgery +/- adjuvant treatment, 29.4 months for unresected definitive CCRT (PFS 10.0 months (range: 9.1-10.9). Molecular profiles as well as updated clinical data will be presented. Conclusions: This unique in-house algorithm enables us to do a rapid and comprehensive analysis of the big data through CDW, which can be also automatically updated daily. This should provide clinically relevant information about real-world treatment outcomes and help implement or develop new treatment strategy in a timely manner.
Association of BAFFR expression in CAFs with overall survival and response to platinum-based chemotherapy in NSCLC.

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**Background:** B-cell activating factor receptor (BAFFR) is a surface receptor, which leads to activation of the Nuclear Factor-kappaB (NF-κB) alternative pathway, a pathway with an important role in non-small cell lung cancer (NSCLC). In addition, cancer associated fibroblasts (CAFs) are major players of the tumor microenvironment promoting NSCLC. The aim of this study was to assess the possible associations of BAFFR expression in CAFs with response to first-line chemotherapy doublet and clinical outcome of NSCLC patients. **Methods:** Immunohistochemical analysis of BAFFR expression on CAFs was performed on tumor and tumor-adjacent formalin fixed and paraffin embedded tissue samples from 124 operated patients with NSCLC. Patients were under follow-up for at least 60 months, while response to chemotherapy was evaluated in patients who relapsed during this period. **Results:** BAFFR expression, which was noted exclusively in the cytoplasm of CAFs, was associated with OS only in patients with no infiltration of regional lymph nodes. Higher expression levels of BAFFR in CAFs were related to worse 2-, 3- and 5-year survival (P = 0.015, P = 0.027 and P = 0.040, respectively). This finding persisted after multivariate analysis with age, gender, histological subtype, histological differentiation and disease stage as coefficients (P = 0.009; HR, 2.734; 95% CI, 1.283-5.828). In addition, response to first line chemotherapy was associated with BAFFR expression in CAFs (P = 0.025). Patients who progressed had lower BAFFR levels. Furthermore, BAFFR expression in CAFs was associated with patients’ age. In particular, older patients had higher expression of BAFFR compared to patients younger than 55 years (P = 0.010). Additionally, carcinomas with better differentiation had lower expression of BAFFR in CAFs (P = 0.005). Finally, BAFFR expression in CAFs was related to development of metastatic disease (P = 0.033) and particularly in liver (P = 0.017) and in bones (P = 0.003). **Conclusions:** The present findings suggest that the expression of BAFFR in CAFs may be a useful biomarker with prognostic and predictive value, representing possibly an unknown biological relation, which merits further investigation.
EGFR L858R mutation as a possible target for individual-independent immunotherapy in Chinese population.

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**Background:** Neoantigens arise from tumor-specific mutations and potentially provoke immune responses. General vaccines targeting these peptides could be beneficial for patients suffering from common cancers, like lung cancer. Therefore, a retrospective analysis was performed on 799 non-small cell lung cancer (NSCLC) tissue samples previously profiled using our 1021-gene panel. Each sample was collected from a unique patient, from whom peripheral blood or normal tissue was also obtained as control.

**Methods:** Sequencing data were generated and pre-analyzed according to our in-house procedures. HLA typing was done using OptiType v1.0 (required sequences were captured by 1021-gene panel) and neoantigens were predicted by netMHCpan v4.0 based on typed HLA alleles and curated non-frameshift somatic mutations with frequency ≥ 5%, which were called in pre-analysis. A neoantigen is considered mutant-specific if IC50 mut is ≤ 500 nM and IC50 wild is > 500 nM, and especially, it is considered a strong-binder if IC50 mut is ≤ 50 nM.

**Results:** HLA typing returned 141 unique alleles, with the top 3 by carrier frequency being A*1101 (39%), C*0102 (33%) and A*2402 (28%). A further investigation into HLA alleles, mutations and neoantigens revealed two mutations on EGFR as candidates for off-the-shelf vaccine development: (1) L858R mutation (19%, 151 out of 799) and (2) E746-A750del mutation (13%, 106 out of 799). Among the four neoantigens derived from EGFR L858R mutation is HVKITDFGR, which can be recognized by A*3303 (IC50 mut = 22.93 nM and IC50 wild = 12,733.96 nM) and the combination is shared by 3% of the patients (23 out of 799), despite that A*3303 is not a very frequent allele in this population (16%, 127 out of 799). Two neoantigens were derived from EGFR E746-A750del mutation, including IPVAIKTSPK, which is mainly recognized by A*1101 (IC50 mut = 158.16 nM and IC50 wild = 31,132.66 nM). This combination is shared by 5% of the patients (41 out of 799). **Conclusions:** (1) EGFR L858R mutation and HLA-A*3303 could be a good target for individual-independent vaccine development. (2) HLA-A*1101 is the most frequent allele in this population. However, HLA-A*1101 and E746_A750del mutation is not so ideal for off-the-shelf vaccine development.
The spatiotemporal evolution of early-stage non-small-cell lung cancer.

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Background: Lung cancer is a genetically heterogeneous disease. The genomic basis of tumorigenesis and cancer cell spread, as well as intratumor heterogeneity (ITH) and subclonal evolutionary patterns might correlate with patients’ clinical outcomes. In this prospective study, we aimed to investigate such associations through comprehensive spatiotemporal genomic profiling in early-stage non-small cell lung cancers (NSCLCs). Methods: We performed deep targeted sequencing (GeneseeqPrime, 425 genes) of 503 primary tumor regions and 141 metastatic lymph node tumors from surgery and 378 longitudinal plasma biopsies (pre- and post-operation) across 128 Stage I-III NSCLC patients. ITH and phylogenetic tree for each patient were analyzed and correlated with clinical outcomes. Longitudinal and phylogenetic ctDNA analyses were further performed. Results: Spatial ITH varied among patients and was associated with clinical phenotypes. Geographical stratification of clonal structure, with localized confinement of subclones, was linked with slower tumor progression. In contrast, early expansion of subclones to multiregions was associated with rapid tumor growth and lymph node metastases. EGFR and TP53 mutations were nearly always clonal, whereas subclonal mutations in PI3K, WNT and TGF-beta pathway that occurred later in evolution were found in more than 50% of the patients. By tracking these phylogenetic events, we identified five evolutionary subtypes with distinct clinical outcomes, including a rare subtype characterized by independent origin of multiple EGFR driver mutations. ctDNA profiling could capture the spatial ITH to a certain extent with additional unique signatures. Further longitudinal and phylogenetic ctDNA analyses indicated early detection of relapse and adjuvant chemotherapy resistance. Conclusions: ITH is a key factor associated with clinical outcomes of early-stage NSCLC patients, which show diverse evolutionary subtypes underpinning the disease progression such as lymph metastasis and relapse. ctDNA sequencing can be used to capture spatial ITH, predict recurrence and track drug resistance.
Comprehensive genomic profiling in Chinese patients with lung squamous cell carcinoma.

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Background: Lung squamous cell carcinoma (LUSC) is a major histological subtype of non-small cell lung cancer (NSCLC) and accounts for 30% of NSCLC. Previous studies had revealed the genomic characterization of LUSC in Western patients (pts). However, the comprehensive genomic features of LUSC in Chinese pts have not been well understood.Methods: Deep sequencing targeting 450 cancer genes was performed on FFPE and matching blood samples collected from 311 LUSC pts. Genomic alterations (GAs) including single nucleotide variations, short and long insertions and deletions, copy number variations, and gene rearrangements were analyzed. Tumor mutational burden (TMB) was measured by an algorithm developed in-house.

Results: The median age of LUSC pts was 63 years old (range 57-68.5), of which 88% were male. The most frequently mutated genes were TP53 (88%), PIK3CA (34%), CDKN2A (33%), SOX2 (26%), LRP1B (22%), KLHL6 (21%), KMT2D (19%), PRKCI (19%), NFE2L2 (18%) and MAP3K13 (17%). Interestingly the mutation rates of PIK3CA (p = 1.93e-05) and CDKN2A (p = 2.48e-05) were significantly higher than that in TCGA cohort. Genomic alterations in eight druggable genes recommended by the NCCN guideline occurred in 32% of pts, and alterations to PI3K/mTOR signaling pathway related genes occurred in 52% of pts. One patient with PIK3CA amplification achieved stable disease for eight months after everolimus treatment. Moreover, variants in the homologous recombination (HR) pathway were identified in 17% of pts. The median TMB of LUSC pts was 10.8 Muts/MB (range 6.9-14.5 Muts/MB) which was higher than Western populations [PMID: 28420421]. The 1st Quartile (TMB-L), median and 3rd Quartile (TMB-H) TMB value was 6.9, 10.8 and 14.5 Muts/MB respectively. Comparing with the TMB-L group, frequencies of CDKN2A (39% vs 19%, p= 0.005), LRP1B (45% vs 8%, p< 0.001) and KMT2D (27% vs 8%, p= 0.002) were higher in TMB-H group.

Conclusions: In summary, we characterized the genomic alteration profile of Chinese LUSC pts. Consistent with previous reports, high mutation rates of TP53, PIK3CA and CDKN2A are the most important genomic features of LUSC. However, the proportion of PIK3CA and CDKN2A mutations in Chinese LUSC pts is higher than that of Western populations. In addition, we also found targetable pathways (including PI3K/mTOR) along with gene related variations and high TMB in many pts, providing potential targeted therapy and immunotherapy options for LUSC pts.
Mutational landscapes and PD-L1 expression in non-small cell lung cancer.

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Background: Programmed death-ligand 1 (PD-L1) serves as a major predictive biomarker for immune checkpoint inhibitors in non-small cell lung cancer (NSCLC). However, the relationship between PD-L1 expression and genetic features of NSCLC remains unclear. The aim of this study was to explore the correlation between genetic profiles and PD-L1 expression in NSCLC. Methods: FFPE tumor and matched blood samples from 568 NSCLC (487 adenocarcinomas (ACAs) and 81 squamous carcinomas (SCAs)) patients were collected for NGS-based targeted panel sequencing. Genomic alterations including single nucleotide variations, short and long insertions/deletions, copy number variations and gene rearrangements were assessed. Tumoral PD-L1 expression was evaluated by immunohistochemical analysis (Dako 22C3 and 28-8).

Results: The prevalence of PD-L1 expression was 9.9% with a ≥50% cutoff and 27.5% with a ≥1% cutoff. High PD-L1 expression (using a ≥1% cutoff) in tumor cells was significantly associated with mutations of MET (p = 0.001), RET (p = 0.036), ROS1 (p < 0.001), TP53 (p = 0.0013) and 11q13 amplification (p = 0.004), and was inversely correlated with EGFR mutations (p = 0.011). SOX2 and KLHL6 mutations were more frequent in SCAs (33.3% and 28.4%, respectively) than in ACAs (0.4% and 1%, respectively) and were adversely associated with PD-L1 expression in SCAs (p = 0.01, p = 0.004). Gene set 1 (GS1) mutations included EGFR, ALK, KRAS, BRAF, MET, RET, ROS1 and ERBB2 and gene set 2 (GS2) mutations included TP53, RB1, PTEN, APC and MYC. According to the mutation status of GS1 and GS2, 18 patients were classified as type I (GS1-, GS2-), 92 as type II (GS1-, GS2+), 202 as type III (GS1+, GS2-) and 256 as type IV (GS1+, GS2+). PD-L1 expression was higher in Type IV tumors than in type III (33.2% vs. 14.4%, respectively, p < 0.001).

