ASCO 2019:
Advanced Stage Disease Highlights

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Disclosures

Support to attend educational conferences:
Astra Zeneca, BMS, Boehringer Ingelheim, Lilly, MSD, Otsuka, Roche, Takeda

Advisory and consultancy work:
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Speaker bureau:
Astra-Zeneca, MSD, Roche
Gefitinib vs. Gefitinib-Pemetrexed-Carboplatin in *EGFR* Mutated Lung Cancer

**ELIGIBILITY CRITERIA**
- Age ≥ 18 yrs
- Histologic/ cytologic NSCLC
- Stage IIIb not amenable to radical therapy or Stage IV
- First-line palliative intent
- Activating *EGFR* mutation (exon 19/21/18)
- ECOG PS 0 to 2
- Adequate organ function
- No h/o ILD, radiation pneumonitis that required steroids or IPF

**STRATIFY**
- ECOG PS (0/1 v. 2)
- *EGFR* mutation (exon 19 v. other)

**Randomized 1:1 Open Label**

- Gefitinib 250mg daily
  - Pem 500 mg/m² + Carbo AUC 5 Q21d × 4 → Pem 500 mg/m² Q21d

**n=174**

**Gefitinib 250mg daily**

**n=176**

**Median follow up 17 months**

- **“Pragmatic” trial**
  - Brain metastases allowed (majority with WBRT)
  - 21% PS 2, 2% PS 0
  - Investigators-assessed PFS as primary endpoint
    - Broad definition
    - Flexible schedule of assessment
  - PROs evaluation

- Reasonable expectation for PFS benefit (median PFS 10–15 months, HR 0.66)
Response, PFS and OS Benefit with Upfront Chemotherapy Combined with Gefitinib

- Impressive PFS benefit:
  - Short median PFS in the control arm (21% PS 2 pts)
  - Improvement of ORR and depth of response
  - No information about DoR
  - No impact of mutation subtype

- No data about resistance mechanisms

- PFS benefit $\rightarrow$ OS benefit: low rate of post-study treatments:
  - 24% Carbo-Pem in the G arm,
  - Osimertinib exposure: 11% G+C, 15% G
The Increase of Toxicity Must Be Taken into Consideration for Risk-Benefit Assessment of CT-TKI Combination

<table>
<thead>
<tr>
<th></th>
<th>Gef + C arm (n=164)</th>
<th>Gef arm (n=170)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinically relevant ≥ gr 3 toxicities</td>
<td>50.6%</td>
<td>25.3%</td>
</tr>
<tr>
<td>Pemetrexed discontinuation for toxicity</td>
<td>16.7%</td>
<td>-</td>
</tr>
<tr>
<td>Grade 3-4 neutropenia</td>
<td>16%</td>
<td>0</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>12%</td>
<td>0</td>
</tr>
<tr>
<td>Grade 3-4 anemia</td>
<td>19%</td>
<td>1%</td>
</tr>
<tr>
<td>Grade 2-4 diarrhea</td>
<td>32%</td>
<td>21%</td>
</tr>
<tr>
<td>Grade 2-3 fatigue grade 2-3</td>
<td>39%</td>
<td>21%</td>
</tr>
<tr>
<td>Grade 3-4 hypokalemia</td>
<td>8%</td>
<td>2%</td>
</tr>
<tr>
<td>Grade 2-4 nephrotoxicity</td>
<td>16%</td>
<td>2%</td>
</tr>
</tbody>
</table>

No significant increase of the gefitinib skin toxicity
So where does gef + C fit in the current treatment algorithm?

