ESMO 2020 LUNG: IMMUNOTHERAPY IN NSCLC AND MESOTHELIOMA

ONCOGENIC DRIVERS AND SMALL CELL LUNG CANCER

September 2020
On September 21 and 23, 2020, Aptitude Health brought together an international group of experts in lung cancer to a panel.

The goal of the panel was to critique and debate evidence in lung cancer and gain strategic insight into the most impactful abstracts from the ESMO 2020 virtual meeting with respect to shaping current research direction and/or changing the scope of practical clinical care.
FACULTY EXPERTS

Chair
Corey Langer, MD

Benjamin Besse, MD, PhD
Julie Brahmer, MD
Enriqueta Felip, MD, PhD
Marina Garassino, MD

Nasser Hanna, MD
Jyoti Patel, MD
Solange Peters, MD, PhD
David Spigel, MD
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<th>Time</th>
<th>Topic</th>
<th>Speaker/Moderator</th>
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<tr>
<td>1.00 PM – 1.05 PM</td>
<td>Welcome, Introductions, and Meeting Objectives</td>
<td>Corey Langer</td>
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<tr>
<td>1.05 PM – 1.25 PM</td>
<td>Immunotherapy in Stage IV NSCLC</td>
<td>Marina Garassino, David Spigel</td>
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<td>1.25 PM – 2.05 PM</td>
<td>Discussion and Key Takeaways</td>
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<td>2.05 PM – 2.20 PM</td>
<td>Immunotherapy in Stage I–III NSCLC</td>
<td>Benjamin Besse</td>
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<td>Biomarkers for Immunotherapy in NSCLC</td>
<td>Jyoti Patel</td>
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<td>Discussion and Key Takeaways</td>
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<td>3.35 PM – 3.40 PM</td>
<td>Immunotherapy in Mesothelioma</td>
<td>Nasser Hanna</td>
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<td>Discussion and Key Takeaways</td>
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<td>3.55 PM – 4.00 PM</td>
<td>Closing Remarks and Adjourn</td>
<td>Corey Langer</td>
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# AGENDA: ONCOGENIC DRIVERS AND SMALL CELL LUNG CANCER

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<td>Corey Langer</td>
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<tr>
<td>1.05 PM – 1.15 PM</td>
<td>EGFR Inhibition (Resectable and Metastatic NSCLC)</td>
<td>Solange Peters</td>
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<td>1.15 PM – 1.45 PM</td>
<td>Discussion and Key Takeaways</td>
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<td>1.45 PM – 2.00 PM</td>
<td>Targeting Other Gene Mutations (<em>BRAF, MET, HER2, KRAS</em>)</td>
<td>Enriqueta Felip</td>
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<td>2.00 PM – 2.25 PM</td>
<td>Discussion and Key Takeaways</td>
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<td>2.25 PM – 2.45 PM</td>
<td>Targeting Gene Fusions (<em>ALK, ROS1, RET, NTRK</em>)</td>
<td>David Spigel</td>
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<td>Discussion and Key Takeaways</td>
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<td>3.15 PM – 3.25 PM</td>
<td>Evolving Standards in SCLC</td>
<td>Julie Brahmer</td>
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<td>3.25 PM – 3.55 PM</td>
<td>Discussion</td>
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Abstracts: Immunotherapy in Stage IV NSCLC

ANTI–PD-1 MONOTHERAPY
IMMUNOTHERAPY COMBINATIONS
OVERCOMING RESISTANCE
NEW TARGETS
LBA51: KEYNOTE-024 5-year OS update: First-line (1L) pembrolizumab (pembro) vs platinum-based chemotherapy (chemo) in patients (pts) with metastatic NSCLC and PD-L1 tumor proportion score (TPS) ≥50%. Brahmer et al

Grade 3–5 irAEs were observed in 8% of 39 patients who received 2 years (35 cycles) of pembrolizumab.

<table>
<thead>
<tr>
<th></th>
<th>Pembrolizumab</th>
<th>Chemotherapy</th>
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</thead>
<tbody>
<tr>
<td><strong>OS</strong></td>
<td>26.3 months</td>
<td>13.4 months</td>
</tr>
<tr>
<td><strong>HR</strong></td>
<td>0.62</td>
<td>0.81</td>
</tr>
<tr>
<td><strong>95% CI</strong></td>
<td>0.48–0.81</td>
<td>0.65</td>
</tr>
<tr>
<td><strong>PFS</strong></td>
<td>7.7 months</td>
<td>5.5 months</td>
</tr>
<tr>
<td><strong>ORR</strong></td>
<td>46%</td>
<td>31%</td>
</tr>
<tr>
<td><strong>DOR</strong></td>
<td>29.1 months</td>
<td>-</td>
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</table>
LBA52: EMPOWER-Lung 1: Phase 3 first-line (1L) cemiplimab monotherapy vs platinum-doublet chemotherapy (chemo) in advanced non-small cell lung cancer (NSCLC) with programmed cell death-ligand 1 (PD-L1) ≥50%. Sezer et al.

- Patients with treated, clinically stable brain metastases, or with controlled hepatitis B/C or HIV were allowed.

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<thead>
<tr>
<th></th>
<th>Cemiplimab</th>
<th>Chemotherapy</th>
<th>HR</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>OS</strong></td>
<td>Not reached</td>
<td>14.2 months</td>
<td>0.57</td>
<td>.0002</td>
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<tr>
<td><strong>PFS</strong></td>
<td>8.2 months</td>
<td>5.7 months</td>
<td>0.54</td>
<td>&lt;.0001</td>
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<tr>
<td><strong>ORR</strong></td>
<td>39%</td>
<td>20%</td>
<td>&lt;.0001</td>
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**Overall ITT (N = 710)**

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<tr>
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<th>Cemiplimab</th>
<th>Chemotherapy</th>
<th>HR</th>
<th>P Value</th>
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<tbody>
<tr>
<td><strong>OS</strong></td>
<td>22.1 months</td>
<td>14.3 months</td>
<td>0.68</td>
<td>.0022</td>
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<tr>
<td><strong>PFS</strong></td>
<td>6.2 months</td>
<td>5.6 months</td>
<td>0.59</td>
<td>&lt;.0001</td>
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<tr>
<td><strong>ORR</strong></td>
<td>36.5%</td>
<td>21%</td>
<td>&lt;.0001</td>
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**Grade 3–5 AEs**

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<thead>
<tr>
<th></th>
<th>Cemiplimab</th>
<th>Chemotherapy</th>
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<tbody>
<tr>
<td>Neutropenia</td>
<td>1%</td>
<td>10%</td>
<td></td>
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<tr>
<td>Thrombocytopenia</td>
<td>0%</td>
<td>8%</td>
<td></td>
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<tr>
<td>Anemia</td>
<td>3%</td>
<td>16%</td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>5%</td>
<td>6%</td>
<td></td>
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LBA54: Randomized phase III trial of nivolumab in combination with carboplatin, paclitaxel, and bevacizumab as first-line treatment for patients with advanced or recurrent non-squamous NSCLC. Lee et al