Conclusions: We highlighted the genomic heterogeneity of NSCLC according to the mutation status of different gene sets. Our results indicate that patients with GS1 and GS2 gene mutations might correlate with higher PD-L1 expression. Our results help to understand the relationship between genomic features and PD-L1 expression and may be a potential guide for immunotherapy.
Retrospective study of capecitabine and temozolomide in advanced lung neuroendocrine neoplasms.

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Background: Patients with advanced lung neuroendocrine neoplasms (NENs) have few treatment options. Capecitabine and temozolomide have recently showed significant activity in patients with pancreatic NETs, but data in lung NETs are limited. Methods: We retrospectively reviewed the records of patients treated at a large NET referral center to identify patients seen between 1/2008 and 9/2018 with metastatic lung NENs who received treatment with capecitabine and temozolomide (CAPTEM). Patients who were not seen at the center within the first month of treatment were excluded. Small cell lung cancer patients were also excluded. The primary endpoint was overall response rate per RECIST 1.1. Secondary endpoints included progression free survival, overall survival, and toxicity. Results: 20 patients were identified who received treatment with capecitabine/temozolomide. 14 (70%) were typical lung NETs, 5 (25%) atypical carcinoids, and 1 (5%) was defined as a large cell neuroendocrine carcinoma. 6 patients (30%) exhibited a best response of PR per RECIST 1.1 criteria, 11 (55%) SD, and 2 (10%) PD. 1 patient died 2 months after starting treatment. 11 eventually progressed (radiographically or clinically), only 6 of whom exhibited progression per RECIST 1.1 criteria. Median PFS was 11 months (95% CI, 6 – 16 months). Median OS was 68 months (95% CI, 35 – 101 months). Toxicity profile was mild with mainly grade 1, expected toxicities. 6 patients required dose reduction due to toxicity (2 for diarrhea and nausea, 1 for hand foot syndrome, 3 for thrombocytopenia). Conclusions: We identified a group of patients with metastatic lung NENs who received treatment with the CAPTEM regimen and exhibited a favorable response rate to treatment with a relatively tolerable toxicity profile. This regimen warrants further exploration in a prospective clinical trial.
Clonal tumor evolution under induction chemotherapy and concurrent radiochemotherapy (RCHT) in patients with resectable stage IIIA (N2) and selected IIb non-small cell lung cancer (NSCLC): Molecular analysis of the ESPATUE randomized phase III trial.

Background: A better understanding of molecular mechanisms governing clonal tumor evolution under RCHT is of utmost importance for development of novel biomarker and targeted therapies. We report here the first attempt to decipher RCHT induced cellular and molecular perturbation in NSCLC on an integrative multiscale level.

Methods: Patients with stage III disease received induction chemotherapy with cisplatin and paclitaxel followed by concurrent RCHT with 45 Gy (1.5 Gy twice daily) and cisplatin/vinorelbine according to the ESPATUE protocol. Tumor tissue was sampled from tumor enriched areas marked by pathologists at diagnosis (biopsies, n=23) and post RCHT during surgical resection (n=22, ESPATUE-Arm B) corresponding to 16 paired samples (PS). Transcriptome analysis (n=45, 16PS), methylome analysis (n=35, 12PS), deep whole exome sequencing (WES) including copy number variation (CNV) analysis by low-pass whole genome sequencing (WGS, n=34, 13PS) were performed. A confirmatory targeted ultra-deep NGS for 41 genes was conducted (n=20PS). Results: Similarity plots of delta transcriptome data identified three distinct clusters of tumor evolution under RCHT. Cluster 1 was highly enriched for STS (5 out of 7 Pat.) compared to cluster 3 enriched for LTS (4 out of 6), p=0.02. 146 transcripts were differentially expressed as the function of RCHT (FDR, 0.05). Among them, 61 genes were upregulated and enriched for ECM and tissue remodeling (COL6A3/4, Col14A1, LAMA2, PAI1, MMP2), p53 signaling (p21, GADD45B) and stress response (FOSB, EGR1) pathways, p=0.01. 39 downregulated genes were enriched for genes attributed to cell cycle- and DDR signaling (FANCI, SLX1A) p=0.05. 4221 CpG were differentially methylated (FDR<0.05). Seven inversely regulated genes were found with SLIT3 and TBX5 being among upregulated and hypomethylated genes. WES analysis revealed patterns of tumor evolution with a range of clonal diversity. In 5/13 pairs the clonal composition remained unchanged after RCHT. Approximately 500 post RCHT exclusive mutations were found. Conclusions: Clonal, transcriptional and methylome dynamic of tumor evolution towards RCHT selection pressure is unrevealed in patients with locally advanced NSCLC. This multi-scale dynamic approach provides novel means for development of biomarker and therapeutic targets. Clinical trial information: ESPATUE.
Immune landscape of the tumor microenvironment to predict prognosis and DNA mutations in patients with lung adenocarcinoma.

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Background: The tumor microenvironment (TME) influences prognosis and response to therapy. The correlation between immune profiles in the TME and cancer DNA mutations is not well established.

Methods: Clinical outcomes data, mRNA-seq, and DNA mutation of 480 patients (pts) with lung adenocarcinoma (LAD) were obtained from TCGA. Pts were clustered into 4 groups using unsupervised machine learning, based on mRNA expression of genes related to antigen presentation (AP) and cytolytic activity (CA): group (G) 1 with high AP and CA (52 pts); G2, high AP, low CA (82); G3, low AP, high CA (66); G4, low AP and CA (280). Analysis of the immune landscape was performed using mRNA-seq of 191 genes enriched in cellular and structural elements of TME. DNA mutations were analyzed using the R package ggpubr and correlated in G1-G4.

Results: Pts in G1 have high expression of genes related to immune activation (IA) and decreased expression of immune suppression (IS) and have the best prognosis. Pts in G2 have intermediate prognosis with decreased IA genes and intermediate expression of genes related to IS and immune checkpoints. Pts in G3 have the worst prognosis with very high expression of genes related to immune checkpoints, desmoplasia, T cell co-inhibition, and IS. They also have low CD39 expression implying low cancer antigen-driven T cells. Pts in G4 have intermediate prognosis with highly depressed IA genes. Out of 70,199 non-synonymous mutations, the top 50 mutated genes in each pt group were identified: 36, 26, 31, and 17 DNA mutations were only found in G1, G2, G3, and G4 (refer to presentation). EGFR mutation was only found in G2; KRAS in G2/4; TP53 in G2/3/4. Conclusions: Our correlation analysis of mRNA-seq and DNA mutation shows that the immune landscape of TME can predict DNA mutations and prognosis. It further demonstrates a close connection between DNA mutations and changes in TME mRNA expressivity which appear to have valuable prognosticating potential in the clinical setting with now widely available genomic testing.
Benefit of combining local treatment and systemic therapy for stage IV NSCLC: Results from the National Cancer Database.

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Background: To determine the potential benefit of combining local and systemic therapy in stage IV non-small cell lung cancer (NSCLC). Methods: Data from stage IV NSCLC patients receiving systemic therapy alone, surgical resection and systemic therapy, or external beam radiation therapy/thermal ablation (EBRT/TA) and systemic therapy were acquired from the 2010-2015 National Cancer Database (NCDB). EBRT and TA patients were combined to enhance the power of the study. Overall survival (OS) was evaluated via multivariable Cox proportional hazards models. Comparison was made between EBRT/TA and systemic therapy alone utilizing 1:1 propensity matching analysis. A multivariable logistic regression model was used to determine variables predictive of lung cancer treatment. Significant variables (p < 0.05) were used to calculate the propensity score, and patients receiving EBRT/TA and systemic therapy were 1:1 matched using a greedy (nearest-neighbor) approach. Results: 46,964 patients from the NCDB database fulfilled inclusion criteria (surgical resection n = 1,235; EBRT/TA n = 12,456; systemic therapy alone n = 33,273.) Treatment differed across patient demographics and disease characteristics. Surgical resection demonstrated superior OS compared to EBRT/TA and systemic therapy alone, even after multivariable adjustment (compared to systemic therapy alone HR = 0.54, 95% CI: 0.50-0.58, p < 0.001; compared to EBRT/TA HR = 0.56, 95% CI: 0.52-0.60, p < 0.001). EBRT/TA treatment demonstrated superior survival compared to systemic therapy alone after accounting for confounders via propensity score matching (HR = 0.95, 95% CI: 0.93-0.98, p = 0.002). Interaction analyses indicated heterogeneous effectiveness of EBRT/TA according to patient demographics and cancer factors: the survival benefit of EBRT/TA over systemic therapy alone was especially pronounced in stage IV squamous cell carcinoma patients with limited nodal and metastatic disease (HR = 0.78, 95% CI: 0.71-0.85, p < 0.001 compared to systemic therapy alone; OS rates at 1-year = 50.9% vs. 42.4%; 2-years = 26.6% vs. 19.8%; 3-years = 17.2% vs. 10.1%). Conclusions: Stage IV NSCLC patients who received EBRT/TA or surgical resection in addition to systemic therapy demonstrated prolonged survival. EBRT/TA in combination with systemic therapy should be preferred in selected patients that are ineligible surgical candidates.
Lung cancer diagnosed by an incidental lung nodule program or lung cancer screening.

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Background: Early detection reduces lung cancer (LC) mortality. We prospectively evaluated LC patients diagnosed through Lung Cancer Screening (LCS) or an Incidental Lung Nodule Program (ILNP) (‘early detection’ programs) compared to routinely diagnosed LC patients in a multidisciplinary program (MDP).

Methods: We compare demographics, tumor characteristics, and survival between the three groups diagnosed within the same healthcare system from 2015-2018. The ILNP prospectively tracks patients with suspicious lung lesions on routinely-performed studies flagged by radiologists using a standard macro text. LCS used Medicare eligibility criteria. Statistical methods include the chi-square test, Kruskal-Wallis test, and proportional hazards models with hazard ratios (HR) and 95% confidence intervals.

Results: ILNP detected 201 lung cancers from 4713 scans (4.3%), LCS yielded 35 lung cancers from 1540 low-dose CT scans (2.3%), while MDC had 926 LC cases not detected by LCS or ILNP. Mean age at diagnosis for ILNP/LCS/MDC was 70/69/67 years (p = 0.0083); African Americans were under-represented in LCS (25%/11%/32%, p = 0.0104). LCS had the highest proportion with commercial insurance (46%/54%/43%, p = 0.3442). Early detection groups were more likely to have adenocarcinoma histology (ILNP/LCS/MDC: 61%/57%/49%, p = 0.0113). Smoking exposure was highest in LCS cohort (mean pack years: 48/64/52, p = 0.0500); 11% of ILNP, 8% MDC patients were never-smokers. Only 36% ILNP and 39% MDC patients were eligible for LCS by NLST criteria and 30%/40% by NELSON criteria. Reasons for ineligibility included smoking status in 73-90% and age in 7-27% of patients. Stage I/II distribution was (66%/58%/21%, p < 0.0001), stage IV 15%/20%/36%; surgical resection rates were (56%/55%/31%, p < 0.0001). Overall survival was longer in early detection groups (LCS HR: 0.31 [0.11,0.82]; ILNP HR: 0.51[0.33,0.81]) compared to MDC (p = 0.0011). Conclusions: The majority of LC patients were ineligible for LCS, but the ILNP identified LC in a high proportion of such patients, with similar stage re-distribution, curative-intent treatment, and survival rates. Structured ILNP complement LCS for early LC detection, such programs need to be built out.
Malignant pleural mesothelioma (MPM) genomic profile in the randomized phase II RAMES Study.