- Gefitinib, erlotinib and afatinib have comparable efficacies (ORR, PFS, OS)
- Osimertinib, dacomitinib, erlotinib + bev and gef + chemo: better PFS
- PFS in our study-17 months, similar to 18.9 months from osimertinib in FLAURA
- But we included PS 2 (20%), FLAURA enrolled only PS ≤ 1
- Thus, several first-line options with comparable efficacy exist.
- Osimertinib has efficacy in T790M mutation, therefore may be better positioned in relapsed setting.
- To maximize survival, sequencing of effective therapies is important.
Antitumor activity of TAK-788 in NSCLC with EGFR exon 20 insertions


1Dana-Farber Cancer Institute, Boston, MA, 2Stanford Cancer Institute, Stanford University, Stanford, CA, 3University of Colorado Cancer Center, Aurora, CO, 4Virginia Cancer Specialists, Fairfax, VA, 5Massachusetts General Hospital, Boston, MA, 6Vanderbilt-Ingram Cancer Center, Nashville, TN, 7Beth Israel Deaconess Medical Center, Boston, MA, 8MD Anderson Cancer Center, Houston, TX, 9University of Chicago, Chicago, IL, 10University of Michigan, Ann Arbor, MI, 11UC San Diego Moores Cancer Center, La Jolla, CA, 12University of California, Irvine School of Medicine, Orange, CA, 13Swedish Cancer Institute, Seattle, WA, 14Millennium Pharmaceuticals, Inc., Cambridge, MA, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited, 15Memorial Sloan Kettering Cancer Center, New York, NY
EGFR Exon 20 Insertions in NSCLC

EGFR Oncogenic Driver Mutations

- Exon 19 \(\approx 45\%\)
- Exon 20 \(\approx 10\%\)
- Insertions \(\approx 6\%\)
- De novo T790M \(<5\%\)
- S768I \(\approx 1\%\)
- Exon 18 \(\approx 4\%\)
- Exon 21 \(\approx 41\%\)
- Other \((=31\%)

- Approximately 6% of EGFR-mutated NSCLC tumors have EGFR exon 20 insertion mutations, and there are no approved targeted treatment options for patients with these mutations. 1
- Currently approved EGFR TKIs have shown efficacy in NSCLC patients with common activating EGFR mutations, but are largely ineffective in patients with EGFR exon 20 insertions, with poor response rates and median PFS of approximately 2 months. 2,4

Study Design: Phase 1/2 Trial of Oral TAK-788 (NCT02716116)

**Phase 1 Dose Escalation: 3+3 Design** (Advanced non-small cell lung cancer; ECOG PS <2)

**Phase 2 expansion (Open, enrolling): TAK-788 160 mg qd**

**Phase 2: Primary endpoint:** ORR by RECIST v1.1

**Secondary endpoints:** Safety, tolerability, PK, efficacy

- **Cohort 1:** Refractory *EGFR* exon 20 insertion CNS metastases (either active or measurable CNS metastases, but not both)
- **Cohort 2:** Refractory *HER2* exon 20 insertion or point mutation CNS metastases (either active or measurable CNS metastases, but not both)
- **Cohort 3:** Refractory *EGFR* exon 20 or HER2 exon 20 insertions or point mutations with measurable, active CNS metastases
- **Cohort 4:** Treatment naive or refractory Other *EGFR* mutations: +/- T790M, uncommon *EGFR*
- **Cohort 5:** Refractory *EGFR* exon 20 insertion with prior response to EGFR TKI
- **Cohort 6:** Treatment naive *EGFR* exon 20 insertions
- **Cohort 7:** Refractory Other tumor types (non-NSCLC) with *EGFR/HER2* mutations

**Locations:** United States only for phases 1 and 2; United States, European Union, and Asia for Extension.

**Active CNS metastases:** Untreated, or treated and progressing; **Measurable CNS metastases:** ≥10 mm in longest diameter by contrast-enhanced MRI.

CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; HER, human epidermal growth factor receptor; MRI, magnetic resonance imaging; ORR, objective response rate; PK, pharmacokinetics; PS, performance status; RECIST, Response Evaluation Criteria in Solid Tumours.
## TAK-788 Antitumor Activity in Patients With \textit{EGFR} Exon 20 Insertions

