Simultaneous WCLC 2020 publication by Baohui Han:

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Disclosures

Daniel SW Tan, BSc, MBBS, PhD
› Advisory role and consultant: Novartis, Bayer, Boehringer Ingelheim, Celgene, Astra Zeneca, Eli-lily, Loxo
› Travel and honorarium: Merck, Pfizer, Novartis, Boehringer Ingelheim, Roche, Takeda
› Research funding: Novartis, Astra Zeneca, GlaxoSmithKline, Bayer, Pfizer

Yi-long Wu, MD
› Honoraria: AstraZeneca, Boehringer Ingelheim, BMS, Eli Lilly, Hengrui, MSD, Pfizer, Roche and Sanofi;
› Consulting or advisory role: AstraZeneca, Boehringer Ingelheim, Novartis, Merck, MSD, Roche and Takeda
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Ross Soo, MBBS, PhD, FRACP
› Advisory Board: Amgen, Astra-Zeneca, Bayer, BMS, Boehringer Ingelheim, Lilly, Merck, Novartis, Pfizer, Roche, Taiho, Takeda, Yuhan
› Research grant: Astra-Zeneca, Boehringer Ingelheim

All other planners, reviewers and staff reported no relevant financial relationships.
All relevant financial relationships have been mitigated
Selected Abstracts from Day 2

Daniel SW Tan, BSc, MBBS, PhD
Associate Professor, Duke-NUS Medical School
Senior Consultant, Division of Medical Oncology
National Cancer Centre Singapore
Overview of abstracts

› Biomarkers for checkpoint inhibitors
› Improving on outcomes for stage III NSCLC
› Antibody drug conjugates and novel targeted therapies
› Adjuvant therapy post surgery for EGFR mutated NSCLC
EMPOWER-Lung 1 Study Design

Key Eligibility Criteria
- Treatment-naïve advanced NSCLC
- PD-L1 ≥50%
- No EGFR, ALK, or ROS1 mutations
- ECOG PS 0 or 1
- Treated, clinically stable CNS metastases and controlled hepatitis B or C or HIV were allowed

Stratification Factors:
- Histology (squamous vs non-squamous)
- Region (Europe, Asia, or ROW)

Arm A
Cemiplimab monotherapy IV 350 mg Q3W
Treat until PD or 108 weeks

Arm B
4–6 cycles of investigator’s choice chemotherapy

Optional continuation of cemiplimab + 4 cycles of chemotherapy

Optional crossover to cemiplimab monotherapy

Endpoints:
- Primary: OS and PFS
- Secondary: ORR (key), DOR, HRQoL, and safety

N=710

ALK, anaplastic lymphoma kinase; CNS, central nervous system; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; HIV, human immunodeficiency virus; HRQoL, health-related quality of life; IV, intravenous; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PD, progressive disease; PD-L1, programmed cell death-ligand 1; PFS, progression-free survival; Q3W, every 3 weeks; R, randomized; ROS1, c-ros oncogene 1; ROW, rest of the world.
Response to cemiplimab by PDL1 status tiers

PD-L1 Expression Levels Correlate with Objective Response Rate (N=475)

- ≥50%
- 25-49%
- 1-24%
- <1%

OS and PFS (N=475)

- OS
- PFS

Data cutoff date: March 1, 2020

JANUARY 28-31, 2021 | WORLDWIDE VIRTUAL EVENT

CONQUERING THORACIC CANCERS WORLDWIDE

*CI* confidence interval, ORR, objective response rate; PDL1, programmed cell death-ligand 1.
Lung MAP Studies: Previously treated, IO-naïve, stage IV Sq NSCLC

**S1400I: Randomized Phase III study:**
Nivolumab + Ipilimumab vs Nivolumab


**S1400A: Single-arm phase II study:**
Durvalumab

Borghaei H et al. Clin Lung Cancer, in press
Tumor Mutational Burden as a Continuous Variable

**TMB by Value**
(per 10-unit difference)

Total pts: 252 on S1400I
  68 on S1400A

**Overall Survival:** higher TMB; HR: 0.80 (95% CI: 0.67;0.94), p=0.008

**Progression Free Survival:** HR: 0.80 (95% CI; 0.69;0.93), p=0.004

**HIGHER TMB WAS SIGNIFICANTLY ASSOCIATED WITH IMPROVED OS AND PFS.**

The relative risk of death comparing OS between patients with TMB levels above versus below the thresholds.
Association between TMB (continuous) and different PD-L1 expression groups: S1400I

HRs ≤ 1.0 in all subgroups of PD-L1 expression.
KEYNOTE-799 (NCT03631784)

Study Population
- Aged ≥18 years
- Stage IIIA–C, unresectable, locally advanced, pathologically confirmed, previously untreated NSCLC
- Measurable disease per RECIST v1.1
- ECOG PS 0 or 1
- Adequate pulmonary function
- No prior systemic immunosuppressive therapy within 7 days

Primary Objectives
- ORR per RECIST version 1.1 by BICR
- Percentage of patients who develop grade ≥3 pneumonitis

Secondary Objectives
- PFS, OS, safety

COHORT A (Squamous and nonsquamous NSCLC)

- Pembrolizumab 200 mg Q3W + Paclitaxel 200 mg/m² Q3W / Carboplatin AUC6 Q3W
- Pembrolizumab 200 mg Q3W + Paclitaxel 45 mg/m² QW / Carboplatin AUC2 QW / Thoracic radiotherapy

Cycles 1, 2–3, 4–17

COHORT B (Nonsquamous NSCLC only)

- Pembrolizumab 200 mg Q3W + Pemetrexed 500 mg/m² Q3W / Cisplatin 75 mg/m² Q3W / Thoracic radiotherapy

Statistical Analysis Details
- Efficacy assessed in all patients with first study dose before or on October 31, 2019 (PE population)
- Safety assessed in all patients in the as-treated population

BICR, blinded, independent central review; PE, primary efficacy.