<table>
<thead>
<tr>
<th></th>
<th>Nivolumab/Carboplatin/Paclitaxel/Bevacizumab</th>
<th>Placebo/Carboplatin/Paclitaxel/Bevacizumab</th>
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<tbody>
<tr>
<td>OS</td>
<td>25.4 months</td>
<td>24.7 months</td>
</tr>
<tr>
<td>HR</td>
<td>0.85</td>
<td>0.63</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.63 – 1.14</td>
<td>0.42 – 0.96</td>
</tr>
<tr>
<td>PFS, All patients</td>
<td>12.1 months</td>
<td>11.0 months</td>
</tr>
<tr>
<td>PD-L1 1%</td>
<td>1% – 49%</td>
<td>0.56 – 9.9 months</td>
</tr>
<tr>
<td>PD-L1 ≥50%</td>
<td>8.1 months</td>
<td>8.4 months</td>
</tr>
<tr>
<td>PFS, PD-L1 1%</td>
<td>6.9 months</td>
<td>8.1 months</td>
</tr>
<tr>
<td>PFS, PD-L1 ≥50%</td>
<td>0.56 – 9.9 months</td>
<td>0.42 – 0.96</td>
</tr>
<tr>
<td>Grade 3–4 AEs</td>
<td>12.5%</td>
<td>1.5%</td>
</tr>
<tr>
<td>Rash</td>
<td>5.5%</td>
<td>1%</td>
</tr>
<tr>
<td>Colitis</td>
<td></td>
<td></td>
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<tr>
<td>Pneumonitis</td>
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LBA55: WJOG @Be Study: A Phase II Study of Atezolizumab (Atez) With Bevacizumab (Bev) for Non-Squamous (Sq) Non-Small-Cell Lung Cancer (NSCLC) with High PD-L1 Expression. Seto et al.

- Patients with metastatic, nonsquamous NSCLC and no prior therapy were eligible.
- Data from 39 patients reported:
  - ORR: 64%
  - Median PFS: 15.9 months
  - 1-year OS: 71%
  - Grade >3 AEs:
    - Hypertension: 15%
    - Colitis: 5%
    - Lung infection: 5%
  - 1 patient with bronchopulmonary hemorrhage.
1313P: Phase 3 LEAP-006 Safety Run-In (Part 1): 1L Pembrolizumab (Pembro) +

- Data from 13 patients reported
- Grade 3–5 adverse events
  - Hypertension: 4 (31%)
  - Hyponatremia: 2 (15%)
  - Pneumonia: 2 (15%)
- Preliminary efficacy: 9 PR (ORR, 69%)
- Trial continues to part 2 (randomization to immunotherapy/chemotherapy with lenvatinib or placebo)
> 1260MO: Activity of OSE-2101 in HLA-A2+ non-small cell lung cancer (NSCLC)

OSE-2101 is a therapeutic cancer vaccine targeting 5 tumor antigens: CEA, HER2, MAGE2, MAGE3, and P53. Restricted to HLA-A2+ genotypes.

ATALANTE-1 enrolled patients failing platinum-based chemotherapy and immunotherapy.

Randomization between OSE-2101 and SOC (docetaxel or pemetrexed).

There were fewer SAEs with OSE-2101 (14%) compared with SOC (43%).

Step 1 results showed a 1-year OS with OSE-2101 of 46%, exceeding the futility boundary of 25%; however, the study was terminated due to the risk posed by the COVID-19 pandemic.
PROGRAM OVERVIEW: ABSTRACTS
IMMUNOTHERAPY IN STAGE IV NSCLC

> 1400P: Vibostolimab, an Anti–TIGIT Antibody, as Monotherapy and in Combination

1400P: Vibostolimab, an Anti–TIGIT Antibody, as Monotherapy and in Combination With Pembrolizumab in Anti–PD-1/PD-L1 Refractory NSCLC. Ahn et al

− 79 patients, approximately 80% with ≥2 prior lines of therapy

- Confirmed ORR
  - Vibostolimab monotherapy: 2%
  - Vibostolimab/pembrolizumab: 5%


− Patients were previously untreated or had received previous cytotoxic regimens, but no anti–PD-(L)1 therapy
  - 41 patients
  - Confirmed ORR: 24%; median PFS: 5.4 months
  - Grade 3–5 AEs (all cause): lymphopenia (7%), rash (2%)

CONTACT US TO OBTAIN A COPY OF THE FULL REPORT
> 1266P: Initial results from a phase II study (TACTI-002) of efotilagimod alpha

- ORR: 53% (1 patient with CR)
- Median PFS: 11.8 months
- 12-month OS: 71%
- Grade 3–4 dyspnea: 9%
524O: Initial results of a phase I study of MK-4830, a first-in-class anti–immunoglobulin-like transcript 4 (ILT4) myeloid-specific antibody in patients (pts) with advanced solid tumours. Siu et al

- Data from 84 patients with solid tumors; 51% with ≥3 prior lines of therapy
- ORR
  - MK-4830: 2%
  - MK-4830/pembrolizumab: 24%
- Grade 3–4 treatment-related AEs
  - MK-4830: 6%
  - MK-4830/pembrolizumab: 8%
- Expansion cohorts in progress, including first-line NSCLC with carboplatin/pemetrexed
Discussion: Immunotherapy in Stage IV NSCLC
Recent Updates/Approvals

There were varied reactions to the 5-year update of KEYNOTE-024 comparing pembrolizumab with chemotherapy in patients with a PD-L1 expression level of ≥50%.

On one hand, the 5-year OS of 32% was seen as exciting, since high long-term survival rates were unheard of just a few years ago. On the other hand, one of the experts stated that their experience has been more modest and similar to the KEYNOTE-042 study, with a median OS of approximately 20 months.

Regarding the updated results from CheckMate 227, which compared nivolumab/ipilimumab with chemotherapy, expert opinion is that the leveling of the OS curve after 2 to 3 years is encouraging.
Recent Updates/Approvals

It was thought by one of the experts that the major effect of the approval of atezolizumab based on the IMpower110 trial is that atezolizumab can be used as the reference arm in future combination studies. Atezolizumab will thus be a direct competitor to the pembrolizumab-based regimens.

Expert opinion is that the EMPOWER-Lung 1 trial of cemiplimab vs chemotherapy in patients with PD-L1 expression ≥50% needs additional follow-up to determine if the outcomes compare with similar studies (eg, KEYNOTE-024).
Choosing a Therapeutic Approach

The experts discussed factors in choosing between the different immunotherapy-based approaches available (eg, single-agent immunotherapy, immunotherapy/chemotherapy, immunotherapy/immunotherapy).

- Patients with a PD-L1 <1% were thought to be a population that could benefit from the addition of a CTLA-4 inhibitor. For example, in CheckMate 227, the 3-year survival was approximately 33% with nivolumab/ipilimumab regardless of PD-L1 expression level.

- Given that nephritis and myelosuppression are associated with cytotoxic agents, chemotherapy-free regimens may be suitable for a subset of patients if they have a modest disease burden.

- On the other hand, for patients with high-volume, symptomatic disease, chemotherapy may be an important component of therapy.

- Never smokers were thought by experts to not respond well to single agents.
**New Targets**

Expert opinion is that TIGIT is a promising target; however, it is also thought that much of the excitement is based on a small, early data set in the CITYSCAPE trial. Similar concerns were raised regarding the small studies of agents targeting LAG3 or ILT4, and one of the experts did not think these approaches would improve outcomes more than nivolumab/ipilimumab or chemotherapy/immunotherapy.