<table>
<thead>
<tr>
<th>EGFR Exon 20 Insertions Treated at 160 mg qd(^a)</th>
<th>All Patients (n=28)</th>
<th>With Baseline CNS Metastases(^b) (n=12)</th>
<th>Without Baseline CNS Metastases (n=16)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Best response (confirmed), n (%)(^c)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Partial response</td>
<td>12 (43)</td>
<td>3 (25)</td>
<td>9 (56)</td>
</tr>
<tr>
<td>Stable disease(^d)</td>
<td>12 (43)</td>
<td>5 (42)</td>
<td>7 (44)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>2 (7)</td>
<td>2 (18)</td>
<td>0</td>
</tr>
<tr>
<td>Not evaluable</td>
<td>2 (7)</td>
<td>2 (18)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Confirmed objective response, n (%) [95% CI]</strong></td>
<td>12 (43) [24–63]</td>
<td>3 (25) [5–57]</td>
<td>9 (56) [30–80]</td>
</tr>
<tr>
<td><strong>Disease control, n (%) [95% CI]</strong></td>
<td>24 (86) [67–96]</td>
<td>8 (67) [35–90]</td>
<td>16 (100) [79–100]</td>
</tr>
<tr>
<td><strong>Median progression-free survival, mo [95% CI]</strong></td>
<td>7.3 [4.4–NR]</td>
<td>3.7 [1.8–NR]</td>
<td>8.1 [5.6–NR]</td>
</tr>
</tbody>
</table>

\(^a\) Patients treated with at least 1 dose of TAK-788. \(^b\) 7 out of 12 patients (58\%) had active brain metastases at baseline. \(^c\) By RECIST v1.1. \(^d\) SD observed ≥6 weeks after first study drug administration.

Data cutoff: 1 Mar 2019. CI, confidence interval; PR, partial response; SD, stable disease.

- At data cutoff, 12/15 responses were confirmed, with 3 PRs unconfirmed at 160 mg qd
- Median time to response among confirmed responders: 1.8 months
# Safety Summary in Patients Treated With TAK-788

<table>
<thead>
<tr>
<th></th>
<th>All Patients Treated at 160 mg qd&lt;sup&gt;a&lt;/sup&gt; (n=72)</th>
<th>All Patients Treated at Any Dose&lt;sup&gt;b&lt;/sup&gt; (N=137)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment-emergent AE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any grade</td>
<td>69 (96)</td>
<td>130 (95)</td>
</tr>
<tr>
<td>Grade ≥3</td>
<td>45 (63)</td>
<td>84 (61)</td>
</tr>
<tr>
<td>Treatment-related AE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any grade</td>
<td>68 (94)</td>
<td>125 (91)</td>
</tr>
<tr>
<td>Grade ≥3</td>
<td>29 (40)</td>
<td>44 (32)</td>
</tr>
<tr>
<td>Dose reduction due to AE</td>
<td>18 (25)</td>
<td>25 (18)</td>
</tr>
<tr>
<td>Dose interruption due to AE</td>
<td>36 (50)</td>
<td>70 (51)</td>
</tr>
<tr>
<td>Discontinuation due to treatment-related AE</td>
<td>10 (14)</td>
<td>18 (13)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Patients who received at least 1 dose of TAK-788 at 160 mg qd (initial dose) during dose escalation or expansion cohorts 1 to 7.  
<sup>b</sup> Patients who received at least 1 dose of TAK-788 (5–180 mg total daily dose) during the escalation or expansion phase.  
Clinical Activity and Tolerability of BLU-667, a Highly Potent and Selective RET Inhibitor, in Patients with Advanced RET-Fusion+ Non-small Cell Lung Cancer

Justin F. Gainor¹, Dae Ho Lee², Giuseppe Curigliano³, Robert C. Doebele⁴, Dong-Wan Kim⁵, Christina S. Baik⁶, Daniel Shao-Weng Tan⁷, Gilberto Lopes⁸, Shirish M. Gadgeel⁹, Philippe Alexandre Cassier¹⁰, Matthew H. Taylor¹¹, Stephen V. Liu¹², Benjamin Besse¹³, Michael Thomas¹⁴, Viola Weijia Zhu¹⁵, Hui Zhang¹⁶, Corinne Clifford¹⁶, Michael R. Palmer¹⁶, Christopher D. Turner¹⁶, Vivek Subbiah¹⁷