60 Gy in 30 daily 2-Gy fractions. Treatment will continue until cycle 17 is completed or until disease progression in nonsquamous subgroups, unacceptable adverse events, withdrawal of informed consent, nonadministration of treatment, or study withdrawal. Pembrolizumab therapy will be discontinued permanently in patients who develop grade ≥3 or recurrent grade 2 pneumonitis.
## ORR and Duration of Response
By BICR per RECIST v1.1 (Primary Efficacy Population)

<table>
<thead>
<tr>
<th>Cohort A</th>
<th>Cohort B</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 112</td>
<td>n = 61</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PE Population</th>
<th>n = 112</th>
<th>n = 61</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR, n (%)</td>
<td>78 (69.6) [60.2–78.0]</td>
<td>43 (70.5) [57.4–81.5]</td>
</tr>
<tr>
<td>CR</td>
<td>4 (3.6)</td>
<td>3 (4.9)</td>
</tr>
<tr>
<td>PR</td>
<td>74 (66.1)</td>
<td>40 (65.6)</td>
</tr>
<tr>
<td>SD, n (%)</td>
<td>21 (18.8)</td>
<td>12 (19.7)</td>
</tr>
<tr>
<td>PD, n (%)</td>
<td>1 (0.9)</td>
<td>0</td>
</tr>
<tr>
<td>Not evaluable, n</td>
<td>2 (1.8)</td>
<td>0</td>
</tr>
<tr>
<td>No assessment, n</td>
<td>10 (8.9)</td>
<td>6 (9.8)</td>
</tr>
</tbody>
</table>

| DOR, median (range), n (%) | NR (1.4–932.1) | NR (2.0–15.9) |
| DOR ≥12 mo, n (%)          | 31 (28.2)      | 9 (14.8)      |

<table>
<thead>
<tr>
<th>PD-L1 Status</th>
<th>TPS &lt;1%</th>
<th>TPS ≥1%</th>
<th>TPS &lt;1%</th>
<th>TPS ≥1%</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n = 21)</td>
<td>(n = 66)</td>
<td>(n = 17)</td>
<td>(n = 26)</td>
<td></td>
</tr>
<tr>
<td>ORR, n (%)</td>
<td>14 (66.7)</td>
<td>49 (74.2)</td>
<td>11 (64.7)</td>
<td>18 (68.9)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Histology</th>
<th>Non-squamous</th>
<th>Squamous</th>
<th>Non-squamous</th>
<th>Squamous</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n = 39)</td>
<td>(n = 73)</td>
<td>(n = 81)</td>
<td>(n = 6)</td>
<td></td>
</tr>
<tr>
<td>ORR, n (%)</td>
<td>27 (69.2)</td>
<td>51 (69.9)</td>
<td>43 (70.2)</td>
<td>NA</td>
</tr>
</tbody>
</table>

CI: confidence interval; DOR, duration of response; NR, not reached.
*Squamous and non-squamous. **Non-squamous only. **Kaplan-Meier estimate. ***Indicates there is no progressive disease by the time of last disease assessment.
Data cutoff date: July 30, 2020.
## Incidence of Grade ≥3 Pneumonitis/Safety
Per NCI-CTCAE Version 4.0 (All-Treated Patients)

<table>
<thead>
<tr>
<th></th>
<th>Cohort A&lt;sup&gt;a&lt;/sup&gt; (n = 112)</th>
<th>Cohort B&lt;sup&gt;b&lt;/sup&gt; (n = 101)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade ≥3 pneumonitis (all cause),&lt;sup&gt;c,d&lt;/sup&gt; n (%) [95% CI]</td>
<td>9 (8.0) [3.7–14.7]</td>
<td>8 (7.9) [3.5–15.0]</td>
</tr>
<tr>
<td>Treatment-related AEs, n (%)</td>
<td>105 (93.8)</td>
<td>96 (95.0)</td>
</tr>
<tr>
<td>Grades 3–5</td>
<td>72 (64.3)</td>
<td>47 (46.5)</td>
</tr>
<tr>
<td>Led to death</td>
<td>4&lt;sup&gt;c&lt;/sup&gt; (3.6)</td>
<td>1 (1.0)</td>
</tr>
<tr>
<td>Led to discontinuation of any treatment component</td>
<td>38 (33.9)</td>
<td>16 (15.8)</td>
</tr>
<tr>
<td>Discontinued pembrolizumab</td>
<td>27 (24.1)</td>
<td>15 (14.9)</td>
</tr>
<tr>
<td>Discontinued radiotherapy</td>
<td>2 (1.8)</td>
<td>0</td>
</tr>
<tr>
<td>Discontinued any chemotherapy</td>
<td>18 (16.1)</td>
<td>3 (3.0)</td>
</tr>
<tr>
<td>Immune-mediated AEs and infusion reactions, n (%)</td>
<td>59 (52.7)</td>
<td>36 (35.6)</td>
</tr>
<tr>
<td>Grades 3–5</td>
<td>18 (16.1)</td>
<td>10 (9.9)</td>
</tr>
<tr>
<td>Led to death&lt;sup&gt;d&lt;/sup&gt;</td>
<td>4 (3.6)</td>
<td>1 (1.0)</td>
</tr>
</tbody>
</table>

<sup>a</sup>Squamous and nonsquamous. <sup>b</sup>Nonsquamous only. <sup>c</sup>Includes immune-mediated AE of “pneumonitis” and the MedDRA preferred term of “radiation pneumonitis”. <sup>d</sup>Includes 4 patients (3.6%) with grade 5 pneumonitis in cohort A and 1 patient (1.0%) with grade 5 interstitial lung disease in cohort B. These events were classified as both treatment-related events and under immune-mediated AEs and infusion reactions.