The experts think the connection between higher PD-L1 expression and benefit from an anti-TIGIT antibody is not clear. However, one of the experts related data from resected patients in which there was a correlation between TIGIT expression and PD-L1 expression on lymphocytes. Additionally, expert opinion is that the biology of TIGIT has not yet been sufficiently investigated, and a lack of robust biomarkers for anti-TIGIT antibodies means that we are back to investigating new agents in an empiric fashion, which poses a higher risk of both failure of clinical trials as well as discarding drugs because proper selection was not done.
New Targets

Expert opinion is that future development of immunotherapeutic agents should focus on first-line therapy, rather than start with relapsed/refractory patients, as has traditionally been done.

Regarding long-term outcomes with immunotherapy, the experts think that while ORR and PFS give rapid answers, these endpoints may not be good predictors of long-term OS.
The experts expressed concern at the lack of patient selection, other than PD-L1 expression, in patient accrual for trials of new immunotherapies, including the anti-TIGIT antibody tiragolumab. The experts recommended to have a more thorough understanding of which patients will respond to new approaches (eg, anti-TIGIT); otherwise the field runs the risk of repeating the previous approach of empiric combinations with chemotherapy, which resulted in many failures of clinical trials. Experts are concerned that there is still heterogeneity even when patients are selected for high PD-L1 expression. This phenomenon was described by one of the experts as being magnified in clinical practice, where responses to a regimen are often less robust than those seen in the corresponding clinical trials.
Combinations

There is support from the experts for further investigation of immunotherapy with antiangiogenic agents (eg, TKIs or antibodies), as is being done in other tumor types such as renal cell carcinoma. The caveat is that bevacizumab was seen as having a history of providing only a modest improvement in efficacy.

Regarding the TASUKI trial (abstract LBA54) of carboplatin/paclitaxel/bevacizumab with either nivolumab or placebo, expert opinion is that additional follow-up is needed, and that taxanes are not the best partners for immunotherapy.
Poor-Performance Patients

The experts think there are insufficient data on immunotherapy in patients with a poor performance status (ie, PS 2). One of the experts with experience in the early development of immunotherapy mentioned that patients with poor PS did well, suggesting PS 2 status does not necessarily disqualify patients from receiving immunotherapy.
Abstracts: Immunotherapy in Stage I–III NSCLC

PERIOPERATIVE IMMUNOTHERAPY

IMMUNOTHERAPY IN UNRESECTABLE STAGE III NSCLC

- Patients received durvalumab 750 mg, days 1, 15, 29
- In 46 patients, the rate of R0 resection (primary endpoint) was 89%
- The rate of MPR was 19%
- However, the trial was stopped due to an excess of 90-day postoperative mortality (4 deaths [9%]); the deaths were not related to durvalumab treatment

1215O: Neoadjuvant atezolizumab (A) for resectable non-small cell lung cancer (NSCLC): results from the phase II PRINCEPS trial. Besse et al

- Patients received 1 injection of atezolizumab 1200 mg
- Data presented from 29 patients
- Major pathological response in 14%; pathological response ≥50% in 41%
> 1237MO: SAKK 16/14: Anti–PD-L1 antibody durvalumab in addition to neoadjuvant chemotherapy in patients with stage IIIA(N2) non–small cell lung cancer (NSCLC) — A multicenter single-arm phase II trial. Rothschild et al — Data from 67 patients — 55 patients proceeded to surgery — Pathologic CR in 10 patients (18%); nodal downstaging in 37 patients (67%) — 1-year EFS: 73% — Median OS not reached with a median follow-up of 28.6 months.
PROGRAM OVERVIEW: ABSTRACTS
IMMUNOTHERAPY IN STAGE I–III NSCLC

> LBA49: Durvalumab after chemoradiotherapy in Stage III NSCLC: 4-year survival update from the PACIFIC trial. Faivre-Finn et al. 1247P – Uptake of durvalumab in the management of stage III NSCLC: The real-world application of PACIFIC. Kuang et al.

- Analysis of 196 patients in British Columbia, Canada, who underwent concurrent CRT
  - 99 patients (51%) did not receive consolidation durvalumab
    - 35 due to no documented discussion with the physician
    - 21 due to patient preference
    - 19 due to disease progression after CRT

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<thead>
<tr>
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<th>Durvalumab</th>
<th>Placebo</th>
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<tr>
<td><strong>OS</strong></td>
<td>Median</td>
<td>HR</td>
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<tr>
<td>4-year</td>
<td>47.5 months</td>
<td>0.71</td>
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<tr>
<td><strong>PFS</strong></td>
<td>Median</td>
<td>HR</td>
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<tr>
<td>4-year</td>
<td>17.2 months</td>
<td>0.55</td>
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Discussion: Immunotherapy in Stage I–III NSCLC
Unresectable Stage III NSCLC

The experts confirmed that patients with unresectable stage III NSCLC and PD-L1 expression <1% should not be excluded from consolidation durvalumab after CRT, as was done in the European approval.

One of the experts pointed out that one-third of the specimens in PACIFIC were not tested, and that results with the SP263 antibody that was used for PD-L1 testing likely do not correlate exactly with those of the 22C3 antibody.

Further, PD-L1 scores can vary widely between the primary tumor and a locoregional lymph node, so it was thought that using PD-L1 to exclude patients from consolidation durvalumab was shortsighted.

Furthermore, in a single-arm, phase II trial of consolidation pembrolizumab after CRT (LUN 14-179), PD-L1 expression was not a predictor of benefit.
IMMUNOTHERAPY IN STAGE I–III NSCLC DISCUSSION (2/4)

Unresectable Stage III NSCLC

There were still data from the PACIFIC trial that the experts think would be of interest. These include the outcome of patients randomized to the placebo arm who received immunotherapy upon disease progression. Additionally, the experts want to know how many patients underwent PET imaging in PACIFIC as part of workup, since it is possible that some patients had occult stage IV disease, which may have resulted in inferior outcomes in the placebo group.

Experts thought that the data on real-world use of consolidation durvalumab (Abstract 1247P) were actually more prognostic, rather than demonstrating the effect of durvalumab, since many of the patients not receiving durvalumab had a poor PS or other unfavorable characteristics.
Regarding patients with stage III NSCLC and a sensitizing EGFR mutation, most of the experts (n = 3), in describing their treatment choice would give consolidation durvalumab, while 1 of the experts would recommend osimertinib. The results of SWOG 0023 were mentioned as a reason not to give an EGFR TKI. In this study, patients received maintenance gefitinib or placebo after CRT and consolidation docetaxel. The patients randomized to gefitinib actually had an OS that was 1 year less than patients receiving placebo. The optimal management of progression on consolidation durvalumab in a patient with EGFR mutation-positive disease is not known; however, the use of osimertinib in proximity to immunotherapy was thought to raise the risk of pulmonary toxicity.

One of the experts expressed concern that ongoing trials of immunotherapy in stage III NSCLC continue consolidation immunotherapy indefinitely, which is perceived as suboptimal in a setting where patients are treated with curative intent. As with the metastatic setting, the optimal duration of consolidation immunotherapy still needs to be investigated; one of the experts referred to research led by Maximilian Diehn at Stanford where ctDNA is being studied as a predictor of recurrence. This research may have possible implications for directing duration of therapy.
Resectable NSCLC

Expert opinion is that immunotherapy will become part of the standard of care in early stage NSCLC.