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RET Alterations: Diverse Oncogenic Drivers Lacking Targeted Therapeutic Approach

Non-small cell lung cancer: ∼1-2% RET fusions\(^1,2\)

Advanced medullary thyroid cancer: ∼90% RET mutations\(^3\)

Papillary thyroid cancer: ∼20% RET fusions\(^4\)

Multiple other tumor types including esophageal, breast, melanoma, colorectal, and leukemia: <1% RET-altered\(^5,6\)

NSCLC patients with RET fusions have not significantly benefited from existing therapy

- Chemotherapy: nonspecific, low response rates, significant toxicity
- Checkpoint inhibition: Preliminary evidence for lack of benefit in RET-altered NSCLC\(^7\)
- Multikinase inhibitors: ↓ activity, ↑ off-target toxicity\(^8,9\)

No selective RET inhibitors are approved
BLU-667 is Well Tolerated by Patients with RET Fusion+ Advanced NSCLC

Among 120 pts with advanced NSCLC receiving BLU-667 starting dose of 400 mg QD:

- Treatment-related toxicity is generally low-grade and reversible
- 7% discontinued BLU-667 due to treatment-related toxicity
  - Pneumonitis, respiratory distress/hypoxemia, mucositis/colitis, myelosuppression, gait disturbance, anemia

### Table: RET Fusion+ Advanced NSCLC 400 mg QD Starting Dose (N=120)

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>Treatment-Emergent (≥15% overall)</th>
<th>Treatment-Related</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All</td>
<td>Grade ≥3</td>
</tr>
<tr>
<td>Constipation</td>
<td>30%</td>
<td>2%</td>
</tr>
<tr>
<td>Neutropeniaa</td>
<td>26%</td>
<td>13%</td>
</tr>
<tr>
<td>AST increased</td>
<td>24%</td>
<td>5%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>21%</td>
<td>3%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>20%</td>
<td>13%</td>
</tr>
<tr>
<td>Anemia</td>
<td>18%</td>
<td>7%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>18%</td>
<td>2%</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>18%</td>
<td>-</td>
</tr>
<tr>
<td>ALT increased</td>
<td>17%</td>
<td>3%</td>
</tr>
<tr>
<td>Cough</td>
<td>17%</td>
<td>-</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>17%</td>
<td>-</td>
</tr>
</tbody>
</table>

Additional grade ≥3 treatment related AEs (≥2%): increased CPK (3%), leukopenia b (3%).

*Across the entire study (n=276), rate of discontinuation due to treatment-related toxicity is 4%.

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*Combined term including decreased neutrophils and neutropenia. aCombined term including leukopenia and white blood cell count decreased. AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CPK, creatine phosphokinase. Data cut-off date: 28 Apr 2019.
BLU-667 Demonstrates Substantial Antitumor Activity in RET Fusion+ Advanced NSCLC

BLU-667 Starting Dose 400 mg QD

<table>
<thead>
<tr>
<th>Best Response</th>
<th>All (N=48)</th>
<th>Prior Platinum (N=35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR (95% CI)</td>
<td>58% (43–72)</td>
<td>60% (42–76)</td>
</tr>
<tr>
<td>CR*</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>PR*</td>
<td>27</td>
<td>20</td>
</tr>
<tr>
<td>SD</td>
<td>18</td>
<td>14</td>
</tr>
<tr>
<td>PD</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td>DCR (95% CI)</td>
<td>96% (86–99)</td>
<td>100% (90–100)</td>
</tr>
</tbody>
</table>

* All responses are confirmed on two consecutive assessments as per RECIST 1.1.