Data cutoff date: July 30, 2020.
Role of PET-directed adaptation of RT

**RTOG1106 Study Schema**

**Control arm**
- A: Continue conc. chem-RT to a total of 60 Gy ED2/26 fxS of MLD of 20 Gy
- (RTOG 0617 60 Gy arm) Uniform dose RT

**Experimental arm**
- A: Conc. chem-RT 50 Gy/25fx (ED2 ~50 Gy)
- B: Concurrent chem-RT to ED2~50 Gy in 17-21 fxS

**Randomize**
- FDG PET/CT based RT plan to 74 Gy ED2
- FDG-PET/CT at 40-50 Gy ED2 for all pts
- Individualized adaptive RT

*Randomization: 1:2 for control and experimental arms, stratified by GTV (200 cc) and MLD (14 Gy)*

**Results-5: Thoracic Adverse Events**

<table>
<thead>
<tr>
<th></th>
<th>Standard RT (n=42)</th>
<th>Adaptive RT (n=80)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Grade 2+ Adverse Event</td>
<td>37 (88.1%)</td>
<td>78 (97.5%)</td>
</tr>
<tr>
<td>Grade 2+ Esophagitis</td>
<td>13 (31.0%)</td>
<td>34 (42.5%)</td>
</tr>
<tr>
<td>Grade 2+ Respiratory, Thoracic, and Mediastinal Disorders</td>
<td>19 (45.2%)</td>
<td>35 (43.8%)</td>
</tr>
<tr>
<td>Grade 2+ Cardiac Disorders</td>
<td>2 (4.8%)</td>
<td>4 (5.0%)</td>
</tr>
</tbody>
</table>

*Adverse events graded per CTCAE v4.0 criteria and reported as possibly, probably, or definitely related to treatment*

**Results-6: Local-Regional Control (Central Review)**

- **% Alive Without Local-Regional Failure**
  - Standard RT
  - Adaptive RT

- **Months Since Randomization**
  - Fail/Total: 15/43 (27.5/14.3, Not reached)
  - Adaptive RT: 31/84 (28.4/19.1, Not reached)

* Censored
  - p=0.6585 (Z-test)
HER3 and Trop2 Antibody drug conjugates
Amivantamab: EGFR-MET bispecific antibody

**CHRYSALIS**
EGFR Ex20ins NSCLC (n=81)
Phase I

- **Dose Escalation Cohorts**
  - 140–1750 mg
  - C1 QW, C2+ Q2W

- **RP2D**
  - 1050 mg (<80 kg)
  - 1400 mg (≥80 kg)

- **Dose Expansion Cohort D**
  - EGFR Ex20ins

**Post-platinum Exon20ins**
Treated at RP2D
(N=114; Safety Population)

**Post-platinum Exon20ins with ≥3 Disease Assessments at Clinical Cut-off**
(n=81; Efficacy Population)

Yun J et al, CCR 2020
Amivantamab in post-platinum Ex20ins NSCLC

ORR 40% (95% CI, 29-51)
Median DOR 11.1 months (95% CI, 6.9-NR)
G3 any event 16%
G3 rash 4%
G3 hypoalbuminemia 3%
G3 infusion-related reaction 3%

25 distinct Exon20ins variants identified by NGS of ctDNA (Guardant360®) from 63 evaluable patient samples
Mobocertinib results in a reduction in target lesion volume in post-platinum treated EGFR Ex20ins patients.

*ORR in EXCLAIM cohort: 23%
Side effect profile of Mobocertinib

All-Grade TRAEs Observed in ≥20% of Patients

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>PPP Cohort (N=114)</th>
<th>% of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>25 (22)</td>
<td>90%</td>
</tr>
<tr>
<td>Rash</td>
<td>45%</td>
<td></td>
</tr>
<tr>
<td>Paronychia</td>
<td>34%</td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>32%</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>32%</td>
<td></td>
</tr>
<tr>
<td>Dry skin</td>
<td>30%</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>30%</td>
<td></td>
</tr>
<tr>
<td>Increased creatinine</td>
<td>25%</td>
<td></td>
</tr>
<tr>
<td>Stomatitis</td>
<td>22%</td>
<td></td>
</tr>
<tr>
<td>Pruritus</td>
<td>20%</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>EXCLAIM Cohort (N=96)</th>
<th>% of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>15 (16)</td>
<td>92%</td>
</tr>
<tr>
<td>Rash</td>
<td>45%</td>
<td></td>
</tr>
<tr>
<td>Paronychia</td>
<td>35%</td>
<td></td>
</tr>
<tr>
<td>Dry skin</td>
<td>30%</td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>29%</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>28%</td>
<td></td>
</tr>
<tr>
<td>Increased creatinine</td>
<td>27%</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>26%</td>
<td></td>
</tr>
<tr>
<td>Stomatitis</td>
<td>25%</td>
<td></td>
</tr>
<tr>
<td>Dermatitis acniform</td>
<td>21%</td>
<td></td>
</tr>
</tbody>
</table>

Grades 3/4 TRAEs in ≥5% of Patients, n (%)

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>PPP Cohort (N=114)</th>
<th>% of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>25 (22)</td>
<td>90%</td>
</tr>
<tr>
<td>Anemia</td>
<td>6 (5)</td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>6 (5)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>EXCLAIM Cohort (N=96)</th>
<th>% of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>15 (16)</td>
<td>92%</td>
</tr>
</tbody>
</table>
ADAURA: Impact of adjuvant chemotherapy and QOL