The experts were divided on major pathologic response (MPR) as an endpoint for trials of neoadjuvant immunotherapy in lung cancer. The main concerns were a lack of prospective data correlating MPR and survival, and the technical complexity of pathologic analysis of resected tumor samples.

At one expert's institution, MPR is assessed according to guidelines specific to immunotherapy, which factor in characteristics such as fibrosis and immune infiltration.

Expert opinion is that postoperative therapy should continue to be investigated for patients with stage IA disease, as ~25% of these patients have disease recurrence.

There is concern from some experts that the quality of surgery has been in decline, with a loss of ability to perform complete resections in some centers.
Abstracts: Biomarkers for Immunotherapy in NSCLC
LBA53: Precision Immuno-Oncology for advanced Non-Small Cell Lung Cancer patients (pts) treated with PD1/L1 immune checkpoint inhibitors (ICIs): a first analysis of the PIONeeR Study. Barlesi et al

Patients receiving immunotherapy underwent rebiopsy and blood biopsy

Results from first 100 patients presented

Potential predictive role for density of cytotoxic T cells in the tumor, density of immunosuppressive cells (Treg, MDSC), and PD-L1-positive cell density
1929O: Soluble PD-L1 and Circulating CD8+PD1+ and NK Cells Enclose a Highly Prognostic and Predictive Immune Effector Score in Immunotherapy Treated NSCLC patients. Mazzaschi et al - Translational study to determine if blood-based descriptors of proinflammatory, immunosuppressive, or antitumor response can form the basis of a predictive profile for immunotherapy - Data reported from 109 patients - Two scores were defined - Immune Effector Score (IES), based on levels of soluble PD-L1, CD8+PD1+ T lymphocytes, and NK cells - Lung Immune Prognostic Index (LIPI), based on derived neutrophil-to-lymphocyte ratio and LDH level - Integration of IES and LIPI was able to stratify patients into 3 prognostic groups in response to immunotherapy.
1265P: IMpower150: a post hoc analysis of efficacy outcomes in patients with mutant KRAS, STK11, and KEAP1 mutations. West et al

Patients with mutant KRAS obtained a greater OS benefit with the addition of atezolizumab to bevacizumab/carboplatin/paclitaxel (HR, 0.50) compared with patients with wild-type KRAS (HR, 0.98).

Patients with mutant KRAS and concomitant mutant STK11 and/or KEAP1 also benefitted from the addition of atezolizumab, although the benefit was somewhat less (HR, 0.60).

Similar trends observed for PFS:
- Mutant KRAS (HR, 0.42) vs wild-type KRAS (HR, 0.65)
- Mutant KRAS and concomitant mutant STK11 and/or KEAP1 (HR, 0.49)
1279P: Impact of KRAS Mutations and Subtypes on Efficacy of Immune-Checkpoints Inhibitors (ICI) in Non-Small Cell Lung Cancer (NSCLC). Mazieres et al

Analysis of data from 913 patients with advanced NSCLC receiving immunotherapy:

- 413 patients had a KRAS mutation
- A trend toward increased benefit from immunotherapy was observed in patients with a KRAS G12C mutation

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<th>Type</th>
<th>ORR</th>
<th>PFS (months)</th>
<th>OS (months)</th>
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<tbody>
<tr>
<td>KRAS G12C</td>
<td>27%</td>
<td>4</td>
<td>15</td>
</tr>
<tr>
<td>Non-G12C</td>
<td>19%</td>
<td>2.9</td>
<td>11.9</td>
</tr>
<tr>
<td>Wild-Type</td>
<td>13%</td>
<td>3.5</td>
<td>14.1</td>
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</table>
> 1280P: Analysis of ARID1A and ARID1B as potential biomarkers for NSCLC

In both cohorts, patients with mutant ARID1A and ARID1B had a higher tumor mutational burden (TMB). In the Simcere cohort, the 40 patients with mutant ARID1A and ARID1B had a longer OS compared with the 310 patients with wild-type genes (P = .038).
Discussion: Biomarkers for Immunotherapy in NSCLC
Despite research efforts over the past years, the experts think that PD-L1 still remains the best biomarker for clinical use. While newer markers such as ARID1A, STK11, and KEAP1 may show some predictive power, one of the experts mentioned that there have been patients with these markers who nevertheless had an outcome opposite of what was predicted. It is thought that single genes or even a collection of a few genes will not provide sufficient predictive power. Experts thought that the proliferation of diagnostic companies may lead physicians to rely on certain biomarkers based on less-than-robust data. The experts think large-scale cooperation will be necessary to generate a predictive profile for immunotherapy beyond the current standard of PD-L1 expression.
One of the experts recommended a robust, integrated analysis of PD-L1 and TMB, which is lacking in some key trials, such as CheckMate 9LA and CheckMate 227. On a related note, expert opinion is that TMB still needs much optimization before becoming a functional biomarker for immunotherapy. Expert opinion is that negative predictive markers in immunotherapy can also represent an opportunity to develop new therapies, as these would identify unmet medical needs.
Abstracts: Immunotherapy in Mesothelioma
**WCLC 2020 Virtual Presidential Symposium, Abstract 3: First-Line Nivolumab + Ipilimumab vs Chemotherapy in Unresectable Malignant Pleural Mesothelioma**

- **Primary endpoint was OS**

<table>
<thead>
<tr>
<th></th>
<th>Nivolumab/Ipilimumab</th>
<th>Chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>OS (All patients)</strong></td>
<td>18.1 months</td>
<td>14.1 months</td>
</tr>
<tr>
<td><strong>OS by histology</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epithelioid</td>
<td>18.7 months</td>
<td>18.1 months</td>
</tr>
<tr>
<td>Non-epithelioid</td>
<td>16.5 months</td>
<td>8.8 months</td>
</tr>
<tr>
<td><strong>OS by PD-L1</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1%</td>
<td>17.3 months</td>
<td>18.0 months</td>
</tr>
<tr>
<td>≥1%</td>
<td>16.5 months</td>
<td>13.3 months</td>
</tr>
<tr>
<td><strong>PFS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>6.8 months</td>
<td>7.2 months</td>
</tr>
<tr>
<td><strong>Grade 3–4 AEs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>5%</td>
<td></td>
</tr>
<tr>
<td>Hepatic</td>
<td>5%</td>
<td></td>
</tr>
<tr>
<td>Skin</td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td>Pulmonary</td>
<td>1%</td>
<td></td>
</tr>
</tbody>
</table>
Discussion: Immunotherapy in Mesothelioma
IMMUNOTHERAPY IN MESOTHELIOMA

DISCUSSION

> The experts think the CheckMate 743 trial comparing nivolumab/ipilimumab with first-line chemotherapy has created a new standard of care of immunotherapy in mesothelioma, but mainly in patients with non-epithelioid histology.

> Experts think that in the future there will be a more pronounced distinction between epithelioid and sarcomatoid histologies.

Regarding the first-line DREAM3R trial of durvalumab plus chemotherapy, expert opinion is that patients with epithelioid histology are a potential target population, as patients with this histology did not benefit from nivolumab/ipilimumab in CheckMate 743.

In light of the benefit seen with nivolumab/ipilimumab, the experts would not open the trial at their institution with a reference arm of chemotherapy alone.