- 5/7 (71%) treatment-naïve patients had confirmed PR.
BLU-667 is Active Against Intracranial Metastases

- 52-year-old woman, RET fusion+ NSCLC, prior platinum and checkpoint inhibitor
- Near-complete resolution of previously untreated target brain metastasis after two months of BLU-667 400 mg QD
- Continues to receive treatment with ongoing confirmed PR (70% shrinkage) at ~6 months

- 59-year-old man, RET fusion+ NSCLC, prior platinum and checkpoint inhibitor
- Complete resolution of previously untreated nontarget brain metastasis after two months of BLU-667 400 mg QD
- Continues to receive treatment with ongoing confirmed PR (67% shrinkage) at ~6 months

Images courtesy of Dr. Stephen Liu, Georgetown University, Washington, D.C.
Images courtesy Dr. P Cassier Centre Leon Berard, Lyon, FR
Phase 1 Study Evaluating the Safety, Tolerability, Pharmacokinetics (PK) and Efficacy of AMG 510, a Novel Small Molecule KRAS^{G12C} Inhibitor, in Advanced Solid Tumors

Marwan G Fakhih, MD; Bert Howard O’Neil, MD; Timothy J Price, MBBS, FRACP; Gerald S Falchook, MD; Jayesh Desai, MBBS, FRACP; James Kuo, MBBS, FRACP; Ramaswamy Govindan, MD; Erik Rasmussen, MS; Phuong Khanh Morrow, MD; Jude Ngang, PharmD; Haby Henary, MD; David Hong, MD

1City of Hope, Duarte, CA, USA; 2Indiana University, Simon Cancer Center, Indianapolis, IN, USA; 3The Queen Elizabeth Hospital, Woodville South, AU; 4Amgen Inc, Thousand Oaks, CA, USA; 5Sarah Cannon Research Institute, Denver, CO, USA; 6Peter MacCallum Cancer Centre, Melbourne, AU; 7Scientia Clinical Research, Randwick, AU; 8Washington University, St Louis, MO, USA; 9MD Anderson Cancer Center, Houston, TX, USA
AMG 510 is a First in Class KRAS$^{G12C}$ Inhibitor

- KRAS is a GTP-binding protein that links receptor tyrosine kinase activation to intracellular signaling.1,2
- Mutation of KRAS favors the GTP-bound active state and constitutive activation of downstream effects (differentiation, proliferation, survival).3
- $KRAS^{G12C}$ mutation has been identified as an oncogenic driver of tumorigenesis
- $KRAS^{G12C}$ mutation is found in approximately 13% of lung cancer, 3% of colorectal (CRC) and appendix cancer, and 1-3% of other solid tumors.4
- Currently there is no approved therapy targeting this mutation
- AMG 510 is a novel, first in class, small molecule that specifically and irreversibly inhibits KRAS$^{G12C}$ by locking it in an inactive GDP-bound state.


GDP, guanosine diphosphate; GTP, guanosine triphosphate; KRAS, Kirsten rat sarcoma viral oncogene homolog; $KRAS^{G12C}$, KRAS protein with a G12C mutation at the protein level.
AMG 510 First in Human Study Design

This is a multicenter, open-label, phase 1, first in human study (NCT 03600883) in adult patients with locally advanced or metastatic KRAS\textsuperscript{G12C} mutant solid tumors.

**Key Eligibility Criteria**
- Documented locally-advanced or metastatic KRAS\textsuperscript{G12C} measurable or evaluable solid tumors
- Received prior standard therapy appropriate for tumor type and stage of disease
- No active brain metastases

**Primary Endpoints**
- Safety and tolerability including the incidence of AEs and DLTs

**Key Secondary Endpoints**
- PK, best response
- Objective response rate, duration of response and duration of stable disease and PFS

**Screening**
- 2-4 patients enrolled in each cohort to evaluate safety; additional subjects may be added to any dose deemed to be safe

**Enrollment**
- Cohort 1: 180 mg
- Cohort 2: 360 mg
- Cohort 3: 720 mg
- Cohort 4: 960 mg

**Treatments**
- Intra-subject dose escalations are allowed
- Treatment Period with Daily Oral Dose
  - Until disease progression, intolerance or consent withdrawal
  - (radiographic scans every 6 weeks)

**End of Treatment**
- ~30 Days After EOT
- Every 12 Weeks

Presented by Marwan Fakih at 2019 ASCO Annual Meeting
### Patient Incidence of Common (>10%) and Serious Treatment Emergent Adverse Events (TEAE)