DFS in patients with and without adjuvant chemotherapy (overall population)

DFS in patients with and without adjuvant chemotherapy, by disease stage

Adjusted mean change in SF-36 physical (PCS) and mental (MCS) component summary T-scores

- In disease-free patients receiving osimertinib, SF-36 PCS and MCS were maintained from baseline to week 96, with no clinically meaningful differences observed compared with the placebo arm
2-year DFS comparable to control arm of ADAURA despite differing rates of adjuvant chemotherapy

- Stage IB: 71%
- Stage II: 56%
- Stage IIIA: 32%

Some patients are cured without EGFR TKI
IASLC 2020 World Conference on Lung Cancer
Singapore: Highlights from Day 3

Yi-Long Wu
Tenured Professor of Guangdong Lung Cancer Institute,
Guangdong Provincial People's Hospital
& Guangdong Academy of Medical Sciences
Guangzhou, China
Topics

Lung Cancer Screen
Perioperative adjuvant treatment
Target KRAS
Immunotherapy combo for advanced NASCLC
Immunotherapy for mesothelioma
PLATFORM trial
National Lung Cancer Screening Program in Taiwan: The TALENT Study

Pan-Chyr Yang MD, PhD
On Behalf of TALENT Study Group

National Taiwan University
Institute of Biomedical Sciences
Center of Genomics, Academia Sinica
Taiwan Lung Cancer Screening in Never Smoker Trial (TALENT)

From Feb 2015 to July 2019, 17 medical centres participated

Key inclusion criteria
- 55-75 y/o
- Never smoking or SI < 10 PY and had quit > 15 yrs
- Having one of the following risks
  - family history of lung cancer (≤ 3-degree)
  - environmental tobacco smoking history
  - chronic lung disease (TB, COPD)
  - cooking index$^b$ ≥ 110
  - cooking without using ventilation
- Negative CXR

Data cutoff: September 30, 2020
- 13,207 subjects screened, 12,011 enrolled
- 6009 (50%) with family history

$^a$ Subjects with lung cancer FH: >50 yrs or > the age at diagnosis of the youngest lung cancer case in the family

$^b$ 2/7 x days with cooking by pan-frying, stir-frying, or deep-frying in 1 week (maximum=21) x Yrs with cooking
What are the discovery from TALENT study?

More early cases with lung cancer were discovered

- T0 lung cancer detection rate: 313/12,011 = 2.6%, NLST: 1.1%, NELSON: 0.9%
- Invasive lung cancer: 255/12,011 = 2.1%. Multiple primary lung cancer: 17.9%
- LDCT positive: 17.4% (GGO > 5mm, S/PS > 6mm) #. Invasive procedures: 3.4%
- Lung cancer confirmed: **96.5% stage 0-1**. LDCT features: GGO 47%, S 19%, PS 34%
- Prevalence of lung cancer w/ or w/o family history: **3.2% vs 2.0%** (p< 0.001)

<table>
<thead>
<tr>
<th>Histologic Diagnosis</th>
<th>(n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenocarcinoma in situ (AIS)</td>
<td>58</td>
</tr>
<tr>
<td>Minimally invasive adenocarcinoma (MIA)</td>
<td>71</td>
</tr>
<tr>
<td>Invasive adenocarcinoma (INAD)</td>
<td>183</td>
</tr>
<tr>
<td>Adenosquamous carcinoma</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>313</td>
</tr>
</tbody>
</table>

Stage 0  58
Stage IA 218
Stage IB 26
Stage IIA 0
Stage IIB 3
Stage IIIA 2
Stage IIIB 1
Stage IV 5

**Stage 0 lung cancer detection rate:** 313/12,011 = 2.6%, NLST: 1.1%, NELSON: 0.9%
## High risk factor for non-smoker lung cancer: Family history

<table>
<thead>
<tr>
<th></th>
<th>Absence</th>
<th>Presence</th>
<th>R.R. (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Lung cancer family history</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First-degree family</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Father</td>
<td>241 (75.70)</td>
<td>423 (83.1)</td>
<td>1.54 (1.08-2.02)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Mother</td>
<td>27 (8.40)</td>
<td>19 (3.73)</td>
<td>2.25 (1.21-4.18)</td>
<td>0.011</td>
</tr>
<tr>
<td>Second-degree family</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Third-degree family</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Environmental tobacco exposure</td>
<td>264 (83.02)</td>
<td>469 (92.14)</td>
<td>2.37 (1.51-3.71)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Chronic lung disease history</td>
<td>208 (93.71)</td>
<td>504 (99.02)</td>
<td>7.31 (2.68-19.93)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Cooking index ≥110</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cooking without ventilation</td>
<td>20 (6.20)</td>
<td>5 (0.98)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### What are the discovery from TALENT study?

- **High risk factor for non-smoker lung cancer: Family history**

- **First-degree family**
  - Father: 241 (75.70) vs. 423 (83.1); R.R. = 1.54 (1.08-2.02), p < 0.001
  - Mother: 27 (8.40) vs. 19 (3.73); R.R. = 2.25 (1.21-4.18), p = 0.011

- **Second-degree family**
  - Environmental tobacco exposure: 264 (83.02) vs. 469 (92.14); R.R. = 2.37 (1.51-3.71), p < 0.001
  - Chronic lung disease history: 208 (93.71) vs. 504 (99.02); R.R. = 7.31 (2.68-19.93), p < 0.001

- **Third-degree family**
  - Environmental tobacco exposure: 20 (6.20) vs. 5 (0.98); R.R. = 0.62 (0.28-1.39), p = 0.238
  - Chronic lung disease history: 104 (2.4) vs. 7 (3.3); R.R. = 0.86 (0.68-1.08), p = 0.201

**References:**
- Lin & Wu, Lung Cancer 2015
- Wu et al. [5]
- Gao et al. [13]
- Brenner et al. [14]
What is clinical significance of the TALENT study?