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Background: Since MPM is an uncommon neoplasia, its rarity has limited available data on molecular drivers. 

Methods: RAMES study evaluated the second-line efficacy of gemcitabine/ramucirumab treatment vs. gemcitabine/placebo. From December 2016 to July 2018 (end of enrolment), 164 patients (pts) were admitted to this study, which involved the collection of tumor samples - with diagnosis - to evaluate 34 genes by NGS (ACTB, ACTG1, ACTG2, ACTR1A, BAP1, CDH8, CDK4, CDKN2A, CDKN2B, COL3A1, COL5A2, CUL1, DHFR, GOT1, KDR, Kit, MXRA5, NF2, NFRKB, NKX6.2, NOD2, PCBD2, PDZK1IP1, PIK3CA, PIK3CB, PSMD13, RAPGEF6, RDX, SETDB1, TAOK1, TP53, TXNRD1, UQRC1, XRCC6). We reported the results of the first 87 pts (54%): histotype was epithelioid in 70 pts (80%), biphasic in 14 pts (16%) and sarcomatoid in 3 pts (4%). Median age was 63 years (range 45-81). 70 pts were male (80%) and 17 pts were female (20%). In the present analysis, we included 55 pts in stage III (63%), 26 pts in stage IV (30%) and 6 pts whose stage was unknown. Median first-line PFS platinum/pemetrexed therapy was for 5.75 months (I.C. 95% 4.75-6.76). PFS was ≤6 months for 40 pts (49%), and 6 months for 41 pts (51%). Results: 187 functional somatic mutations were identified. Genomic alterations/patient were 1 gene in 29 pts (33%), 3 genes in 18 pts (21%) and ≥5 genes in 2 pts (2%). The most frequent somatic mutations were RDX in 35 pts (40%), MXRA5 in 20 pts (23%), BAP1 in 13 pts (15%) and ACTG1 in 9 pts (11%). When patients were collated by stage, the most frequent mutations were: MXRA5 in 16 pts in stage III (29%), BAP1 in 5 pts in stage IV (19%) and RDX in 16 pts in stage IV (62%). The percentage of somatic mutations in patients with PFS as first-line chemotherapy for ≤6 and >6 months was 2.2 and 1.6 (p=0.032), respectively. The most frequent mutations/patient for ≤6 and >6 months PFS were: RDX in 14 pts (35%) with PFS < 6, RDX in 19 pts (46%) with PFS >6 and MXRA5 in 11 pts (27%) with PFS >6. Conclusions: This preliminary data suggests a possible role that a genetic signature may play in distinguishing MPM with different clinical-pathological features. The results are expected to be clarified further in the second step of the study, which is ongoing. Clinical trial information: 2016-001132-36.
Outcome of neo-adjuvant chemotherapy in 225 surgical candidates with malignant pleural mesothelioma.

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Background: Since any surgery for malignant pleural mesothelioma (MPM) are cytoreductive, effective chemotherapy is a prerequisite for surgery. In this context, we give neo-adjuvant chemotherapy (NAC) to all surgical candidates. Methods: Hyogo College of Medicine MPM Surgery Program mandates all surgical candidates to receive NAC, and only patients with stable disease (SD) or better response proceeds to surgery. The program comprised NAC followed by extrapleural pneumonectomy (EPP) and hemithoracic radiation until 2012, and NAC followed by pleurectomy/decortication (P/D) and postoperative chemotherapy thereafter. Eligibility criteria are histologically confirmed non-sarcomatoid MPM, clinically resectable stage (T1-3N0-1M0), performance status 0–1, and no major comorbidity. Results: From December 2006 to December 2018, 225 patients were enrolled. Of 225, 24 patients (10.7%, Group A) did not proceed to surgery because of progressive disease (n=23) or serious adverse events (n=2). Of the remaining 201 patients with partial response (n=38, 16.9%) or stable disease (n=163, 72.4%), 19 refused surgery (Group B), 16 received exploratory thoracotomy (Group C), and 165 completed surgery (Group D, EPP58, P/D107). Surgical mortality rates at 30 and 90 days were 1.1% (n=2) and 2.8% (n=5), and surgical morbidity (≥ grade 3) was 26.0% (n=47). Median survival time and survival rates of each group were shown in the table. Briefly, 2-yr survival competed among Group B, C and D, whereas 5-yr survival rapidly dropped in Group B and C. Conclusions: Approximately 90% of MPM patients with surgical intent successfully underwent either of EPP or P/D after effective chemotherapy with acceptable surgical mortality and morbidity. Comparison of patients who refused or accepted surgery suggested that surgery contributed to long-term survival.

<table>
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Phase 2 study of tremelimumab plus durvalumab for previously-treated malignant pleural mesothelioma (MPM).

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Background: Treatment options are limited for patients (pts) with MPM who experience disease progression after first-line pemetrexed-based chemotherapy. This study was designed to explore the activity of combined CTLA-4 + PD-L1 immune checkpoint inhibition using tremelimumab plus durvalumab in previously-treated MPM. Methods: We conducted a phase 2 study of tremelimumab 75 mg plus durvalumab 1500 mg administered intravenously every 4 weeks for four cycles followed by durvalumab maintenance every 4 weeks. Eligible pts had previously received pemetrexed-based platinum doublet chemotherapy and had measurable disease using modified RECIST criteria for mesothelioma. The primary endpoint was overall response rate (ORR) and secondary endpoints were progression-free survival (PFS), overall survival (OS), and duration of response (DoR) as well as safety and tolerability of this combination. A Simon two-stage design was employed to enroll up to 40 patients if 4 or more responses were observed among the first 19 study patients. Pre-treatment, on-treatment, and optional post-progression biopsies underwent flow cytometric immunoprofiling for correlative studies. Results: Among 19 pts enrolled in this study, the best objective response was a confirmed partial response in one patient (5%), stable disease in 9 pts (47%), progressive disease in 8 pts (42%), and not evaluable in one patient. At a median follow-up of 7.1 months, the median PFS was 2.8 months (95% CI 2.04-5.72), and the median OS was 7.8 months (95% CI 6.24-not reached). Of 17 PD-L1 evaluable cases, 10 (59%) were PD-L1 negative, and 7 (41%) had a PD-L1 tumor proportion score of ≥1%. Treatment was generally well-tolerated and there were no treatment-related study discontinuations or deaths. Flow cytometric immunologic changes over the course of treatment associated with disease control will be presented. Conclusions: Tremelimumab + durvalumab was well-tolerated in unselected pts with previously-treated MPM. This study did not meet its primary endpoint. Additional strategies are necessary to develop novel immunotherapeutics and biomarkers of response in MPM. Clinical trial information: NCT03075527.
Radiological response patterns in the phase 2 STELLAR trial of TTFields with chemotherapy for first-line treatment of malignant pleural mesothelioma (MPM).

Federica Grosso, Giovanni Luca Ceresoli; SS Antonio e Biagio Hospital, Department of Oncology, Alessandria, Italy; Cliniche Humanitas Gavazzeni, Department of Oncology, Bergamo, Italy

Background: Tumor Treating Fields (TTFields) are an anti-mitotic, regional treatment modality, utilizing low intensity alternating electric fields delivered non-invasively to the tumor using a portable, medical device. TTFields have significantly extended survival of patients with glioblastoma. In-vitro, human MPM cells were highly susceptible to TTFields. In the STELLAR study, patients with unresectable MPM treated with first line chemotherapy in combination with TTFields had a significantly higher median overall survival compared to historical controls (18.2 vs. 12.1 months). We report on analysis of radiological data from STELLAR patients whose tumors responded while receiving the combined therapy. Methods: The STELLAR trial accrued 80 patients with unresectable, previously untreated mesothelioma. Patients were treated with continuous 150 kHz TTFields (>18h/day) in combination with pemetrexed and cisplatin or carboplatin (at standard dosing). Inclusion criteria included ECOG PS of 0-1, pathologically proven mesothelioma and at least one measurable lesion according to modified RECIST criteria. Patients were followed q3w (CT scan q6w) until disease progression. Radiological assessments were done at each study site. Results: Partial responses (PRs) were seen in 40.3% of evaluable patients and clinical benefit (PR+SD) was seen in 97.2% of these patients. The median time between treatment start and PR was 1.8 months (range: 1.4-4.4 months). All patients presenting with PR during the STELLAR study had continuous reduction in the total sum of lesion diameters, suggesting no initial / pseudo-progression. 83% of the patients who responded to the combined therapy finally had disease progression within a median response duration of 5.7 months (range: 1.4-13 months), per Kaplan-Meier Estimator. One patient did not progress for more than 27 months. Conclusions: The STELLAR study met its primary endpoint of significant survival extension for previously untreated mesothelioma patients. Response rates were similar to the ones reported for the current standard of care treatment, but lasted longer with the addition of TTFields. Clinical trial information: NCT02397928.
Association of BAP1 alterations with malignant pleural mesothelioma treated with trimodality therapy.