There was still interest from the experts regarding antiangiogenic agents in mesothelioma, potentially as a partner for nivolumab/ipilimumab to address T-lymphocyte trafficking and normalization of vasculature.
Abstracts: EGFR Inhibition (Resectable and Metastatic)

ADJUVANT THERAPY
COMBINATIONS
OVERCOMING RESISTANCE
EGFR EXON 20 MUTATIONS
LBA1: Osimertinib adjuvant therapy in patients (pts) with early stage EGFR mutated (EGFRm) NSCLC after tumour resection (ADAURA): sites of disease recurrence. Tsuboi et al

DFS events occurred in 11% of patients in the osimertinib arm and 46% of patients receiving placebo. The probability of CNS recurrence at 18 months was <1% with osimertinib and 9% with placebo.

<table>
<thead>
<tr>
<th></th>
<th>Osimertinib</th>
<th>Placebo</th>
<th>HR</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNS DFS Median</td>
<td>Not reached</td>
<td>48.2</td>
<td>98%</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Year</td>
<td></td>
<td>82%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CONTACT US TO OBTAIN A COPY OF THE FULL REPORT
> 1294P: RELAY, erlotinib plus ramucirumab or placebo in untreated EGFR-mutated metastatic NSCLC: outcomes by EGFR mutation type. Nakagawa et al

− PFS benefit appeared similar between exon 19/exon 21 subgroups
− DOR appeared to trend in favor of exon 19 mutations

<table>
<thead>
<tr>
<th>HR</th>
<th>95% CI</th>
<th>Exon 19</th>
<th>Exon 21</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.595</td>
<td>0.588–0.60</td>
<td>19.6</td>
<td>19.4</td>
</tr>
<tr>
<td>0.42</td>
<td>0.41–0.45</td>
<td>12.5</td>
<td>11.2</td>
</tr>
<tr>
<td>DOR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.542</td>
<td>0.731–0.75</td>
<td>18.2</td>
<td>16.2</td>
</tr>
<tr>
<td>0.38</td>
<td>0.49–0.54</td>
<td>11.0</td>
<td>11.1</td>
</tr>
</tbody>
</table>
1259O: A randomized phase II study of osimertinib with or without bevacizumab in advanced lung adenocarcinoma patients with EGFR T790M mutation (West Japan Oncology Group 8715L). Toi et al

Trial randomized 81 patients with EGFR-TKI–resistant, T790M-positive NSCLC

Despite higher ORR with the combination, no PFS improvement was observed—Grade 3 proteinuria or hypertension significantly higher with the addition of bevacizumab ($P<.05$; values not quantified on presentation)

<table>
<thead>
<tr>
<th></th>
<th>Osimertinib/Bevacizumab</th>
<th>Osimertinib</th>
<th>HR</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS</td>
<td>9.4 months</td>
<td>13.5 months</td>
<td>1.44</td>
<td>.20</td>
</tr>
<tr>
<td>OS</td>
<td>Not reached</td>
<td>22.1 months</td>
<td>1.02</td>
<td>.96</td>
</tr>
<tr>
<td>ORR</td>
<td>72%</td>
<td>55%</td>
<td></td>
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</tr>
</tbody>
</table>
1284P: MET Inhibitor Capmatinib Plus EGFR Tyrosine Kinase Inhibitor Nazartinib

For EGFR mutant non-small cell lung cancer. Felip et al. Potential benefit with the addition of capmatinib observed in MET-positive patients, but not in unselected cohorts (Groups 1 and 3). Efficacy:

- Group 1 (Pretreated): n = 52
  - MET Positive: n = 23
  - MET Negative: n = 43
  - ORR: 29%
  - PFS: 5.55 months

- Group 3 (Frontline): n = 47
  - MET Positive: n = 23
  - MET Negative: n = 43
  - ORR: 62%
  - PFS: 11.01 months

Grade 3-4 AE:

- Group 1 (Pretreated)
  - Peripheral edema: 6%
  - Nausea: 8%
  - Rash: 15%
  - Lipase increase: 11.5%

- Group 3 (Frontline)
  - Peripheral edema: 6%
  - Nausea: 4%
  - Rash: 4%
  - Lipase increase: 6%
> 1258O: Amivantamab (JNJ-61186372), an EGFR-MET bispecific antibody, in combination with lazertinib, a 3rd generation tyrosine kinase inhibitor (TKI), in advanced EGFR NSCLC. Cho et al − Data reported from 2 cohorts: Treatment-naive (n = 20) and osimertinib-resistant (n = 45) − ORR • Treatment naive: 100% • Osimertinib-resistant: 36% − Safety results • All-cause grade 3 AEs: 34% • Grade ≥3 TRAEs: rash (4%), hypoalbuminemia (2%) − Phase III MARIPOSA trial (NCT04487080) ongoing in treatment-naive patients • Arm A: Amivantamab/lazertinib • Arm B: Osimertinib • Arm C: Lazertinib
1293P: IMpower150: updated efficacy analysis in patients with EGFR mutations.

<table>
<thead>
<tr>
<th></th>
<th>Any EGFR mutation</th>
<th>Sensitizing EGFR mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PFS</strong></td>
<td>Any EGFR mutation</td>
<td>Sensitizing EGFR mutation</td>
</tr>
<tr>
<td></td>
<td>10.2 months</td>
<td>7.1 months</td>
</tr>
<tr>
<td></td>
<td>10.3 months</td>
<td>6.1 months</td>
</tr>
<tr>
<td><strong>OS</strong></td>
<td>Any EGFR mutation</td>
<td>Sensitizing EGFR mutation</td>
</tr>
<tr>
<td></td>
<td>26.1 months</td>
<td>20.3 months</td>
</tr>
<tr>
<td></td>
<td>29.4 months</td>
<td>18.1 months</td>
</tr>
</tbody>
</table>

**HR**

- **PFS**
- **OS**

**95% CI**

- **PFS**
- **OS**

**P**

- **PFS**
- **OS**

**CONTACT US TO OBTAIN A COPY OF THE FULL REPORT**
PROGRAM OVERVIEW: ABSTRACTS
EGFR INHIBITION (RESECTABLE AND METASTATIC)

> 1296P: BLU-945, a highly potent and selective 4th generation EGFR TKI for the treatment of EGFR T790M/C797S resistant NSCLC. Schalm et al

- Highly selective for EGFR T790M with or without C797S
- Preclinical study using cell-line derived and patient-derived tumor xenografts
- Single-agent BLU-945 resulted in stable disease in a T790M/C797S PDX model, while combination with osimertinib or gefitinib resulted in tumor regression
- Clinical trials anticipated to begin in the first half of 2021
LBA62: Efficacy and Safety of Patritumab Deruxtecan (U3-1402), a Novel HER3 Directed Antibody Drug Conjugate, in Patients (Pts) with EGFR-mutated (EGFRm) NSCLC. Yu et al

- 57 patients
- 100% with prior EGFR TKI; 86 with prior osimertinib
- ORR: 25%
- Activity observed with multiple mechanisms of TKI resistance, including alterations in MET, HER2, BRAF, PIK3CA, and EGFR C797S
- Median DOR: 6.9 months
- Grade ≥3 AEs
  - Neutropenia (19%)
  - Thrombocytopenia (28%)
  - Fatigue (9%)
- Three ILD events considered to be related to therapy
1388P: Poziotinib in advanced NSCLC with *EGFR* or *HER2* exon 20 insertion