Lung Cancer Screen:

Not only for tobacco exposure also for family lung cancer history
Topics

Lung Cancer Screen

Perioperative adjuvant treatment

Target KRAS

Immunotherapy combo for advanced NASCLC

Immunotherapy for mesothelioma

PLATFORM trial
International Tailored Chemotherapy Adjuvant (ITACA) Phase III study of Pharmacogenomic-Driven versus Standard Adjuvant Chemotherapy in completely Resected Stage II-IIIA Non-Small Cell Lung Cancer

Silvia Novello
(on behalf of the ITACA investigators)

University of Turin,
Department of Oncology
silvia.novello@unito.it
ITACA trial: Design of the study

- Completely resected NSCLC R0 stage II-IIIA, Complete mediastinal LN resection or sampling
- ECOG PS 0-1
- Interval of 45-60 days between surgery and start of chemotherapy
- Adequate organ functions
- No prior malignancies except for treated basal cell or squamous cell skin cancer, in situ cervical cancer, or other cancers from which the patient has been disease-free for at least five years prior to enrolment

ERCC1 mRNA expression

Molecular Diagnostic Analysis after Surgery

Cisplatin not allowed in the tailored arms

TS mRNA expression

Profile 1

High

Profile 2

Low

Profile 3

High

Profile 4

Low

Cisplatin allowed in the tailored arms

- Randomization (allocation ratio of 1:1) performed in each genomic profile, stratified by disease stage (stage II v IIIA) and smoking status (never/former versus current)
- For the primary statistical analysis all control arms were grouped together (standard arm) as well as all tailored arms (tailored arm)

N=773

Paclitaxel alone
Cisplatin-doublet, investigator choice

Pemetrexed alone
Cisplatin-doublet, investigator choice

Cisplatin- gemcitabine
Cisplatin-doublet, investigator choice

Cisplatin- pemetrexed
Cisplatin-doublet, investigator choice

8Aug 2008: first pt randomized; 29Aug 2014 last pt randomized

Dec 2010: Study Amendment for Staging (21% pts randomized)

Novello S. et al. WCLC 2015
Surgical and Clinical Outcomes With Neoadjuvant Atezolizumab in Resectable Stage IB-IIIB NSCLC: LCMC3 Trial Primary Analysis


¹David Geffen School of Medicine at UCLA, Los Angeles, CA, USA; ²Memorial Sloan Kettering Cancer Center, New York, NY, USA; ³Genentech, Inc, South San Francisco, CA, USA; ⁴Washington University School of Medicine, St Louis, MO, USA; ⁵Moffitt Cancer Center, Tampa, FL, USA; ⁶City of Hope Comprehensive Cancer Center Los Angeles, CA, USA; ⁷Cedars Sinai (previously City of Hope Comprehensive Cancer Center), Los Angeles, CA, USA; ⁸The Ohio State University Wexner Medical Center, Columbus, OH, USA; ⁹Dartmouth-Hitchcock Medical Center, Lebanon, NH, USA; ¹⁰Brigham and Women’s Hospital, Boston, MA, USA; ¹¹Yale School of Medicine, New Haven, CT, USA; ¹²University of Colorado Cancer Center, Aurora, CO, USA; ¹³Wayne State University, Detroit, MI, USA; ¹⁴Karmanos Cancer Institute, Detroit, MI, USA; ¹⁵New York University, New York, NY, USA; ¹⁶Dana-Farber Cancer Institute, Boston, MA, USA; ¹⁷The University of Texas MD Anderson Cancer Center, Houston, TX, USA
LCMC3 study design

**Primary endpoint:**
- Major pathologic response (≤10% viable tumor cells)

**Secondary endpoints:**
- Pathologic response by PD-L1
- Radiographic response by PD-L1, TMB, neoantigen, gene expression profiling

**Exploratory endpoints:**
- DFS, OS
- Biomarkers
  - ctDNA, TCRseq, flow cytometry, IF, IHC, NGS

**Safety:**
- Adverse events

Resectable, untreated, unselected stage IB-IIIA, select IIIB\(^a\) NSCLC N=181

CT, PET-CT

Atezolizumab (2 cycles)

Surgical resection

30-d post-surgery visit

Surveillance + optional adjuvant atezolizumab (12 mo) or stage-appropriate therapy per investigator

- Blood\(^b\)
- Progression biopsy

Tumor biopsy\(^b\)
- Lymph nodes
- Blood\(^b\)

- Tumor\(^b\)
- Lymph nodes, normal lung
- Blood\(^b\)

Scans as SOC or q3mo

NCT02927301

cDNA, circulating tumor DNA; DFS, disease-free survival; IF, immunofluorescence; NGS, next-generation sequencing; PET-CT, positron emission tomography–computed tomography; q3mo, every 3 months. SOC, standard of care; TCRseq, T-cell receptor sequencing; TMB, tumor mutational burden.

\(^a\) T4 due to mediastinal organ invasion were excluded, \(^b\) Mandatory
What are the discovery from ITACA study?

- **Median follow up** of 28.2 months (IQR: 9.9-55.8 months)
- **N. of deaths**: 154 (46% of expected events; 22% of ITT population)
- **HR (95%CI)**: 0.76 (0.55-1.04)
- **Median OS, Tailored**: 96.4 (81.8- NR)
- **Median OS, Control**: 83.5 (60.1- NR)
What are the discovery from LCMC3 study?