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Gr 1 n</th>
<th>Gr 2 n</th>
<th>Gr 3 n</th>
<th>All Grades n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Treatment Emergent Adverse Event</td>
<td></td>
<td></td>
<td></td>
<td>25</td>
</tr>
<tr>
<td>Decreased Appetite</td>
<td>3</td>
<td>3</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>5</td>
<td>0</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Fatigue</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Headache</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Cough</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Hot Flush</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Nausea</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>4</td>
</tr>
</tbody>
</table>

6 of 35 patients reported serious AEs:
- 2 Grade 3
  - Pneumonia
  - Malignant biliary obstruction
- 1 Grade 4
  - Pericardial effusion
- 3 Fatal
  - Dyspnea
  - 2 Colorectal cancer metastatic
- None of these serious AEs were reported as related to AMG 510
NSCLC: Best Tumor Response* (n=10)

5 out of 10 patients had PR
- 4 are confirmed
- All 5 are still on treatment

* Based on local radiographic scans every 6 weeks using RESIST 1.1 criteria
1 patient had clinical progression prior to week 6 and is not on this graph
☑ Confirmed response
☑ 2 additional patients had confirmed PR post data cutoff
$Patient had a CR of the target lesions at week 18, post data cutoff

Patients Receiving AMG 510

- SD
- PR
- PR
- PR
- PR
- PR

Planned Dose
- 180 mg
- 360 mg
- 720 mg
- 960 mg

Presented By Marwan Fakih at 2019 ASCO Annual Meeting
Duration of Treatment by Tumor Types and Responses (n=29)

Presented By Marwan Fakih at 2019 ASCO Annual Meeting

Duration on Treatment (as of 4 April 2019)
- NSCLC Partial Response (n=5): 7.3 – 27.4 weeks
- Stable Disease (n=4): 8.4 – 25.1 weeks
- CRC/Other Stable Disease (n=14): 7.3 – 24.0 weeks

Legend:
- △: First Response
- ●: Best Overall Response
  - PR: 5
  - SD: 18
  - PD: 6
- ◻: Disease Progression
- ➔: Ongoing on-study

* Appendix adenocarcinoma patient
SD → PD: Patient with best response of SD but who later progressed
Abstract 9013: KEYNOTE-189: Updated OS and progression after the next line of therapy (PFS2): Study Design

Key Eligibility Criteria
- Untreated stage IV nonsquamous NSCLC
- No sensitizing EGFR or ALK alteration
- ECOG PS 0 or 1

Stratification Factors
- PD-L1 expression
- Cisplatin vs carboplatin
- Smoking history (never vs former/current)

Rationale for PFS2 analyses (per EMA)
1. To assess effect of maintenance therapy
2. To assess impact of crossover on OS assessment
3. To assess whether therapy positively or negatively affects efficacy in the next line of therapy

Therapy 1
- Pembrolizumab + Pemetrexed + Carboplatin OR Cisplatin Q3W for 4 cycles

Therapy 2
- Pembrolizumab Q3W

Off Therapy
- Pembrolizumab 200 mg Q3W for up to 35 cycles

Crossover Allowed at PD

Death
Abstract 9013: KEYNOTE-189: Updated OS analysis by PD-L1 TPS

**TPS ≥50 %**
- Pembrolizumab/Pembrolizumab/Placebo: 43.9% (59) HR (95% CI: 0.39–0.88)
- Placebo/Pembrolizumab/Placebo: 60.0% (66)

**TPS 1-49%**
- Pembrolizumab/Pembrolizumab/Placebo: 52.3% (65) HR (95% CI: 0.42–0.92)
- Placebo/Pembrolizumab/Placebo: 69.0% (73)

**TPS <1%**
- Pembrolizumab/Pembrolizumab/Placebo: 59.1% (68) HR (95% CI: 0.36–0.74)
- Placebo/Pembrolizumab/Placebo: 81.0% (85)

Survival curves showing OS (%), Median (95% CI) for each group:
- Pembrolizumab/Pembrolizumab/Placebo: NR (20.4 mo-NE) 10.1 mo (7.5-NE)
- Placebo/Pembrolizumab/Placebo: 21.8 mo (17.7-25.9) 12.1 mo (8.7-19.4)
- Pembrolizumab/Pembrolizumab/Placebo: 17.2 (13.8-22.8) 10.2 mo (7.0-13.5)