- Data from 30 patients with *EGFR* or *HER2* exon 20 insertions and any line of therapy
- Previous lines of therapy not detailed in the poster, but the abstract stated a median of 1 prior line of therapy
- ORR: 30%
- PFS: 5.6 months
- OS: 9.5 months
- Grade 3–4 AEs
  - Rash (50%)
  - GI toxicity (31%)
  - Mucositis (7%)
PROGRAM OVERVIEW: ABSTRACTS
EGFR INHIBITION (RESECTABLE AND METASTATIC)

> 1261MO: Updated results from a phase 1/2 study of mobocertinib (TAK-788) in NSCLC with EGFR exon 20 insertions (exon20ins). Riely et al

- Expansion cohort of mobocertinib 160 mg/day in 28 previously treated patients with an EGFR exon 20 insertion
  - 21% had received prior EGFR/HER2 TKIs
  - ORR: 43%
  - DOR: 13.9 months
  - Grade ≥3 AEs
    - Diarrhea (32%)
    - Nausea (11%)
    - Vomiting (7%)

CONTACT US TO OBTAIN A COPY OF THE FULL REPORT
LBA61: First Analysis of RAIN-701: Study of Tarloxitinib in Patients with Non-small Cell Lung Cancer (NSCLC) EGFR Exon 20 Insertion, HER2-activating Mutations & Other Solid Tumors with NRG1/ERBB Gene Fusions. Liu et al

- Prodrug activated under hypoxic conditions to a pan-HER TKI
- No responses in 11 patients with EGFR exon 20 insertions
- 2 PRs in 9 patients (22%) with HER2 exon 20 insertions
- Grade ≥3 AEs
  - QT prolongation (35%)
  - Rash (4%)

CONTACT US TO OBTAIN A COPY OF THE FULL REPORT
> 1345P: Preliminary Safety and Activity of CLN-081 in NSCLC with *EGFR* Exon 20 Insertion Mutations (Ins20). Piotrowska et al. Data from 22 patients presented:

- Median 3 prior systemic therapies
- Prior TKI, including poziotinib or mobocertinib in 12 patients (55%)
- ORR: 35% (6 of 17 evaluable patients)
- No grade ≥3 rash, stomatitis, or dry skin
- Grade 2 rash in 27% of patients
Discussion: EGFR Inhibition (Resectable and Metastatic)
Resectable Disease

The experts discussed implications of the ADAURA trial.

-most of the experts think the CNS data from ADAURA are encouraging and increase confidence in recommending adjuvant osimertinib in the absence of OS data. One of the experts still expressed concern with recommending adjuvant osimertinib, given the number of negative trials with adjuvant EGFR TKIs, and would like to see an OS benefit in ADAURA.

-the data in patients with stage II/IIIA disease was otherwise seen as clearly convincing; for stage IB disease, experts would carefully discuss with the patient.

-the experts thought that osimertinib should follow, not replace, adjuvant chemotherapy.

-there was concern from one of the experts at the lack of PET scans prior to surgery in ADAURA, as there may have been patients with occult metastatic disease.

-following progression on adjuvant osimertinib, most of the experts would manage patients the same way as progression on first-line osimertinib in the metastatic setting (eg, chemotherapy with bevacizumab or immunotherapy).

-as a result of ADAURA, the experts believe it would be unethical to recruit patients to adjuvant trials using earlier-generation EGFR TKIs.
Metastatic Disease

The combination of osimertinib with first-line chemotherapy is seen by experts as challenging, as it involves the patient coming in for IV infusions, so the benefit with the combination will need to be substantially better than osimertinib alone for wide uptake in community settings.

Regarding the combination of amivantamab/lazertinib, expert opinion is that the data in the first-line setting are impressive, but are based on small numbers and short follow-up (4 to 7 months).

The experts' opinions were mixed in terms of developing amivantamab/lazertinib in the first-line setting or after recurrence on adjuvant osimertinib. One of the experts discussed that although toxicities were generally grade 1/2, the therapies would be given long-term. Additionally, using this combination in the second-line setting would allow chemotherapy to be pushed to the next line of therapy.
Experts think that phase III data would be needed to replace osimertinib in the first-line setting, as phase II trials with surrogate endpoints are not always reliable. The bar for a new regimen would be a median PFS of 2 years and an OS of at least 4 years to offset toxicity.

Expert opinion is that although circulating tumor DNA is a useful tool for upfront testing for EGFR mutations when there is insufficient tissue, there does not appear to be a role for choosing subsequent therapy, due to lower sensitivity and the inability to detect SCLC transformation compared with tissue-based testing.
The experts think agents for EGFR exon 20 mutations, such as mobocertinib (TAK-788) and poziotinib, are associated with significant toxicity, which would complicate development in the first-line setting. Chemotherapy is sometimes preferred ahead of these agents because of toxicity. However, one of the experts mentioned that unlike patients with the classical sensitizing EGFR mutations, patients with EGFR exon 20 mutations are not extremely responsive to chemotherapy, so mobocertinib and poziotinib may be able to compete in terms of efficacy.
Abstracts: Targeting Other Gene Mutations (BRAF, MET, HER2, KRAS)
PROGRAM OVERVIEW: ABSTRACTS
TARGETING OTHER GENE MUTATIONS (BRAF, MET, HER2, KRAS)

> 1285P: Capmatinib in patients with METex14-mutated advanced non-small cell lung cancer who received prior immunotherapy: the phase 2 GEOMETRY mono-1 study. Vansteenkiste et al

- Data presented on 32 patients with and 68 patients without prior immunotherapy
- ORR was numerically higher in patients with prior immunotherapy (62.5%) than those without (34%)

1346P: Comparison of clinical outcomes of patients with MET∆ex14 NSCLC treated with first-line capmatinib in the GEOMETRY mono-1 study with those of a cohort of real-world patients. Wolf et al

- Efficacy appears to be higher with capmatinib compared with standard first-line chemotherapy with or without immunotherapy; however, this is not a prospective, randomized comparison
  - PFS: 12.0 months vs 6.2 months
  - OS: 20.8 months vs 14.8 months

CONTACT US TO OBTAIN A COPY OF THE FULL REPORT
1283P: Tepotinib in patients (pts) with advanced NSCLC with MET exon 14 skipping: overall efficacy results from VISION Cohort A. Mazieres et al - Updated results presented from 146 patients - 50% with prior platinum-based chemotherapy - ORR: 45% - PFS: 8.9 months - Grade ≥3 peripheral edema was reported in 7.5%.

1286P: Activity of tepotinib in brain metastases (BM): Preclinical models and clinical data from patients (pts) with MET exon 14 skipping NSCLC. Viteri et al - 22 patients with baseline brain metastases - ORR by independent review: 57% - PFS by independent review: 10.9 months

PROGRAM OVERVIEW: ABSTRACTS TARGETING OTHER GENE MUTATIONS (BRAF, MET, HER2, KRAS)

CONTACT US TO OBTAIN A COPY OF THE FULL REPORT
LBA60: ZENITH20, a multinational, multi-cohort phase 2 study of poziotinib in NSCLC patients with EGFR or HER2 exon 20 insertion mutations. Socinski et al.

The current presentation focused on previously treated patients with HER2 exon 20 insertions.

Data from 90 patients presented, of whom 19% received previous chemotherapy, anti-HER2 therapy, or immunotherapy.