Marjorie Glass Zauderer, Hira Rizvi, Mariel A. DuBoff, Prasad S. Adusumilli, Valerie W. Rusch, Jennifer L. Sauter, Marc Ladanyi, Andreas Rimner; Memorial Sloan Kettering Cancer Center, New York, NY; Memorial Sloan-Kettering Cancer Center, New York, NY; Department of Pathology, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Trimodality therapy with pleurectomy/decortication, cytotoxic chemotherapy, and adjuvant pleural intensity modulated radiation therapy (IMPRINT) is an emerging standard of care for locally advanced epithelioid mesothelioma (Rimner, Zauderer et al. JCO 2016). Some patients, however, progress rapidly and we therefore sought to identify potential predictive markers of response to this treatment. Given the putative role of BAP1 in DNA damage repair, we hypothesized that alteration in BAP1 would be associated with improved local control after radiation therapy. Methods: We identified patients previously treated at our institution with IMPRINT to a median dose of 4680cGy in 26 fractions. Targeted next generation sequencing was performed with MSK-IMPACT on archival tissue samples. Chart review was undertaken for clinicopathologic features and outcome data. Results: MSK-IMPACT testing was successfully performed on 58 patients who completed IMPRINT. The majority were male with a median age of 70 years. Ninety-seven percent had epithelioid subtype while 3% were biphasic with predominantly epithelioid histology. Median overall survival was 30.2 months with a median follow-up of 45.3 months, consistent with prior reports. Somatic BAP1 mutations were identified in 34% of the specimens. Those with BAP1 mutant tumors had a median time to local failure of 22.4 months (IQR 10.9 – 36.9 months) while those with BAP1 wild type tumors only had a median of 12.1 months (IQR 8.7-15.85 months) to local failure (p = 0.057). We identified a trend towards improved overall survival among those with BAP1 altered tumors compared to those with BAP1 wild type (HR = 0.61, p = 0.14). Conclusions: BAP1 alteration may be associated with improved duration of local control and improved overall survival after IMPRINT therapy. Further analysis and validation in a large data set is needed and a platform for identifying and validating predictive biomarkers should be included in the planned NRG randomized trial of IMPRINT.
Background: Information on the optimal therapy beyond the second-line treatment of small cell lung cancer (SCLC) is very limited and controversial. Inhibiting the components of the VEGF signaling pathway is an attractive treatment option for SCLC patients. Apatinib, a selective inhibitor of VEGF receptor-2 (VEGFR-2) tyrosine kinase, has been proven to be safe and effective for the treatment of a broad range of advanced solid tumors. In our prospective clinical study, we aim to evaluate the efficacy and safety of single-agent apatinib as treatment of extensive-stage (ES) SCLC patients after failure from at least two prior chemotherapy regimens. Methods: Twenty-two ES-SCLC patients treated with single-agent apatinib after failure from at least two prior chemotherapy regimens in our institution between November 2016 to August 2018 were enrolled in the clinical study. Apatinib mesylate was orally administered at a dose of 500 mg once daily on a 28-day cycle until evaluation of disease progression (PD) or the occurrence of unacceptable toxicity. Dosage reduction to either 425 mg or 250 mg once daily were permitted based on the evaluation of toxicities. The primary endpoint was progression-free survival (PFS). The secondary endpoints included overall survival (OS), objective response rate (ORR), disease control rate (DCR) and adverse events (AE). Results: The median age was 56 years, ranging from 36 to 70 years. A majority (63.6%, 14/22) received apatinib as third-line treatment, while 22.7% (5/22) and 13.6% (3/22) received it as fourth or fifth-line treatment, respectively. Partial response (PR) was achieved by 3 (13.6%) patients and stable disease exhibited by 18 (81.8%) patients. The median PFS and OS were 5.4 and 10.0 months, respectively. Apatinib demonstrated a manageable toxicity profile, with grade I-III secondary hypertension and proteinuria as the most common AE. Grade III adverse events were only observed in 3 (13.6%) patients with either hypertension (1 patient) or proteinuria (2 patients). Except for these 3 patients, all the other patients experienced grade I-II adverse events. No grade IV and V AE were observed among the patients. Multivariate analysis revealed secondary hypertension as an independent predictor of OS (p= 0.047). Conclusions: Apatinib is safe and effective in the management of ES-SCLC patients and can be considered as a treatment option after failure from at least two prior chemotherapy regimens. Secondary hypertension can be a potential prognostic factor for apatinib treatment. Clinical trial information: NCT02995187.

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Background: Although many clinical prognostic factors for SCLC outcome have been described, there are no models that incorporate the combination of clinical and genomic details into a risk model defining high and low risk patients. Methods: From a total of 791 SCLC patients seen between 2013-2018, 91 were evaluated by exome sequencing. Using the univariate Cox regression model, 19 genes were prognostic for survival and included RET, ERBB4, MAP3K1, ABL1, CCND1, TSC1, PRKCI, FGFR3, JAK3, ZNF217, BRCA1, GPR124, LRP1B, GNAS, TAF1, FGF3, STAT3, CD79A and FLT. LASSO, elastic-net Cox and traditional Cox model with stepwise selection along with traditional clinical factors (age and stage) were further used to build the final model. The final risk groups were defined based upon the prognostic index from multivariable Cox model involving age, stage (extensive/limited) and 6 genes (MAP3K1, ABL1, CCND1, PRKCI, BRCA1, GNAS). Results: The overall survival (OS) for the entire cohort was 11.2 (95% CI: 9 – 13.4) months and the median age was 65 (range: 39 - 90) years. Eighty percent (N = 74) of evaluated patients had extensive stage (ES) disease. The HR for death of age and stage (ES/LS) was 1.06 (CI: 1.03-1.08, p < 0.0001) and 4.33 (CI: 2.23-8.41, p < 0.0001) respectively. ABL1 demonstrated the highest HR of 10.14 (2.81-36.6, p = 0.0004) followed by PRKCI (HR: 5.05, CI: 1.43-17.8, p < 0.012), CCND1 (HR: 4.52, CI: 1.23-16.57, p < 0.023), MAP3K1 (HR: 3.38, CI: 1.37-8.33, p = 0.008) and GNAS (HR: 2.21, CI: 1.11-4.43, p < 0.025). Interestingly, BRCA1 mutation was protective as patients with BRCA1 mutation had significantly better overall survival (HR: 0.3, CI: 0.1-0.85, p < 0.023). Our model categorized patients into three groups of low risk (N= 31), intermediate risk (N= 30) and high risk (N= 30) with significantly different survival outcomes (p < 0.0001). Those with low risk had the median OS of 27.4 (95% CI: 16.8-55.5) months, intermediate risk with median OS of 10.8 (95% CI: 7 - 14.7) months and high risk with median OS of 5.4 (95% CI: 3.9-9) months. Conclusions: This clinical-genomic risk group stratification represents a useful model to estimate SCLC survival outcome and may have value in future clinical trials.

Phase II study of consolidation amrubicin after concurrent chemoradiotherapy for patients with limited-stage small cell lung cancer.

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Background: Concurrent chemoradiotherapy (CCRT) using etoposide and cisplatin has been the gold standard for limited-stage small-cell lung cancer (LS-SCLC) for decades; however, approximately three out of four cases treated by CCRT inevitably relapse. Amrubicin (AMR), a synthetic anthracycline with a structure similar to doxorubicin, has demonstrated strong antitumor activity against relapsed SCLC and has been the standard second-line treatment for SCLC in Japan. We consider consolidation AMR following CCRT to be a potential treatment for patients with LS-SCLC. Methods: In this single-arm, multicenter phase II study, all patients enrolled were treated using induction CCRT consisting of four cycles of etoposide at 100 mg/m² on days 1-3 and cisplatin at 60 mg/m² on day 1 every 3 weeks, plus concurrent thoracic radiotherapy (1.5 Gy twice daily, total 45 Gy) concomitant with the first cycle of chemotherapy. Then, eligible patients received three cycles of AMR at 40 mg/m² on days 1-3 every 3 weeks as consolidation treatment. The primary endpoint was the 2-year progression-free survival (PFS) rate in patients who received consolidation AMR, and the secondary endpoints were objective response rate (ORR), PFS, overall survival (OS), and safety. This study was terminated early due to slow patient accrual. Results: Of the 36 patients who underwent induction CCRT (ITT population), 28 (78%) received AMR as consolidation therapy (consolidation population) and 24 (67%) completed all planned treatments. The 2-year PFS rate and ORR were 35.7% and 86% (8 CR and 16 PR), respectively, in the consolidation population. The median PFS and median OS were 14.3 months (95%CI, 10.8-46.6) and 60.9 months (95%CI, 29.8-NR), respectively, in the consolidation population. In the ITT population, the median PFS and the median OS were 13.4 months (95%CI, 7.5-19.0) and 60.9 months (95%CI, 29.8-NR), respectively. Grade 3/4 toxicities during the consolidation phase included neutropenia (39%), thrombocytopenia (14%), and febrile neutropenia (7%). There were no treatment-related deaths in the ITT population. Conclusions: Consolidation AMR following standard CCRT consisting of etoposide and cisplatin plus concurrent thoracic radiotherapy was feasible, and demonstrated promising efficacy for LS-SCLC. Clinical trial information: 000002352.
Real-world experience and molecular features of response to immune checkpoint blockade in patients with recurrent small cell lung cancer.

Wei-Chu Victoria Lai, Hira Rizvi, Jacklynn V. Egger, Andrew J. Plodkowski, Michelle S. Ginsberg, Mark G. Kris, Amanda Beras, Natasha Rekhtman, John T. Poirier, Matthew David Hellmann, Charles M. Rudin; Memorial Sloan Kettering Cancer Center, New York, NY; Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY; Department of Pathology, Memorial Sloan Kettering Cancer Center, New York, NY; Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York, NY

Background: Immune checkpoint blockade (ICB) is now a routine component of treatment in recurrent small cell lung cancer (SCLC). We evaluated the response to ICB in patients (pts) with recurrent SCLC and genomic features of response using next-generation sequencing (NGS). Methods: Pts with recurrent SCLC treated with ICB were identified. The majority of pts were treated outside of a clinical trial to focus emphasis on the real-world experience. Tumor mutation burden (TMB) and the landscape of somatic variants were determined by targeted NGS using MSK-IMPACT. Objective response rate (ORR) to ICB was determined using RECIST v1.1. PFS and OS were measured from the start of ICB and analyzed using Kaplan-Meier. Results: Between December 2013 and October 2018, 108 pts with SCLC were treated with ICB (57 subjected to NGS). Pts received PD-1 monotherapy alone (n = 28) or in combination with CTLA-4 blockade (n = 80). Median line of therapy was 2 (range 1-6). ORR was 14% (15/108, 95% CI 8-22%). From the start of ICB, median PFS was 1.4 months in non-responders and 10.8 months in responders (HR 0.2; 95% CI 0.13-0.32). Median OS was 6.3 months in non-responders and undefined in responders (range 8-44 months) (HR 0.26, 95% CI 0.16-0.44). Four responders remain on ICB treatment. TMB in the ICB-treated cohort was similar to that of an unselected cohort (median 8.8 Mt/MB vs 8.2 Mt/MB, p = 0.71). Clinical benefit was enriched among those with a higher TMB (upper vs middle/lower tertile PFS HR 0.48, 95% CI 0.28-0.84, p = 0.01 and ORR 26% [5/19] vs ORR 8% [3/38]). Rates of whole genome duplication and commonly altered genes in SCLC (TP53, RB1, KMT2C/D, NOTCH1/2/4, PTPRD, APC) were similarly distributed across responders and non-responders. Completion of whole-exome sequencing and PD-L1 testing is in progress. Conclusions: In pts with recurrent SCLC receiving routine clinical care, the ORR to ICB is comparable to reports from clinical trials. A high TMB was associated with a longer median PFS and better response. Further investigation into the genomic landscape of recurrent SCLC is needed to identify biomarkers predictive of response to ICB.
Phase I study on preliminary safety and efficacy of rovalpituzumab tesirine in Japanese patients (pts) with advanced, recurrent small cell lung cancer (SCLC).

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Background: SCLC rapidly recurs after first-line platinum therapy, and while several agents are approved in the relapsed/refractory setting, there is no approved agent or existing standard of care for third-line in Japan. Rovalpituzumab tesirine (Rova-T™) is an antibody-drug conjugate targeting Delta-like 3 protein (DLL3), an atypical Notch ligand that is highly expressed in SCLC but not in normal tissue. This was the first study evaluating safety, PK, and preliminary anti-tumor activity of Rova-T in Japanese pts. Methods: This was an open label Phase 1, 3+3 dose-escalation study of Rova-T in Japanese pts with advanced recurrent SCLC (NCT03086239). Eligibility: progressive disease after $\geq 2$ prior systemic regimens incl. $\geq 1$ platinum-based regimen; ECOG 0-1. Pts received 0.2 or 0.3 mg/kg Rova-T IV on Day 1 of a 6-week cycle for 2 cycles. Objective was to evaluate safety, tolerability, PK, and preliminary efficacy and expression of DLL3. Antitumor activity was measured by RECISTv1.1, and DOR, PFS, OS were evaluated. Results: 29 pts were treated with Rova-T (6 at 0.2mg/kg, 23 at 0.3 mg/kg). Median age 68 yrs; 76% male; 64% DLL3 high (≥75% expression); 86% DLL3 positive (≥25%). 20 pts (69%) had received ≥3 prior lines of therapy. Similar PK and AEs were seen compared to previous studies in non-Japanese pts. The most frequently reported study drug-related AEs were platelet count decreased, pleural effusion, oedema peripheral, and aspartate aminotransferase increased, the majority Grade 1/2. No DLTs occurred, and both dose levels were tolerated. Three pts previously treated with ≥3 prior lines of therapy had confirmed partial response by investigator (10% of all pts; 17% of DLL3 high pts). For DLL3 high pts, mDOR was 3.0 mos (95% CI: 2.9, 4.1), mPFS was 2.9 mos (1.2-3.6), and mOS was 7.4 mos (4.1-11.9). Individual responses were analyzed in detail and radiographic data with tumor shrinkage will be shown. Conclusions: Rova-T demonstrated a manageable safety profile with promising preliminary efficacy in Japanese SCLC pts, in particular pts with DLL3 high expression. These data support further exploration of Rova-T treatment in Japanese pts with SCLC in global Phase 3 studies. Clinical trial information: NCT03086239.