Pathologic response in surgery population (n=159)

Major pathologic response in primary efficacy population (n=144)

Pathologic regression defined as % viable tumor cells – 100%.

MPR, major pathologic response; pCR, pathologic complete response.

\(^a\) Error bars indicate 95% CI.
What is clinical significance of the ITACA & LCMC3 study?

- It is impossible to tailor adjuvant chemotherapy for complete resected lung cancer patients selected by precision genomic aberration

- Monotherapy with PD-L1 inhibitor atezolizumab as neoadjuvant treatment achieved a promising results with MPR of 21% and pCR of 7%
Topics

Lung Cancer Screen
Perioperative adjuvant treatment

Target KRAS

Immunotherapy combo for advanced NASCLC

Immunotherapy for mesothelioma

PLATFORM trial
CodeBreaK 100: Registrational Phase 2 Trial of Sotorasib in KRAS p.G12C Mutated Non-small Cell Lung Cancer

Bob T. Li, 1 Ferdinandos Skoulidis, 2 Gerald Falchouk, 3 Adrian Sacher, 4 Vamsidhar Velcheti, 5 Grace K. Dy, 6 Timothy J. Price, 7 Hossein Borghaei, 8 Martin Schuler, 9 Terufumi Kato, 10 Toshiaki Takahashi, 11 Alexander Spira, 12 Suresh Ramalingam, 13 Benjamin Besse, 14 Fabrice Barlesi, 15 Qui Tran, 16 Agnes Ang, 16 Abraham Anderson, 16 Haby Henary, 16 Gataree Ngarmchamnanrith, 16 Ramaswamy Govindan, 17 Jürgen Wolf 18

1 Memorial Sloan Kettering Cancer Center, New York, New York, USA; 2 The University of Texas MD Anderson Cancer Center, Houston, Texas, USA; 3 Sarah Cannon Research Institute at HealthONE, Denver, Colorado, USA; 4 Princess Margaret Cancer Centre, University Health Network, Toronto, Ontario, Canada; 5 Thoracic Medical Oncology, Perlmutter Cancer Center, New York University, New York, New York, USA; 6 Roswell Park Cancer Institute, Buffalo, New York, USA; 7 The Queen Elizabeth Hospital and University of Adelaide, Woodville South, Australia; 8 Fox Chase Cancer Center, Philadelphia, PA, USA; 9 Department of Medical Oncology, West German Cancer Center, University Hospital Essen, Essen, German Cancer Consortium (DKTK), Germany; 10 Kanagawa Cancer Center, Yokohama, Japan; 11 Division of Thoracic Oncology, Shizuoka Cancer Center, Shizuoka, Japan; 12 Virginia Cancer Specialists Research Institute, Fairfax, VA, The US Oncology Network, TX; Johns Hopkins Medicine, Baltimore, MD, USA; 13 Division of Medical Oncology, Emory University School of Medicine, Winship Cancer Institute, Atlanta, GA, USA; 14 Department of Cancer Medicine, Gustave Roussy, Villejuif, France; 15 Gustave Roussy, Villejuif, France; 16 Amgen Inc. Thousand Oaks, California, USA; 17 Alvin J Siteman Cancer Center at Washington University School of Medicine, St Louis, Missouri, USA; 18 Department of Internal Medicine, Center for Integrated Oncology, University Hospital Cologne, Cologne, Germany
Key Eligibility:
- Locally advanced or metastatic NSCLC
- KRAS p.G12C mutation as assessed by central testing of tumor biopsies
- Progressed on prior standard therapies\textsuperscript{a}
- No active brain metastases

Sotorasib was orally administered at 960 mg once daily until disease progression\textsuperscript{b}

Radiographic scan every 6 weeks up to week 48 and once every 12 weeks thereafter

**Primary endpoint:** ORR (RECIST 1.1) by blinded independent central review

**Key secondary endpoints:** DoR; disease control rate; TTR; PFS; OS; safety

**Exploratory endpoints:** Evaluation of biomarkers (PD-L1, co-occurring mutations)

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\textsuperscript{a}: no more than 3 prior lines of therapies were allowed; \textsuperscript{b}: treatment beyond disease progression was allowed if certain criteria were met; \textsuperscript{c}: safety follow-up occurs 30 (+7) days after the last dose of sotorasib; long-term follow-up occurs every 12 (±2) weeks for up to 3 years.

NSCLC: non-small cell lung cancer; ORR: objective response rate; DoR: duration of response; TTR: time to response; PFS: progression-free survival; OS: overall survival; PD-L1: programmed death-ligand 1; RECIST: Response Evaluation Criteria in Solid Tumors.
Tumor shrinkage of any magnitude was observed in 81% of patients (101/124). Median percentage of best tumor shrinkage among all responders was 60%.

Median progression-free survival was 6.8 months (95% CI: 5.1, 8.2).
## What are the discovery from CodeBreaK 100 study?

<table>
<thead>
<tr>
<th>Drug</th>
<th>Trial</th>
<th>N</th>
<th>RR</th>
<th>DOR</th>
<th>PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sotorasib</td>
<td>Phase I</td>
<td>59</td>
<td>32.2%</td>
<td>10.9 months</td>
<td>6.3 months</td>
</tr>
<tr>
<td>Adagrasib</td>
<td>Phase I/II</td>
<td>51</td>
<td></td>
<td>Results of Phase 2 trial repeated that of Phase 1 trial</td>
<td></td>
</tr>
<tr>
<td>Sotorasib</td>
<td>Phase II</td>
<td>126</td>
<td>37.1%</td>
<td>10.0 months</td>
<td>6.8 months</td>
</tr>
</tbody>
</table>

- Most common TRAEs are GI toxicities (nausea, vomiting, diarrhea, ALT/AST increases)
- Most TRAEs are grade 1 and 2
- TRAEs leading to discontinuations < 10%

Hong et al., NEJM 2020; Jänne et al. ENA 2020; Li et al. WCLC 2020
What is clinical significance of the CodeBreaK100 study?