In 74 evaluable patients:

- ORR: 35%
- DOR: 5.1 months
- PFS: 5.5 months

Grade 3 AEs:

- Diarrhea (26%)
- Rash (30%)
- Stomatitis (23%, includes grade 4 in 1%)
1257O: Durability of clinical benefit and biomarkers in patients (pts) with advanced non-small cell lung cancer (NSCLC) treated with AMG 510 (sotorasib). Hong et al.

P: Clinicopathological characteristics and treatment patterns observed in real-world care in patients with advanced non-small cell lung cancer (NSCLC) and KRAS G12C mutations in the Flatiron Health (FH) - Foundation Medicine (FMI) Clinico-Genomic Database (CGDB). Aggarwal et al. In 743 patients with advanced NSCLC and KRAS G12C, 61% were female. Nearly all patients were former/current smokers (97%), and most patients had nonsquamous histology (91%).

**Results/Efficacy**

All Sotorasib Doses (N = 59)

- Sotorasib 960 mg/day (n = 34)
  - Median prior lines of therapy: 3 lines
  - ORR: 32%
  - Median PFS: 6.3 months
  - Median DOR: 10.9 months

Selected Grade ≥3 Adverse Events

<table>
<thead>
<tr>
<th>All Sotorasib Doses (N = 59)</th>
<th>Any</th>
<th>Diarrhea</th>
<th>ALT increase</th>
<th>AST increase</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>19%</td>
<td>5%</td>
<td>10%</td>
<td>5%</td>
</tr>
</tbody>
</table>

**PROGRAM OVERVIEW: ABSTRACTS**

TARGETING OTHER GENE MUTATIONS (*BRAF, MET, HER2, KRAS*)

CONTACT US TO OBTAIN A COPY OF THE FULL REPORT
Discussion: Targeting Other Gene Mutations (BRAF, MET, HER2, KRAS)
The experts discussed the development of the KRAS G12C inhibitor sotorasib. While the updated response rate was lower than previous reports, the experts think this agent nevertheless showed activity in patients with refractory disease, for whom there is a lack of options besides chemotherapy. Additionally, sotorasib is viewed by the experts as a tolerable drug. It is thought by most of the experts that docetaxel is an appropriate comparator for sotorasib in the CodeBreak 200 trial. Since the trial is enrolling previously treated patients, many, if not most, patients will have had prior immunotherapy. One of the experts mentioned that the efficacy of docetaxel may be higher following immunotherapy, risking a negative result in CodeBreak 200. It was therefore recommended to identify the patients most likely to respond to sotorasib, and to enrich the trial for those patients. Alternatively, it may be necessary to combine other agents with sotorasib to extend activity. Another aspect of importance to the experts is the CNS activity of the KRAS inhibitors, which may become a distinguishing factor between the different agents in this class.
TARGETING OTHER GENE MUTATIONS (*BRAF, MET, HER2, KRAS*)
DISCUSSION (2/3)

HER2

For patients with HER2 mutations, expert opinion is that the response rate with trastuzumab deruxtecan in the DESTINY-Lung01 trial warrants investigation in the first-line setting. However, there is concern over the pulmonary toxicity observed with this agent across tumor types.

There was enthusiasm from the experts for antibody-drug conjugates, which are seen as agents that may change the way patients are treated in the future.
In patients with MET exon 14 mutations, the experts use capmatinib in the first-line setting (in the US, where it is approved). There are issues reported with edema, as diuretics do not seem to ameliorate this toxicity.

Expert opinion is that MET gene amplification needs to be better defined, and that amplification needs to be distinguished from polysomy. Furthermore, tissue is required for this assessment.
Abstracts: Targeting Gene Fusions (ALK, ROS1, RET, NTRK)
LBA2: Lorlatinib vs Crizotinib in the First-line Treatment of Patients (pts) with Advanced ALK-Positive Non-Small Cell Lung Cancer (NSCLC): Results of the Phase 3 CROWN Study. Solomon et al

Grade 3–4 AEs observed in 72% of patients in the lorlatinib arm and 56% of patients treated with crizotinib.

Specific grade 3–4 toxicities not quantified, but hypercholesterolemia, hypertriglyceridemia, weight increase, and hypertension were higher with lorlatinib compared with crizotinib.

1302P: Lorlatinib in Patients With ALK+ NSCLC Treated Beyond Initial Disease Progression. Ou et al

Retrospective analysis suggesting better outcomes in patients continuing lorlatinib beyond disease progression compared with patients not continuing.

- OS in patients with ≥1 second-generation ALK TKI: 26.5 months vs 14.7 months

<table>
<thead>
<tr>
<th></th>
<th>Lorlatinib</th>
<th>Crizotinib</th>
<th>HR</th>
<th>P Value or 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS</td>
<td>Not reached</td>
<td>9.3 months</td>
<td>0.28</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>OS</td>
<td>Not reached</td>
<td>Not reached</td>
<td>0.72</td>
<td>0.41 (0.41–1.25)</td>
</tr>
<tr>
<td>ORR Systemic</td>
<td>76%</td>
<td>82%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ORR Intracranial</td>
<td>58%</td>
<td>23%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intracranial TTP</td>
<td>Not reached</td>
<td>16.6 months</td>
<td>0.07</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>
> 1300P: Intracranial efficacy of brigatinib (BRG) vs crizotinib (CRZ): Updated results

<table>
<thead>
<tr>
<th></th>
<th>Brigatinib</th>
<th>Crizotinib</th>
<th>HR</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS (Overall)</td>
<td>24.0 months</td>
<td>11.0 months</td>
<td>0.49</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>PFS (Intracranial) ITT</td>
<td>24.0 months</td>
<td>24.0 months</td>
<td>5.6 months</td>
<td>0.45</td>
</tr>
<tr>
<td></td>
<td>24.0 months</td>
<td>5.6 months</td>
<td>0.31</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>BM at Baseline</td>
<td>32.3 months</td>
<td>24.0 months</td>
<td></td>
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</tbody>
</table>
PROGRAM OVERVIEW: ABSTRACTS
TARGETING GENE FUSIONS (ALK, ROS1, RET, NTRK)

> WCLC 2020 Virtual Presidential Symposium, Abstract 2: Phase 3 randomized study of ensartinib vs crizotinib in anaplastic lymphoma kinase (ALK)–positive NSCLC patients: eXalt3. Horn et al

Serious treatment-related AEs reported in 8% of patients in the ensartinib arm and 6% of patients treated with crizotinib. Specific toxicities were not quantified, but grade 3–4 rash was higher in the ensartinib arm (approximately 10%).