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Background: The clinical impact of PD-L1 expression and oncogenic gene status in patients with small cell lung cancer (SCLC) is not well characterized. We initiated this immuno-oncology biomarker study as part of nationwide genomic screening by LC-SCRUM-Japan (LC-SCRUM-IBIS).

Methods: Tumor samples from lung cancer patients enrolled in LC-SCRUM-IBIS were primarily subjected to targeted next-generation sequencing (NGS) with Oncomine® Comprehensive Assay. The PD-L1 expression was also analyzed by 4 immunohistochemistry (IHC) assays for 22C3, 28-8, SP263 and SP142. At this analysis, 22C3, 28-8, and SP263 were assessed in tumor cells (TC) as positive in >1%, and SP142 in both TC and tumor-infiltrating immune cells (IC) as positive in > TC1/IC1, as previously reported. The association of PD-L1 expression, oncogenic gene status and clinical outcome was investigated in SCLC patients.

Results: Between Feb 2017 and May 2018, 1017 lung cancer patients were enrolled in LC-SCRUM-IBIS. Among them, 933 patients had adequate tumor samples including 101 SCLC and 832 non-small cell lung cancer. Of 101 SCLC patients, the results of PD-L1 expression by 4 IHC assays were 18% in 22C3, 17% in 28-8, 11% in SP263 and 8% in SP142, respectively. Targeted NGS showed that 8 patients had at least one targetable oncogenic alterations, including 3 PIK3CA and 1 KRAS as mutations and 3 PTEN and 1 TSC2 as inactivating mutations. PD-L1 expression by 22C3 was associated with good performance status (P = 0.05) and the presence of oncogenic alterations (P = 0.004). PD-L1 status was not associated with response to cytotoxic chemotherapy and progression-free survival and overall survival in first-line treatment of SCLC patients.

Conclusions: The frequency of PD-L1 expression in SCLC patients was relatively lower compared with that reported in other solid tumors. PD-L1 status by TC in 22C3 appears to be not correlated with clinical outcomes for cytotoxic chemotherapy of SCLC patients. Further investigation is needed to explore a predictive biomarker for immune checkpoint inhibitors. Updated results will be presented at the meeting.
Impact of large-scale nationwide genomic screening project for small cell lung cancer (LC-SCRUM-Japan).

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Background: A variety of genetic analyses have been performed in small cell lung cancer (SCLC), however the clinical relevance of them remains unclear. We prospectively analyzed clinical samples of small-cell lung cancer using a nationwide genomic screening project (LC-SCRUM-Japan). Methods: Submitted tumor samples were subjected to a next-generation sequencing (NGS) system, Oncomine™ Comprehensive Assay, enabling the simultaneous analysis of 143 (ver.1) or 161 (ver.3) cancer-related genes. Results: From July 2015 to January 2019, 707 SCLC patients had been enrolled. The median age was 68 years. 77% were male and 94% were smokers. Among 588 samples completed analysis, we identified high prevalence of inactivating TP53/RB1 mutations in 426 (72%) /194 (33%) of cases, respectively. MYC/MYCL1/MYCN amplifications were detected in 21 (4%) /30 (5%) /9 (2%) of cases, respectively. This NGS analysis also showed that 32 (5%) of cases had well-known genetic alterations in receptor tyrosine kinase genes: 9 EGFR mutations, 9 KRAS mutations and 14 FGFR1 copy number gains. Mutations in the PI3K pathway were detected in 44 (7%) of the tumors. Among them, 8 cases enrolled in the investigator-initiated phase II study of gedatolisib (UMIN 000020585). Survival data was available in 463 patients receiving platinum-based chemotherapy. Multivariate analysis revealed that the presence of PIK3CA mutation (HR: 2.56; 95% CI 1.19 – 5.52; p = 0.016) and MYCN amplification (HR: 4.36; 95% CI 1.91 – 9.97; p < 0.001) were significantly associated with unfavorable survival. The frequency of amplifications in MYC family genes was higher in the samples obtained ≥ 90 days after the first-line platinum-based chemotherapy (18.1%) than in those < 90 days (8.1%, p = 0.01), suggesting MYC family amplification as one of the resistance mechanisms. Conclusions: This large-scale nationwide screening system is helpful for identifying therapeutically relevant genetic alterations, prognostic prediction, and exploring resistance mechanism in SCLC. Updated screening results will be presented at the 2019 ASCO Annual Meeting. Clinical trial information: UMIN000018656.

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Background: Although thoracic twice-daily radiotherapy (TDRT) is one of standards of care for small cell lung cancer, its impact on brain metastases remains unknown. This study aimed to compare TDRT with once-daily radiotherapy (ODRT) for the brain metastases rate after prophylactic cranial irradiation in patients with small cell lung cancer. Methods: Consecutive patients received TDRT (45Gy/30f)/ ODRT(50-66Gy/25-33f), chemotherapy and prophylactic cranial irradiation were retrieved from eight hospitals’ databases between 2003 and 2016. The endpoints included brain metastases, progression-free survival and overall survival. Brain metastases rate was evaluated using competing risk analysis. A 1:1 propensity score matching approach was used to control confounding between these two groups. Confounding covariates included eight demographic variables and eight treatment related covariates. Results: Of the 778 eligible patients with median age of 55-year (IQR, 48-61), 204 (26.2%) were female. At a median follow-up time of 23.6 months (IQR, 14.2- 38.2), 131 (16.8%) experienced brain metastases. The rates in TDRT were significantly higher than ODRT (3-year, 26.0% vs. 16.9%; HR = 1.55, 95%CI 1.06-2.26, P = 0.03). Of the 338 matched patients (169 in ODRT vs. 169 in TDRT), 60 (17.8%) experienced brain metastases with 3-year rate of 14.9% in ODRT vs 26.0% in TDRT (HR = 1.71, 95%CI 1.02-2.88, P = 0.04). Progression-free survival was similar in both the whole cohort and the matched one. Overall survival in ODRT tended to be significantly longer after matching (median, 47.2 months in ODRT vs. 32.8 months in TDRT; HR = 1.41, 95%CI 0.99-2.01, P = 0.06). When jointly evaluated biologically effective dose (BED), start of any therapy to the end of radiotherapy (SER) and TDRT/ODRT in the multivariable analysis, the impact of ODRT/TDRT on overall survival become more significant (HR = 1.69, 95%CI 1.05-2.71, P = 0.03). Conclusions: Patients with small cell lung cancer who were treated with thoracic TDRT appeared to have higher risk of brain metastases than those with ODRT, which strongly supports the need for further prospective randomized clinical trials, especially in China or other parts of Asia.
RESILIENT: Study of irinotecan liposome injection (nal-IRI) in patients with small cell lung cancer—Preliminary findings from part 1 dose-defining phase.

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Background: Nal-IRI is investigated as monotherapy in patients with SCLC who progressed on or after platinum regimen. The RESILIENT study is a Part 1 study of a Phase 2/3 trial to assess safety, tolerability, and efficacy of Irinotecan Liposome Injection in patients with SCLC. Methods: Nal-IRI is evaluated in patients ≥18 yrs with advanced SCLC with an ECOG performance status ≤1 and adequate organ function; prior exposure to immunotherapy is allowed. Safety and tolerability at dose levels of 85 mg/m² and 70 mg/m² are the primary endpoints, with assessment of exploratory efficacy signal. Results: At 24 Dec 2018 safety cutoff 12 patients in Part 1 received ≥1 dose of nal-IRI (Cohort 1 [C-1] at 85 mg/m² dose n=4; Cohort 2 [C-2] at 70 mg/m² dose n=8; median age 60.0 yrs; range 49–73 yrs). Three patients experienced ≥1 DLT (Cohort 1 n=3/4; Cohort 2 n=0/8). Most frequent treatment-emergent adverse events (TEAE) were gastrointestinal (GI) disorders (any grade): diarrhea (91.7%), nausea (58.3%), vomiting (41.7%), decreased appetite (58%), abdominal pain (33%) manageable by antidiarrheal regimen and antiemetics; as well as fatigue (50%) and asthenia (37.5%). Overall, hematologic toxicity was neutropenia (any grade) at 16.7% and anemia (any grade) at 16.7%. At 11 Dec 2018 efficacy cutoff the best objective response was partial response (PR) at 33.3% in 4/12 patients (C-1 n=1/4; C-2 n=3/8), median time to response was 6 wks. Overall disease control rate (DCR) was 58.3%; progressive disease (PD) was observed in 2 patients (16.7%), and 3 patients were non-evaluable (25%). Conclusions: Initial assessment suggests that nal-IRI at 70 mg/m² dose given bi-weekly is well-tolerated and has promising antitumor activity in patients with SCLC who progressed on or after platinum regimen. Part 1 dose expansion is ongoing. Clinical trial information: NCTN03088813.

Best Objective Response (BOR).

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BIOLUMA: A phase II trial of nivolumab in combination with ipilimumab to evaluate efficacy and safety in lung cancer and to evaluate biomarkers predictive for response—Preliminary results from the SCLC cohort.

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Background: Patient selection, dosing regimens and resistance mechanisms for immune checkpoint inhibitor combination therapy remain unmet medical needs in lung cancer. We present interim data from the small-cell lung cancer (SCLC) cohort of the ongoing BIOLUMA trial which evaluates efficacy and safety of nivolumab and ipilimumab in lung cancer with a broad translational program to identify potential biomarkers predictive of response and/or resistance including whole exome sequencing (WES) of serial biopsies, functional analysis of peripheral T-cells and gut microbiome analyses.

Methods: BIOLUMA is an investigator initiated, multicentre non-randomised phase II trial in 2nd line patients with SCLC. The initial all-comer SCLC cohort was recently amended for inclusion of patients with high tumor mutation burden (TMB) only. Patients are pre-screened for TMB by WES at the time of first diagnosis. After progression on platinum-based therapy, 4 cycles of nivolumab 1 mg/kg q3w in combination with ipilimumab 3 mg/kg q3w and subsequent nivolumab 240 mg flat dose as mono-therapy are given. Primary endpoint is overall response rate (ORR) of the upfront combination therapy. Analysis of sequential tumor biopsies, blood and gut microbiome is performed at different timepoints.

Results: The SCLC cohort was amended to include TMB high patients only, after two treatment-related deaths had occurred and emerging data indicated treatment benefit depends on high TMB status for the combination therapy. Both patients with treatment-related death had a CT-scan documented partial response (not confirmed according to RECIST due to death). One each died of pneumonitis and encephalitis. From the all-comer cohort, efficacy data are available for 18 patients. ORR was 38.8% with 7 partial and no complete responses. Stable disease occurred in 16.7% (n = 3) resulting in a DCR of 55.5%. TMB pre-screening for the amended cohort is currently ongoing.