FDA Approval Sought for Sotorasib for KRAS G12C–Mutated Advanced or Metastatic NSCLC on Dec 17, 2020
Topics

Lung Cancer Screen
Perioperative adjuvant treatment
Target KRAS
Immunotherapy combo for advanced NSCLC
Immunotherapy for mesothelioma
PLATFORM trial
Pembrolizumab Plus Ipilimumab vs Pembrolizumab Plus Placebo as 1L Therapy For Metastatic NSCLC of PD-L1 TPS ≥50%: KEYNOTE-598

Michael Boyer,1 Mehmet A.N. Şendur,2 Delvys Rodríguez-Abreu,3 Keunchil Park,4 Dae Ho Lee,5 Irfan Çiçin,6 Perran Fulden Yumuk,7 Francisco J. Orlandi,8 Ticiana A. Leal,9 Olivier Molinier,10 Nopadol Soparattanapaisam,11 Adrian Langleben,12 Raffaele Califano,13 Balazs Medgyasszay,14 Te-Chun Hsia,15 Gregory A. Otterson,16 Lu Xu,17 Bilal Piperdi,17 Ayman Samkari,17 Martin Reck18

1Chris O’Brien Lifehouse, Camperdown, NSW, Australia; 2Ankara Yıldırım Beyazıt University, Faculty of Medicine and Ankara City Hospital, Ankara, Turkey 3Complejo Hospitalario Universitario Insular Materno-Infantil de Gran Canaria, Universidad de Las Palmas de Gran Canaria, Las Palmas de Gran Canaria, Spain; 4Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea; 5Asan Medical Center, Seoul, South Korea; 6Trakya University, Erdine, Turkey; 7Marmara University School of Medicine, Istanbul, Turkey; 8Orlandi-Oncologia, Providencia, Chile; 9University of Wisconsin Carbone Cancer Center, Madison, WI, USA; 10Hospital of Le Mans, Le Mans, France; 11Mahidol University, Sriraj Hospital, Bangkok, Thailand; 12St. Mary’s Hospital – ODIM, McGill University Department of Oncology, Montreal, QC, Canada; 13The Christie NHS Foundation Trust, and Division of Cancer Sciences, The University of Manchester, Manchester, UK; 14Veszprém Megyei Tudógyógyintézet Farkasgyepű, Farkasgyepű, Hungary; 15China Medical University and China Medical University Hospital, Taichung, Taiwan; 16The Ohio State University-James Comprehensive Cancer Center, Columbus, OH, USA; 17Merck & Co., Inc., Kenilworth, NJ, USA; 18LungenClinic, Airway Research Center North, German Center for Lung Research, Grosshansdorf, Germany
**KEYNOTE-598 Study Design**

**Key Eligibility Criteria**
- Stage IV NSCLC
- No prior systemic therapy
- ECOG PS 0 or 1
- PD-L1 TPS ≥50%\(^a\)
- No targetable \textit{EGFR} mutations or \textit{ALK} translocations\(^b\)
- No known untreated CNS metastases
- ≥1 lesion measurable per RECIST v1.1

**Stratification Factors**
- ECOG PS (0 vs 1)
- Region (East Asia vs not East Asia)
- Histology (squamous vs nonsquamous)

**End Points**
- **Dual primary**: OS and PFS per RECIST v1.1 by BICR
- **Key secondary**: ORR and DOR per RECIST v1.1 by BICR and safety

Pembrolizumab 200 mg Q3W for up to 35 doses +
- Ipilimumab 1 mg/kg Q6W for up to 18 doses
- Saline Placebo Q6W for up to 18 doses

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\(^a\)Assessed centrally using the PD-L1 IHC 22C3 pharmDx assay (Agilent).

\(^b\)Patients with \textit{ROS1} rearrangement were also excluded if \textit{ROS1} testing and treatment were locally approved and accessible.

KEYNOTE-598 ClinicalTrials.gov identifier, NCT03302234. BICR, blinded independent central review.
What are the discovery from KeyNote 598 study?

Combo immunotherapy group in KN598 and CM227 demonstrate comparable efficacy data but one negative & one positive results
What are the discovery from KeyNote 598 study?

No suggestion of further OS advantage with immunochemotherapy over immuotherapy in PD-L1≥50% population