No. at Risk: 132 114 95 85 29 0 128 107 91 74 26 2 127 104 79 61 17 0
Abstract 9013: KEYNOTE-189: Updated OS and progression after 2\textsuperscript{nd} line of therapy (PFS2): subsequent therapy

<table>
<thead>
<tr>
<th>Subsequent Therapy, n (%)</th>
<th>Pembro/Pem/Platinum (N = 410)</th>
<th>Placebo/Pem/Platinum (N = 206)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remaining on ≥1 component of allocated study therapy</td>
<td>58 (14.1)</td>
<td>7 (3.4)</td>
</tr>
<tr>
<td>Discontinued all components of allocated study therapy</td>
<td>352 (85.9)</td>
<td>199 (96.6)</td>
</tr>
<tr>
<td>Alive, no subsequent therapy</td>
<td>116 (28.3)</td>
<td>15 (7.3)</td>
</tr>
<tr>
<td>Died without subsequent therapy</td>
<td>111 (27.1)</td>
<td>69 (33.5)</td>
</tr>
<tr>
<td>≥1 subsequent therapy</td>
<td>183 (44.6)</td>
<td>122 (59.2)</td>
</tr>
<tr>
<td>≥1 subsequent immunotherapy</td>
<td>55 (13.4)</td>
<td>111 (53.9)</td>
</tr>
</tbody>
</table>
Abstract 9013: KEYNOTE-189: Updated OS and progression after the 2\textsuperscript{nd} line of therapy (PFS2): Conclusions

**Rationale for PFS2 analyses (per EMA)**

1. To assess effect of maintenance therapy
   - Both arms have maintenance therapy, unlikely to have an impact
2. To assess impact of crossover on OS assessment
   - OS difference remains substantial despite crossover
3. To assess whether therapy positively or negatively affects efficacy in the next line of therapy
   - No analysis provided here (some prior suggestion that chemotherapy may be more effective after I/O)
EFFICACY AND SAFETY PROFILE OF LURBINECTEDIN
IN SECOND-LINE SCLC PATIENTS:
Results from a phase II single-agent trial

Paz Ares L.1; Trigo JM.2; Besse B.3; Moreno V.4; Lopez R.5; Sala MA.6; Ponce S.1; Fernandez C.7; Siguero M.7; Kahatt C.7; Zeaiter A.7; Zaman K.8; Boni V.9; Arroncado J.10; Martinez M.11; Delord JP.12; Awada A.13; Kristeleit R.14; Olmedo ME.15; Subbiah V.16

Hospital Universitario 12 de Octubre, CNIO, Universidad Complutense & Ciberonc, Madrid, Spain1; Hospital Universitario Virgen de la Victoria, Málaga, Spain1; Gustave Roussy Cancer Campus, Villejuif, France2; Hospital Universitario Fundación Jiménez Díaz, Madrid, Spain3; Hospital Clínico Universitario de Santiago de Compostela, Santiago De Compostela, Spain4; Hospital Universitario de Basurto, Bilbao, Spain5; PharmaMar, Colmenar Viejo, Spain5; University Hospital CHUV, Lausanne, Switzerland6; START Madrid-CIOCC, Hospital Universitario Sanchinarro, Madrid, Spain7; Hospital Cochin, Paris, France8; Complejo Hospitalario de Navarra, Pamplona, Spain9; Institut Claudius Regaud, Toulouse, France10; Institut Jules Bordet, Université Libre de Bruxelles, Brussels, Belgium11; UCL Cancer Institute, London, United Kingdom12; Hospital Universitario Ramón y Cajal, Madrid, Spain13; Md. Anderson Cancer Center, Houston, USA14

Presented By Luis Paz-Ares at 2019 ASCO Annual Meeting
# Antitumor Activity According to Sensitive or Resistant Population