Conclusions: In the SCLC cohort, upfront combination therapy of nivolumab and ipilimumab shows remarkable ORR but is accompanied by high toxicity rates. In order to ensure a reasonable balance of risks and treatment benefit, only TMB high patients are included after an amendment of the cohort to improve the risk/benefit ratio. Clinical trial information: NCT03083691.
Phase II study of S-1 in patients (pts) with previously treated Invasive thymoma (IT) and thymic carcinoma (TC): North Japan Lung Cancer Study Group Trial 1203.

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Background: Invasive thymoma and thymic carcinoma are rare epithelial neoplasms arise in the anterior mediastinum. Platinum-based chemotherapies are widely used for the first-line treatment for unresectable IT and TC. Although no standard treatment has been established for previously treated IT and TC, S-1 has demonstrated promising efficacy in some retrospective studies. Thus we conducted the first prospective multicenter phase II trial to evaluate the efficacy of S-1 for previously treated pts with advanced IT and TC. Methods: Eligible pts were aged 20 years or older with: advanced IT or TC not feasible to potentially curative treatments; disease progression after at least one regimen of platinum-based chemotherapy; Eastern Cooperative Oncology Group performance status 0-2; adequate organ function; written informed consent. Pts received S-1 orally, at a dose based on body surface area for 2 weeks in 3 weeks cycle until tumor progression or unacceptable toxicities. The primary endpoint was overall response rate (ORR) and secondary endpoints were progression-free survival (PFS), overall survival (OS), and toxicity profile. Assuming that ORR of 25% in eligible pts would indicate potential usefulness while ORR of 10% would be the lower limit of interest, with alpha = 0.05 and beta = 0.2 according to a Simon’s two-stage design, the estimated accrual was 40 pts. Results: Between June 2012 and August 2018, 40 pts were enrolled and all pts were eligible (IT, n = 20; TC, n = 20). Median age was 64.5 years (range, 40-82), 75% (30/40) were male. Median treatment cycle was 5.5 (range, 1-82). ORR was 17.5% (95% CI: 7.3-32.8; IT, 10%, TC, 25%), and disease control rate was 85% (IT, 95%, TC, 75%). With a median follow-up of 51.9 months, median PFS was 7.0 months (IT, 11.3 months; TC, 5.4 months), and median OS was 40.3 months (IT, 58.5 months; TC, 22.7 months). The major grade 3-4 toxicities were anorexia (10%) and pneumonitis (5%). No treatment-related death was observed. Conclusions: Although the primary endpoint was unmet, S-1 monotherapy showed the moderate effects and could be available option especially for previously treated advanced TC. Clinical trial information: 000008174.
Progression free survival and time to local failure after radiosurgery of pleural metastases in twenty-two patients with thymomas.

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Background: Thymomas but not thymic carcinomas can benefit of cytoreductive surgery even if a complete resection is not achievable. Surgical resection of pleural metastases, the most common site of progression, can be performed in selected patients. We evaluated the outcome of stereotactic body radiation therapy (SBRT) for treatment of pleural metastases in patients’ not eligible for surgery. 

Methods: We retrospectively identified 22 patients treated with SBRT for pleural metastases between 2004 and 2019. According to RECIST criteria, time to local failure and progression free survival (PFS) were calculated using Kaplan-Meier estimation.

Results: Twelve of the 22 patients were male. The median age was 40 years (range 29-73). There were 1 A, 3 AB, 3 B1, 3 B2, 3 B2/B3 and 9 B3 thymomas. The Masaoka stage at diagnosis was IIA in 2, IIB in 7, III in 5, IVA in 7 and IVB in 1 patient. Pleural metastases and primary tumor were synchronous in 8 patients. Thymectomy was performed in 21 patients. Seven patients received pre-operative chemotherapy and 12 post-operative radiotherapy. One patient received chemotherapy and radiotherapy after a macroscopically incomplete thymectomy. Five patients had a single pleural metastatic site and 17 presented multiple localizations. Sixteen patients received SBRT on multiple sites of pleural metastases. At the time of the analysis a patient received SBRT exclusively on one of 3 pleural metastases. The median dose of radiation was 30Gy (range 25-40) given in 3 fractions. Ten patients experienced a progression of treated lesions with a median time to local failure of 25.5 months (95%CI 20.9-30.1). The median PFS was 20.4 months (95%CI 10.7-30). There were not significant differences in PFS between patients diagnosed with synchronous and metachronous metastases (p=0.477), across those treated with chemotherapy or naive (p=0.189) and between those who received or not a previous surgical resection of the pleural metastases (p=0.871).

Conclusions: SBRT of pleural metastases is feasible and offer an interesting local control of diseases. The impact of this treatment on patients’ survival is hardly predictable because of the heterogenous clinical behavior of thymomas.
Clinical application of circulating cell-free DNA for monitoring the biological course of thymic epithelial tumors.

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Background: Thymic epithelial tumors (TETs) are rare thoracic malignancies. Widely recognized as different histopathological entities, thymoma (T) and thymic carcinoma (TC), show a different biological behavior with a higher tendency to hematogenous dissemination for TC and thoracic recurrence for T, sharing, however, a poor prognosis when characterized by high tumor burden. Up to date, there are no specific biomarkers for monitoring the biological course of these rare tumors. Analysis of circulating cell-free DNA (cfDNA) has potential applications throughout the natural course of cancer development, diagnosis and treatment, never the less several studies have suggested that cfDNA levels closely parallel overall tumor burden. For the first time the detection and the correlation of cfDNA levels with tumor burden and histological subtype of TET, has been carried on in this monocentric study.

Methods: Starting from July 2018, serum samples from 19 patients with TET, 4 with completely resected TET (rTET) and 15 with advanced (aTET), were prospectively obtained before the initiation of therapy. Serum samples from 15 healthy donors were used as control. Five ml of blood was collected and processed within one hour or less, followed by centrifugation at 3000g for 10 minutes and storage at -80°C. The serum samples were processed for QiAamp MinElute cell-free DNA mini kit extraction (Qiagen). cfDNA quantification was assessed using Qubit Fluorometric Quantitation (Thermo Fisher Scientific). Clinical, and histopathological features of TET were assessed. Results: A median cfDNA amount in healthy donors of 0.108 ng/μl (0.083-0.868) was registered. A median cfDNA of 0.512 ng/μl (0.178-1.42) resulted for the rTET, including the value of 0.178 for the resected TC. A median cfDNA of 2.53 ng/μl (1.20-6.11) resulted for the aTET, with respectively a median of 2.845 ng/μl (1.3-5.24) and of 1.5 ng/μl (1.2-6.11) for TC and T. The highest registered level for both group of thymoma (6.11 ng/μl) and thymic carcinoma (5.24 ng/μl) correlates with the highest tumor burden. Conclusions: To the best of our knowledge, this is the first study that explore detection and quantification of cfDNA in TET. Higher baseline levels than the control group and the rTET group have been registered for both advanced T and TC. Highest levels of cfDNA may be associated with high tumor burden despite the histological subtype. We envision that further valuable information will be obtained with mutational analysis.
Anti-EGFR target therapy in advanced thymic epithelial tumors.

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Background: Thymic epithelial tumors (TETs), show a high rate of EGFR immunohistochemistry (IHC) positivity, however, the prognostic and predictive role of EGFR has not yet been well defined, and contradictory data have emerged regarding the delivering of anti-EGFR monoclonal antibodies in TETs. The outcomes of the largest series of thymoma patients treated with cetuximab, and its hypothetic immune-modulatory role, are here described.

Methods: Seven patients with diagnosis of pre-treated advanced thymoma and score positivity 2+ and 3+ at EGFR-IHC, were treated with cetuximab as off-label modality, with a dose of 400 mg/m2 in the first cycle and 250 mg/m2 in the following cycles every 7 days, until disease progression, unacceptable toxicity, withdrawal of consent. Primary endpoint was Overall Response Rate ORR, assessed radiologically. Secondary endpoints were progression Free Survival (PFS), safety, and relationship between time to cetuximab progression (TTPc) and time to previous treatment progression (TTP1). During treatment with cetuximab lymphocyte subpopulations have been carefully monitored in 4 patients affected by both thymoma and Good syndrome (GS) defined as B-cell lymphocyte counts (CD19+) <100 cells/mm3 and/or Immunoglobulin G (IgG) levels <8 g/L. Results: With a median response duration of 17 months, a partial response was achieved in five patients (ORR=71%). Statistically significant correlation was found between disease response and EGFR-IHC score 2+ vs 3+ (P, .008), which statistically correlated also with the mPFS of 14 months (95% CI, 0.0-34.5). No grade 3 or 4 adverse events were registered. TTPc was longer than TTP1 in 6/7 patients (86%), with a TTPc / TTP1 ratio equal to 2.12. During cetuximab treatment, in the longest responder patient affected also by GS, a progressive increase of IgG level and of CD4/CD8 ratio has been registered as well as an increase of both CD19+lymphocytes and CD16+ 56+ lymphocytes has been detected in all the included patients with GS.

Conclusions: Despite of the small number of patients and the off-label treatment modality, the data presented are worthy of confirmation in validated prospective studies in selected population with hyper-expression of EGFR. Further studies are also needed for deeply investigate the immunomodulatory role of cetuximab which seemed to temporarily revert sever immunodeficiency in our population.
The risk of second primary malignancy in patients with localized thymoma: A U.S. population-based study.

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Background: Thymoma is a rare neoplasm of anterior mediastinum. Patients often have an indolent disease. The prognosis of limited stage disease is excellent with a 10-year survival rate of 70 to 80%. Data regarding the risk of second primary malignancy in thymoma survivors are limited in recent years. In this study, we aimed to determine the risk of second primary malignancies (SPMs) among patients with limited stage thymoma.

Methods: We utilized the Surveillance, Epidemiology and End Results (SEER)-13 registry to identify adult patients (≥ 18 years) with limited stage thymoma. We calculated the risk of SPM, developing ≥ 6 months after an index thymoma diagnosis, using Multiple Primary Standardized Incidence Ratio and an Absolute Excess Risk (AER) between 2004 and 2010. Statistical significance was defined as p < 0.05. Results: The database identified a cohort of 1,544 patients with limited stage thymoma with a median follow-up duration of 107 months (11-281 months). A total of 176 (11.39%) patients developed SPMs with a median latency of 62.5 months (range 6-272 months). Median age at diagnosis of SPM was 69 years (range 25-96 years). Overall, SPM occurred at an observed to expected (O/E) ratio of 1.53 (95% CI 1.32-1.76), p < 0.001 with an AER of 60.52 per 10,000 patient-years at risk. A significantly increased risk was noted for cancer of lung and bronchus (O/E 1.77, 95% CI 1.21-2.52, p = 0.004; AER 12.17/10,000), skin excluding basal and squamous (O/E 2.09, 95% CI 1.04-3.75, p = 0.03; AER 5.17/10,000), urinary bladder (O/E 2.14, 95% CI 1.17-3.6, p = 0.014; AER 6.72/10,000), thyroid (O/E 3.48, 95% CI 1.4-7.17, p = 0.009; AER 4.49/10,000), and leukemia (O/E 3.26, 95% CI 1.63-5.83, p = 0.001; AER 6.86/10,000), including acute lymphocytic leukemia (O/E 16.09, CI: 1.95-58.11; AER 1.69/10,000), acute myeloid leukemia (O/E 3.83, CI: 1.04-9.8; AER 2.66/10,000) and other acute leukemia (O/E 29.45, CI: 3.57-106.39; AER 1.74/10,000). The risk was not significant for lymphoma (Hodgkin and non-Hodgkin), chronic leukemia, oropharyngeal, digestive tract and hepatobiliary cancer as SPM. Conclusions: The risk for SPMs is significantly increased in patient with thymoma compared to general population. Given the long-term risk of SPM, patient should be followed closely with judicious use of age-appropriate cancer screening.