<table>
<thead>
<tr>
<th></th>
<th>Ensartinib</th>
<th>Crizotinib</th>
<th>HR</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS</td>
<td>25.8 months</td>
<td>12.7 months</td>
<td>0.51</td>
<td>.0001</td>
</tr>
<tr>
<td>OS</td>
<td>Not reached</td>
<td>Not reached</td>
<td>0.88</td>
<td>.6470</td>
</tr>
<tr>
<td>ORR Systemic</td>
<td>75%</td>
<td>64%</td>
<td>67%</td>
<td>21%</td>
</tr>
<tr>
<td>ORR Intracranial</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
PROGRAM OVERVIEW: ABSTRACTS
TARGETING GENE FUSIONS (ALK, ROS1, RET, NTRK)

> 1287P: Efficacy and safety of entrectinib in locally advanced/metastatic ROS1 fusion-positive NSCLC: An updated integrated analysis. Krebs et al

- Updated analysis with data from 161 patients and a median follow-up of 15.8 months
- ORR: 67%
- PFS: 15.7 months
- 1-year OS: 81%
- Treatment-related SAEs were reported in 11% of patients
PROGRAM OVERVIEW: ABSTRACTS
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> 1349P – Lorlatinib for advanced ROS1+ Non-Small Cell Lung Cancer (NSCLC):

Efficacy

N = 71
ORR 45.6%
PFS 7.6 months
OS 20.7 months

Grade ≥3 AEs

All Patients
Hypercholesterolemia 14%
Hypertriglyceridemia 6%
Cognitive effects 7%
Mood effects 4%

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> 1290P: Efficacy and safety with selpercatinib (LOXO-292) by last prior systemic

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> 1289P: Efficacy and safety of larotrectinib in patients with tropomyosin receptor

**Efficacy**

- N = 14
- ORR 71%
- 1-year PFS 69%
- 1-year OS 91%

**Grade 3 AEs**

- N = 14
- Anemia 7%
- Hypotension 7%
- Myalgia 7%
PROGRAM OVERVIEW: ABSTRACTS
TARGETING GENE FUSIONS (ALK, ROS1, RET, NTRK)

> 543P: Entrectinib in NTRK Fusion-Positive NSCLC: Updated Integrated Analysis of

> 1288P: Efficacy of entrectinib in patients with NTRK or ROS1 fusion-positive NSCLC with CNS metastases at baseline. Dziadziuszko et al

> 540P: Entrectinib in ROS1 fusion-positive non-small cell lung cancer (NSCLC) or NTRK fusion-positive solid tumours: analysis of response by line of therapy. Liu et al.

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Discussion: Targeting Gene Fusions (ALK, ROS1, RET, NTRK)
TARGETING GENE FUSIONS (ALK, ROS1, RET, NTRK)
DISCUSSION (1/6)

ALK

Most of the experts use alectinib as the first-line agent for ALK-rearranged NSCLC, citing the first-mover advantage and long-term follow-up data. The expert preferring brigatinib mentioned the once-daily dosing as an advantage over the twice-daily dosing required with alectinib.

While the data with lorlatinib in the CROWN study are seen as impressive by the experts, generally they would save lorlatinib for later lines of therapy.

Lorlatinib is perceived by the experts as being particularly active in subsequent lines of therapy, as it is active in the context of multiple ALK mutations; it is therefore possible that the long-term OS with lorlatinib will exceed that of the other agents.

Toxicity with lorlatinib was again mentioned by one of the experts, a panelist who participated in clinical trials of lorlatinib. They noted that CNS toxicity is more manageable in the first-line setting, compared with previously treated patients who may have undergone RT to the brain. Furthermore, the hypertriglyceridemia and hypercholesterolemia observed with lorlatinib did not lead to cardiovascular events.
Experts value having several next-generation ALK inhibitors showing superior PFS and CNS activity compared with crizotinib; while alectinib is perceived as tolerable, elevated liver enzymes can occur, so it is desirable to have alternate agents available.
The experts generally prefer entrectinib as the first-line agent in ROS1-rearranged NSCLC. Lorlatinib is perceived as active but is associated with lipid and psychiatric toxicities. However, one of the experts related that the toxicities can be managed by stopping treatment and restarting at a lower dose. It is thought by one of the experts that crizotinib could still be used in a patient with low disease burden and no brain metastases, and who is willing to sequence therapies.
The experts are enthusiastic about the new generation of RET inhibitors (eg, selpercatinib, pralsetinib) and support their use in the first-line setting. It is thought by the experts that selpercatinib and pralsetinib are interchangeable.

The requirement for randomized phase III registrational trials in Europe was criticized by the experts, as with these drugs a group of patients will be randomized to inferior treatment in the comparator arm. The experts plan to draft an international position paper to communicate this to European regulatory authorities.
Currently available TRK inhibitors (larotrectinib, entrectinib) were perceived as being tolerable and active systemically; activity in the CNS may be a point of differentiation to the extent that the data are available.

Regarding testing for NTRK fusions, expert opinion is that education of community physicians is important, as DNA-based assays may not detect fusions. Furthermore, some genetic tests may detect NTRK mutations (as opposed to or in addition to fusions), and physicians who are not aware of the difference may inappropriately prescribe a TRK inhibitor.
TARGETING GENE FUSIONS (ALK, ROS1, RET, NTRK) DISCUSSION (6/6)

General

Expert opinion is that comprehensive NGS testing is the standard approach, and that single-gene testing is suboptimal, especially given that more molecular markers are anticipated to emerge. The experts believe that the role of immunotherapy in patients with oncogene-driven NSCLC should be reassessed, as certain oncogenes (e.g., BRAF) may be associated with response.
Abstracts: Evolving Standards in SCLC
> 1781MO: IMpower133: characterisation of long-term survivors treated first-line with...
LBA86: Durvalumab (D) ± tremelimumab (T) + platinum-etoposide (EP) in 1L ES-SCLC: Characterization of long-term clinical benefit and tumour mutational burden (TMB) in CASPIAN. Goldman et al.

- Long-term clinical benefit defined as PFS ≥12 months
- Tissue-based TMB was not predictive of OS benefit with the addition of durvalumab with or without tremelimumab to chemotherapy
- Furthermore, clinical characteristics did not identify a subgroup of patients who derive long-term benefit

- Efficacy of lurbinectedin was evaluated in patients who were candidates for platinum re-challenge, according to either ESMO guidelines (relapse ≥90 days; n = 60) or NCCN guidelines (relapse ≥180 days; n = 20)

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<tr>
<th></th>
<th>Relapse ≥90 Days</th>
<th>Relapse ≥180 Days</th>
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<tbody>
<tr>
<td>ORR per investigators</td>
<td>45%</td>
<td>60%</td>
</tr>
<tr>
<td>PFS per investigators</td>
<td>4.6 months</td>
<td>4.6 months</td>
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<tr>
<td>OS</td>
<td>11.9 months</td>
<td>16.2 months</td>
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Discussion: Evolving Standards in SCLC
Expert opinion is that both atezolizumab-based and durvalumab-based regimens are acceptable for patients with newly diagnosed extensive-stage SCLC. The experts are currently treating all immunotherapy-eligible patients with these regimens, as there is still no selective biomarker. The KEYNOTE-604 trial was seen as demonstrating efficacy of pembrolizumab in ES-SCLC; however, since the trial did not meet the significance threshold, atezolizumab and durvalumab remain the only immune checkpoint inhibitors supported by clinical data. While a panel-wide poll was not taken, one of the patients mentioned using a 4-weekly dosing schedule for maintenance immunotherapy.
Experts believe that in patients with brain metastases, it is preferable to begin systemic therapy as soon as possible. If local therapy is needed for brain lesions, this could be intercalated between cycles. Where there is availability, the experts are using lurbinectedin as second-line therapy after chemotherapy/immunotherapy; the toxicity profile is seen by the experts as favorable. Two of the experts mentioned using nivolumab/ipilimumab successfully in patients with SCLC, raising the possibility of increased use of this combination in lung cancer. The experts thought that DLL3 is still a viable target in SCLC, with a bispecific agent in clinical investigation; TIGIT was also thought to be an interesting therapeutic target.