<table>
<thead>
<tr>
<th></th>
<th>Resistant CTFI&lt; 90 days (n=45)</th>
<th>Sensitive CTFI ≥ 90 days (n=60)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ORR, % (95% CI)</strong></td>
<td>22.2 (11.2-37.1)</td>
<td>45.0 (32.1-58.4)</td>
</tr>
<tr>
<td><strong>Best response (confirmed)</strong></td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>- <strong>PR</strong></td>
<td>10 (22.2) #</td>
<td>27 (45.0) #</td>
</tr>
<tr>
<td>- <strong>SD</strong></td>
<td>13 (28.9)</td>
<td>22 (36.7)</td>
</tr>
<tr>
<td>- <strong>PD</strong></td>
<td>18 (40.0)</td>
<td>10 (16.7)</td>
</tr>
<tr>
<td>- <em><em>NE</em> (non-evaluable)</em>*</td>
<td>4 (8.9)</td>
<td>1 (1.7)</td>
</tr>
<tr>
<td><strong>Disease Control Rate, % (95% CI)</strong></td>
<td>51.1 (35.8-66.3)</td>
<td>81.7 (69.6-90.5)</td>
</tr>
</tbody>
</table>

* 3 of 5 patients with resistant disease and 2 of 3 patients with sensitive disease who failed prior immunotherapy had confirmed response

* Treatment discontinuation without any tumor assessment performed

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**Duration of Response (DoR)**

- **mDoR**
  - Sensitive: 6.2 months (95% CI 3.5-7.3)
  - Resistant: 4.7 months (95% CI 2.6-5.6)
Progression Free Survival: Sensitive and resistant SCLC populations

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>PFS median (95% CI)</th>
<th>PFS at 6 mo % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>105</td>
<td>3.9 (2.6-4.6)</td>
<td>33.6 (24.0-43.1)</td>
</tr>
<tr>
<td>Resistant CTFI&lt; 90d</td>
<td>45</td>
<td>2.6 (1.3-3.9)</td>
<td>18.8 (6.8-30.9)</td>
</tr>
<tr>
<td>Sensitive CTFI≥ 90d</td>
<td>60</td>
<td>4.6 (3.0-6.5)</td>
<td>44.6 (31.2-57.9)</td>
</tr>
</tbody>
</table>
Overall Survival: Sensitive and Resistant SCLC Populations

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>OS median (95% CI)</th>
<th>OS at 12 mo % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>105</td>
<td>9.3 (6.3-11.8)</td>
<td>34.2 (23.2-45.1)</td>
</tr>
<tr>
<td>Resistant CTFI&lt;90d</td>
<td>45</td>
<td>5.0 (4.1-6.3)</td>
<td>15.9 (3.6-28.2)</td>
</tr>
<tr>
<td>Sensitive CTFI≥90d</td>
<td>60</td>
<td>11.9 (9.7-16.2)</td>
<td>48.3 (32.5-64.1)</td>
</tr>
</tbody>
</table>
### Safety and Tolerability: Related or Unknown Adverse Events (AE)

<table>
<thead>
<tr>
<th>Event</th>
<th>n (% )</th>
</tr>
</thead>
<tbody>
<tr>
<td>AE</td>
<td>89 (84.8)</td>
</tr>
<tr>
<td>- Grade ≥3</td>
<td>36 (34.3)</td>
</tr>
<tr>
<td>SAEs</td>
<td>11 (10.5)</td>
</tr>
<tr>
<td>Related AEs leading to death</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Related AEs leading to treatment discontinuation</td>
<td>2 (1.9)</td>
</tr>
<tr>
<td>Dose delays treatment related</td>
<td>21 (22.1*)</td>
</tr>
<tr>
<td>Dose reductions #</td>
<td>25 (26.3*)</td>
</tr>
<tr>
<td>G-CSF</td>
<td>23 (21.9)</td>
</tr>
<tr>
<td>Transfusions <em>(red blood cells and/or platelets)</em></td>
<td>10 (9.5)</td>
</tr>
</tbody>
</table>

* Per protocol: dose had to be reduced in case of grade 4 neutropenia

* Based on 95 patients who received ≥ 2 cycles of treatment