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Background: Patients with early-stage NSCLC (stage IA–IIIA) account for ~40% of cases at diagnosis; despite surgery, 5-year survival rates are low. Platinum-based adjuvant chemotherapy is the standard of care (SoC) for stage II–IIIA disease. Although patients with stage IA NSCLC do not benefit from adjuvant chemotherapy, patients with stage IB disease and large tumors (≥4cm) do. Adjuvant chemotherapy produces a 4–5% increase in 5-year survival rates, leaving significant unmet need for improved treatments. Approximately 5% of patients with NSCLC harbor an oncogenic fusion of the ALK gene. Treatment of advanced ALK+ NSCLC with ALK inhibitors improves efficacy and safety compared with chemotherapy. Alectinib, a potent ALK inhibitor, is the SoC first-line treatment for advanced ALK+ NSCLC. The ongoing ALINA trial will compare alectinib versus chemotherapy as adjuvant treatment for patients with stage IB–IIIA ALK+ NSCLC. Methods: ALINA is a randomized, multicenter, open-label phase III study investigating the efficacy and safety of adjuvant alectinib versus chemotherapy in ALK+ NSCLC (confirmed by an FDA-approved and CE-marked test). Adult patients (≥18 years) with completely resected stage IB (tumors ≥4cm) to IIIA disease and ECOG PS 0–1 are eligible for inclusion. Patients (N=255) from ~170 centers across ~30 countries will be randomized 1:1 to receive twice-daily alectinib 600mg for 24 months or four 21-day cycles of platinum-based chemotherapy (cisplatin 75mg/m² [day 1] plus vinorelbine 25mg/m² [days 1 and 8] or gemcitabine 1250mg/m² [days 1 and 8] or pemetrexed 500mg/m² [day 1]) according to local prescribing information. Stratification factors are disease stage (stage IB [≥4cm] vs stage II vs stage IIIA) and race (Asian vs non-Asian). Treatment will continue until planned completion, disease recurrence, unacceptable toxicity, withdrawal of consent, or death, whichever occurs first. The primary endpoint is disease-free survival per investigator; secondary endpoints are overall survival, safety, and pharmacokinetics. Clinical trial information: NCT03456076.

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Background: Overexpression of interleukin (IL)-1β has been described in solid tumors, including lung. IL-1β can promote angiogenesis, tumor invasiveness, and induce tumor-associated immunosuppression through myeloid-derived suppressor cell (MDSC) accumulation in tumors. Pre-clinical data has shown that IL-1β inhibition stably reduces tumor growth, by limiting inflammation and inducing the maturation of MDSCs into M1 macrophages. Canakinumab is a human monoclonal antibody with high affinity and specificity for IL-1β. Recently, it was found that canakinumab was associated with a significant and dose-dependent reduction in incidence and mortality from lung cancer based on CANTOS study.

Methods: CANOPY-A is a phase III, randomized, double-blind, placebo-controlled study designed to evaluate efficacy and safety of adjuvant canakinumab versus placebo in patients with surgically resected NSCLC. This trial will enroll adult patients, with completely resected (R0) AJCC/UICC v.8 stages II–IIIA and IIIB (T>5 cm and N2) NSCLC, who have completed standard-of-care adjuvant treatments, including cisplatin-based chemotherapy and mediastinal radiation therapy (if applicable). Prior treatment with neoadjuvant chemotherapy or neoadjuvant radiotherapy is not permitted. Approximately 1500 patients will be randomized 1:1 to receive canakinumab (200 mg Q3W, s.c) or placebo (Q3W, s.c.) for 18 cycles or until disease recurrence, unacceptable toxicity, treatment discontinuation at the discretion of the investigator or patient, death, or loss to follow-up. Randomization will be stratified by AJCC/UICC v.8 stage, tumor histology, and region. The primary objective is disease-free survival, per investigator assessment. Secondary objectives include overall survival (key secondary objective), lung cancer-specific survival, safety, pharmacokinetics and immunogenicity of canakinumab, and patient-reported outcomes. Enrollment is ongoing. Clinical trial information: NCT03447769.
The selective personalized radioimmunotherapy for locally advanced NSCLC trial (SPRINT).

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Background: Concurrent chemoradiotherapy for locally advanced non-small cell lung cancer (LA-NSCLC) can cause significant toxicities, and disease recurrence after treatment is common. We previously demonstrated that a dose-painted radiotherapy approach provides excellent local disease control and has a favorable toxicity profile. Consolidation immunotherapy was recently shown to improve outcomes after chemoradiotherapy for LA-NSCLC, and pembrolizumab monotherapy is now a standard of care for patients with advanced high PD-L1-positive NSCLC. We hypothesize that dose-painted thoracic radiotherapy and immunotherapy without chemotherapy will be safe and effective for the treatment of biomarker-selected patients with LA-NSCLC. Methods: Patients with a new diagnosis of unresectable stage II or stage III NSCLC and performance status 0-1 will be enrolled on this phase II trial at one of three participating institutions. Twenty-five subjects with PD-L1 Tumor Proportion Score (TPS) of at least 50% will receive three cycles of induction pembrolizumab (200 mg every 3 weeks). Subjects then receive 20 fractions of dose-painted radiotherapy, where lesions with metabolic tumor volume exceeding 20 cc on FDG-PET receive a dose of 55 Gy, while smaller lesions receive a dose of 48 Gy. Subjects then receive 12 additional cycles of pembrolizumab. The primary endpoint is progression-free survival one year following study enrollment, which we hypothesize will be achieved for at least 65% of study subjects. Other endpoints include overall survival, distant metastasis-free survival, freedom from intrathoracic disease progression, adverse events, patient-reported outcomes, and physical activity metrics captured using wearable devices. In addition, we will explore markers of immune activation as prognostic factors. Approximately 38 patients with PD-L1 TPS below 50% will receive standard chemoradiotherapy and adjuvant therapy to serve as a contemporary comparison cohort. SPRINT is an innovative biomarker-driven study that explores a paradigm shift in the local and systemic therapy used to treat LA-NSCLC. This trial opened in August of 2018, and 5 subjects have been enrolled to date. Clinical trial information: NCT03523702.
Gemstone-301: A phase III clinical trial of CS1001 as consolidation therapy in subjects with locally advanced/unresectable (stage III) non-small cell lung cancer (NSCLC) who have not progressed after prior concurrent/sequential chemoradiotherapy (CRT).

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Background: In China, the standard of care for patients with unresectable Stage III NSCLC is platinum-based doublet chemotherapy given concurrently or sequentially with radiotherapy. However, the median progression-free survival (PFS) of those patients is poor (approximately 8-10 months) and 5-year overall survival (OS) rate is only 15%. Recently, treatment with durvalumab resulted in significantly longer PFS and OS than placebo for patients with locally advanced/unresectable NSCLC whose disease did not progress after definitive concurrent chemoradiotherapy (cCRT) in PACIFIC trial. CS1001 is the first full-length, fully human programmed death ligand-1 (PD-L1) targeted immunoglobin G4 (IgG4, s228p) monoclonal antibody (mAb) developed by the OMT transgenic rat platform. The Phase Ia/Ib study (GEMSTONE-101, NCT03312842) demonstrated that CS1001 was well tolerated and had promising anti-tumor activities across a range of tumors including NSCLC. GEMSTONE-301 is a randomized, double-blind, Phase III study to compare the efficacy and safety of CS1001 versus placebo as consolidation therapy in Stage III unresectable NSCLC patients. This is the first Phase III trial on an anti-PD-(L)1 mAb initiated in China for this indication.

Methods: In this trial, eligible patients with locally advanced/unresectable (Stage III) NSCLC who have not progressed after prior concurrent/sequential CRT are 2:1 randomized to receive CS1001 1200 mg, every 3 weeks or placebo, every 3 weeks. Stratification factors for randomization include ECOG status (0 versus 1), chemoradiotherapy (concurrent versus sequential) and total radiotherapy dose (≤ 60 Gy versus > 60 Gy). Study treatment will be given for up to 24 months or until disease progression, intolerable toxicity, consent withdrawal, or discontinuation for other reason. Tumor assessments will be performed every 9 weeks in the first year and every 12 weeks thereafter by RECIST v1.1. AEs will be monitored throughout the study and graded according to NCI-CTCAE v4.03. Primary endpoint is PFS evaluated by investigators according to RECIST v1.1. Secondary endpoints are PFS evaluated by Blinded Independent Center Review (BICR), objective response rate, OS, time to death/distant metastasis (TTDM), safety and pharmacokinetics (PK) profile. Enrollment is ongoing across sites in China and will continue until 402 patients are randomized. Clinical trial information: NCT03728556.
PACIFIC-2: Phase 3 study of concurrent durvalumab and platinum-based chemoradiotherapy in patients with unresectable, stage III NSCLC.

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Background: Durvalumab, a selective, high-affinity, engineered human IgG1 mAb that blocks PD-L1 binding to PD-1 and CD80, is approved in the US, Japan and several other countries, for the treatment of patients (pts) with unresectable, stage III non-small cell lung cancer (NSCLC) whose disease has not progressed following concurrent chemoradiotherapy (cCRT). These approvals were based on results from the phase 3 PACIFIC study, in which durvalumab was given 1–42 days after completion of definitive cCRT and significantly improved progression-free survival (PFS) vs placebo (median 16.8 vs 5.6 months; HR 0.52, 95% CI 0.42–0.65; p<0.001) and overall survival (OS) vs placebo (stratified HR 0.68; 99.73% CI 0.47–0.997; p=0.0025). Increasing evidence suggests additional benefit when anti-PD-1/PD-L1 therapies are administered alongside cCRT. The PACIFIC 2 study therefore aims to assess whether durvalumab plus cCRT provides additional benefit, in terms of PFS and objective response rate (ORR), compared with cCRT alone. Methods: PACIFIC 2 is a phase 3, randomized, double-blind, placebo-controlled, multicenter, international study. Approximately 300 pts with unresectable stage III NSCLC will be randomized (2:1) to receive either durvalumab (intravenous 1500 mg) every 4 weeks (q4w) + cCRT, or placebo q4w + cCRT. Eligible pts must have histologically or cytologically confirmed stage III disease; ECOG performance status 0 or 1; and life expectancy >12 weeks at randomization. Pts who discontinue treatment will be followed for safety and OS. Primary endpoints are PFS and ORR (RECIST v1.1) assessed via blinded independent central review. Secondary endpoints include OS; OS at month 24; complete response (CR) rate; duration of response; disease control rate; time to death/distant metastases; time from randomization to second progression; safety; and symptoms, functioning and global health status. Pts with a CR, partial response or stable disease will continue to receive durvalumab or placebo until clinical or RECIST v1.1-defined disease progression, or until another discontinuation criterion is met. Study enrollment began in March 2018 and recruitment is ongoing. Clinical trial information: NCT03519971.
Tislelizumab (BGB-A317) + concurrent chemoradiotherapy (cCRT) followed by tislelizumab monotherapy for newly diagnosed locally advanced, unresectable, stage III non-small cell lung cancer (NSCLC) in a phase III study (RATIONALE 001).

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**Background:** cCRT improves survival vs RT alone and is a global standard of care in patients (pts) with stage III NSCLC, but survival remains poor for these pts. Combining PD-1/PD-L1-targeting immunotherapies and cCRT may lead to synergistic activity and improved outcomes. Tislelizumab (anti–PD-1) demonstrated clinical activity and tolerability in solid tumors, including NSCLC. This phase III, randomized, double-blind, placebo-controlled study (RATIONALE 001) will evaluate efficacy and safety of tislelizumab + cCRT. **Methods:** Pts (N = 840) will be randomized 1:1:1 in a 3-arm study design to evaluate whether the timing of giving tislelizumab earlier upfront with cCRT in addition to as consolidation (Arm 1) or giving tislelizumab as consolidation only (Arm 2) will improve outcomes vs cCRT alone (Arm 3; Table). RT will be given in 2 Gy fractions to a target dose of 60 Gy (30 fractions). Chemotherapy will be investigator’s choice of cisplatin + etoposide or carboplatin + paclitaxel. A safety analysis specific to the cisplatin + etoposide component of the cCRT + tislelizumab combination is planned. All sites must pass a radiation quality assurance review process. The primary endpoint is PFS. Secondary endpoints include ORR, OS, OS at 24 months, and safety. As an exploratory endpoint, blood and tumor biomarkers will be assessed for correlations with clinical benefit. With a one-sided \( \alpha \) of 1.25%, a total of 580 PFS events are required to allow \( = 90\% \) power to detect a HR for progression or death of 0.7 for either pairwise comparison (Arm 1 vs Arm 3 or Arm 2 vs Arm 3). Key eligibility criteria are locally advanced, unresectable, stage III NSCLC; FDG-PET and brain imaging confirmation of stage III status; no prior treatment; and ECOG PS \( \leq 1 \). PD-L1 expression assessment is not required prior to randomization. EudraCT number 2018-001132-22. Clinical trial information: NCT03745222.

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* Primary objective: Assess efficacy of Arm 1 or Arm 2 vs Arm 3.
Phase 2 trial of first-line pembrolizumab with platinum doublet chemotherapy and radiotherapy in patients (pts) with unresectable, locally advanced stage III non–small-cell lung cancer (NSCLC): KEYNOTE-799.

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Background: Standard therapy for pts with unresectable stage III NSCLC is concurrent platinum doublet chemotherapy with radiotherapy (CCRT); however, this therapy does not reduce the risk of distant relapse, and the 5-y survival rate is low. The anti–PD-1 checkpoint inhibitor pembrolizumab has durable clinical activity as first-line therapy for advanced/metastatic NSCLC: as monotherapy for PD-L1–positive tumors and in combination with chemotherapy irrespective of PD-L1 status. KEYNOTE-799 evaluates the safety/efficacy of first-line pembrolizumab plus CCRT for unresectable, locally advanced stage III NSCLC. Methods: This nonrandomized, open-label phase 2 study enrolls pts ≥18 y with previously untreated, unresectable, pathologically confirmed stage IIIA–C NSCLC with measurable disease per RECIST 1.1. Pts receive 17 cycles of pembrolizumab 200 mg Q3W plus standard thoracic radiotherapy in cycles 2 and 3 (60 Gy in 30 daily 2 Gy fractions). In cycles 1–3, treatment also includes investigator’s choice of either paclitaxel 200 mg/m² and carboplatin area under the curve (AUC) 6 Q3W for 1 cycle, followed by paclitaxel 45 mg/m² and carboplatin AUC 2 weekly for 6 weeks, or cisplatin 75 mg/m² and pemetrexed 500 mg/m² Q3W (nonsquamous only). Tumor imaging occurs at baseline and Q9W until week 54, verified PD, initiation of new cancer therapy, study withdrawal, or death. AEs are graded by NCI CTCAE v4.0. Primary endpoints are the rate of grade ≥3 pneumonitis and ORR (RECIST 1.1 by blinded independent central review [BICR]); confidence intervals for both will be estimated by the Clopper-Pearson method. Secondary endpoints are PFS (RECIST 1.1 modified to follow ≤10 target lesions; ≤5 per organ by BICR), OS, and safety. PFS and OS will be analyzed by Kaplan-Meier method. Approximately 216 pts (108 per cohort) will be enrolled in 59 sites in 10 countries beginning on Nov 5, 2018. As of Feb 12, 2019, 30 pts have enrolled. Continuous interim analyses using binomial sequential testing will be performed after ≥36 pts have ≥15 weeks of follow up in each cohort, to allow earlier treatment discontinuation, if required. Clinical trial information: NCT03631784.
Phase 1 study of AMG 119, a chimeric antigen receptor (CAR) T cell therapy targeting DLL3, in patients with relapsed/refractory small cell lung cancer (SCLC).

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Background: SCLC is an aggressive neuroendocrine tumor, with initial sensitivity to chemotherapy and radiotherapy often followed by chemoresistant disease progression. Notch signaling is a key regulator of neuroendocrine differentiation in SCLC, and delta-like ligand 3 (DLL3) is an inhibitory ligand of Notch receptors. DLL3 is expressed in most SCLC tumors but minimally expressed in normal tissues, suggesting that it may be a promising target for cancer immunotherapy. AMG 119 is an adoptive cellular therapy that consists of a patient's autologous T cells that have been genetically modified ex vivo to express a transmembrane CAR that targets DLL3 and redirects cytotoxic T cell specificity to DLL3-positive cells. AMG 119 CAR T cells show potent killing of SCLC cells expressing DLL3 in vitro and inhibit tumor growth in an SCLC xenograft model in vivo.

Methods: This phase 1 study will evaluate the safety and tolerability of AMG 119 administered as a single infusion in adult patients with relapsed/refractory SCLC who have progressed after at least 1 platinum-based chemotherapy regimen. The primary objectives are to evaluate safety and tolerability and determine the maximum tolerated cell dose (MTCD) or recommended phase 2 cell dose (RP2CD). Secondary objectives are to evaluate preliminary evidence of antitumor activity, expansion and persistence of AMG 119, and trafficking of AMG 119 to the tumor in post-treatment biopsy. Key inclusion criteria include histologically confirmed SCLC with radiographically documented disease progression or recurrence after at least 1 platinum-based regimen, ECOG performance status 0–1, at least 2 measurable lesions per modified RECIST 1.1, no untreated or symptomatic brain metastases, and adequate organ function. In the cell dose exploration phase, 3–4 patients will receive a single IV infusion of AMG 119 at each cell dose. Cell dose escalation/de-escalation decisions will be guided by a modified toxicity probability interval design. The dose expansion phase will seek to confirm the MTCD or RP2CD and obtain further safety and efficacy data. Clinical trial information: NCT03392064.
Phase 1 study of AMG 757, a half-life extended bispecific T cell engager (BiTE) antibody construct targeting DLL3, in patients with small cell lung cancer (SCLC).

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Background: SCLC is an aggressive neuroendocrine tumor; response to initial chemotherapy and radiotherapy is often followed by recurrence, rapid progression, and resistance to current therapies. Delta-like ligand 3 (DLL3) is an inhibitory ligand of Notch receptors that is expressed in most SCLC tumors but minimally expressed in normal tissues. DLL3 may therefore be a promising target for T cell–redirecting immunotherapy. AMG 757 is a half-life extended BiTE antibody construct that is designed to transiently connect DLL3-positive cells to CD3-positive T cells and induce T cell–mediated cell lysis and concomitant T cell proliferation. AMG 757 induces potent killing of SCLC cell lines in vitro and inhibits tumor growth in the SHP-77 human SCLC xenograft model in vivo. AMG 757 was well tolerated in a preclinical multi-dose toxicology study in cynomolgus monkeys, with no evidence of tissue damage at weekly doses up to 4.5 mg/kg. Methods: NCT03319940 is an open-label, ascending, multiple dose, phase 1 study evaluating AMG 757. The study will initially enroll adult patients with relapsed/refractory SCLC who have progressed after at least 1 platinum-based chemotherapy regimen. Additional inclusion criteria include ECOG performance status 0–2, at least 2 measurable lesions per modified RECIST 1.1, no untreated or symptomatic brain metastases, and adequate organ function. Primary objectives are to evaluate safety and tolerability and to determine the maximum tolerated dose (MTD) or recommended phase 2 dose (RP2D). Secondary objectives are to characterize pharmacokinetics (PK) and evaluate preliminary antitumor activity. In the dose exploration phase, patients will be monitored for dose-limiting toxicities during the first 28 days. A Bayesian logistic regression model will be used to inform dose escalation/de-escalation decisions. The dose expansion phase will confirm the MTD or RP2D and collect further safety and efficacy data. AMG 757 will be administered as a short-term intravenous infusion once every 2 weeks. Alternative dosing schedules may be explored based on emerging PK and safety data. Clinical trial information: NCT03319940.
NRG Oncology CC003: A randomized phase II/III trial of prophylactic cranial irradiation with or without hippocampal avoidance for small cell lung cancer.

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Background: Multiple clinical trials have shown that prophylactic cranial irradiation (PCI) prevents brain metastases and may prolong survival in small cell lung cancer (SCLC). However, prophylactic cranial irradiation can lead to decline in cognitive function. Preclinical evidence suggests that the pathogenesis of this toxicity includes inflammatory injury to proliferating neuronal progenitor cells in the peri-hippocampal stem cell niches. We hypothesized that conformal avoidance of the hippocampal neural stem cell compartment during brain irradiation using intensity-modulated radiotherapy (IMRT) would decrease the likelihood and/or severity of this toxicity. This hypothesis was recently validated by positive results from NRG Oncology CC001, a phase III trial of hippocampal avoidance during whole-brain radiotherapy for patients with brain metastases. NRG Oncology CC003 is an ongoing randomized phase II/III trial of hippocampal avoidance during prophylactic cranial irradiation (HA-PCI) for small cell lung cancer, conducted in parallel with NRG Oncology CC001.

Methods: The primary endpoints of the phase IIR and III components are 12-month intracranial relapse rate and 6-month deterioration in Hopkins Verbal Learning Test-Revised (HVLT-R) Delayed Recall, respectively. This is a seamless phase IIR/III trial, with the phase IIR designed to demonstrate non-inferiority. If the non-inferiority margin of the phase IIR component is not exceeded, then the trial would transition to the phase III component. Following accrual of 182 of planned 172 patients on the phase IIR component, the trial closed to accrual on 10/13/17 to assess the phase IIR primary endpoint. The DSMB evaluated the IIR outcomes, and on 1/9/19, the trial was reactivated to accrue an additional 122 patients to the phase III component. Eligibility criteria include: 1) small cell lung cancer with at least partial response to chemotherapy; 2) contrast-enhanced thin-slice volumetric MRI scan; and, 3) Zubrod performance status 0-2. Supported by grant UG1CA189867 (NCORP) from the National Cancer Institute. Clinical trial information: NCT02635009.