<table>
<thead>
<tr>
<th></th>
<th>KN024¹</th>
<th>KN042²</th>
<th>IMPOWER 110³</th>
<th>IMPOWER- Lung1⁴</th>
<th>KN189⁵</th>
<th>KN407⁶</th>
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<tbody>
<tr>
<td>Nᵃ</td>
<td>154</td>
<td>299</td>
<td>107</td>
<td>365</td>
<td>132</td>
<td>73</td>
</tr>
<tr>
<td>Design</td>
<td>Pembro vs Chemo</td>
<td>Pembro vs Chemo</td>
<td>Atezo vs Chemo</td>
<td>Cemipli vs Chemo</td>
<td>Pem+Chemo vs Chemo</td>
<td>Pem+Chemo vs Chemo</td>
</tr>
<tr>
<td>PDL1 Stratum</td>
<td>≥50%</td>
<td>≥50%</td>
<td>TC3 or IC3</td>
<td>≥50%</td>
<td>≥50%</td>
<td>≥50%</td>
</tr>
<tr>
<td>mPFS, mo HR</td>
<td>7.7 vs 5.5 HR 0.5</td>
<td>7.1 vs 6.4 HR 0.81</td>
<td>8.1 vs 5.0 HR 0.63</td>
<td>6.2 vs 5.6 HR 0.59</td>
<td>11.1 vs 4.8 HR 0.36</td>
<td>8.0 vs 4.2 HR 0.37</td>
</tr>
<tr>
<td>mOS, mo HR</td>
<td>26.3 vs 13.4 HR 0.62</td>
<td>20.0 vs 12.2 HR 0.7</td>
<td>20.2 vs 13.1 HR 0.59</td>
<td>22.1 vs 14.3 HR 0.68</td>
<td>27.7 vs 10.1 HR 0.59</td>
<td>NR HR 0.64</td>
</tr>
<tr>
<td>2-y OS, %</td>
<td>51.7 vs 34.5</td>
<td>44.7 vs 31.1</td>
<td>NR</td>
<td>48.6 vs 29.7</td>
<td>51.9 vs 39.4</td>
<td>NR</td>
</tr>
<tr>
<td>5-y OS, %</td>
<td>31.9 vs 16.3</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

Single-agent Immunotherapy has become the new standard care for PD-L1≥50% advanced NSCLC

¹.Brahmer et al. ESMO(2020); ². Mok et al. Lancet (2019); ³. Spigel et al. ESMO (2019); ⁴.Sezer et al. ESMO(2020); ⁵.Rodríguez-Abru KN189 ASCO (2020); ⁶. Paz-Ares et al. ASCO(2018)
Topics

Lung Cancer Screen
Perioperative adjuvant treatment
Target KRAS
Immunotherapy combo for advanced NASCLC

Immunotherapy for mesothelioma

PLATFORM trial
Nivolumab Versus Placebo in Relapsed Malignant Mesothelioma: Preliminary results from the CONFIRM Phase 3 Trial

Dean Fennell\(^1\), Christian Ottensmeier\(^2\), Raffaele Califano\(^3\), Gerard G Hanna\(^4\), Sean Ewings\(^5\), Kayleigh Hill\(^5\), Sam Wilding\(^5\), Sarah Danson\(^6\), Mavis Nye\(^5\), Nicola Steele\(^7\), Lucy Johnson\(^5\), Joanne Lord\(^8\), Calley Middleton\(^5\), Ellice Marwood\(^5\), Peter Szlosarek\(^9\), Sam Chan\(^10\), Aarti Gaba\(^1\), Liz Darlison\(^11\), Peter Wells-Jordan\(^1\), Cathy Richards\(^1\), Charlotte Poile\(^1\), Jason F Lester\(^12\), Gareth Griffiths\(^5\)

\(^1\)University of Leicester, UK; \(^2\)University of Liverpool, UK; \(^3\)The University of Manchester, UK; \(^4\)Peter MacCallum Cancer Centre, University Melbourne, Australia; \(^5\)CRUK Southampton Clinical Trials Unit, University of Southampton, UK; \(^6\)University of Sheffield, UK; \(^7\)Beatson West of Scotland Cancer Centre, UK; \(^8\)Southampton Health Technology Assessments Centre, University of Southampton, UK; \(^9\)Barts Cancer Institute, UK; \(^10\)York Teaching Hospital NHS Foundation Trust, UK; \(^11\)Mesothelioma UK; \(^12\)South West Wales Cancer Centre, UK.
CONFIRM Trial Design

**Key eligibility criteria:**
- Mesothelioma
- > 1 prior line of therapy
- ECOG status 0 or 1

**Randomised 2:1**
Stratified by histology
(epithelioid or non-epithelioid)

**Recruited**
April 2017 – March 2020

**Nivolumab (n=221)**
- 240mg in 30-min IV infusion on day 1 of 14-day cycle
- Administered until progression, unacceptable toxicity, withdrawal or 12m

**Placebo (n=111)**
- 240mg sterile solution in 30-min IV infusion on day 1 of 14-day cycle

**Target sample size: 336**
Study halted recruitment at n=332 due to COVID-19 pandemic but sufficient event/follow-up

**Co-primary outcomes:**
- Overall survival
- Investigator-reported progression-free survival

**Secondary outcomes:**
- RECIST-determined progression-free survival
- Response rate
- EQ-5D
- Safety

**Funders:**
- Cancer Research UK/SU2C (C16728/A21400)
- BMS (investigator initiated)

**COORDINATING GROUP:**
Southampton Clinical Trials Unit

**SPONSOR:**
University of Southampton
What are the discovery from CONFIRM study?

CONFIRM: Met Co-Primary Endpoints

OS

12.6% crossover rate

PFS

(Investigator-Assessed)

12m survival, %

OS

Median OS, mo

PFS

Median PFS, mo

HR (95% CI)
P value

OS

9.2 (7.5–10.8)

Nivolumab

Placebo

Median OS, mo

PFS

12m PFS, %

Nivolumab

Placebo

Median PFS, mo

PFS

12m PFS, %

Nivolumab

Placebo

Median PFS, mo

P value

0.018

14.5 (10.2–19.7)

HR (95% CI)
P value

0.61 (0.48–0.77)

<0.001

0.72 (0.55–0.94)
## Immunotherapy Studies in Relapsed Mesothelioma

<table>
<thead>
<tr>
<th>Study</th>
<th>Phase</th>
<th>Agent (s)</th>
<th>n</th>
<th>ORR</th>
<th>mPFS (m)</th>
<th>mOS (m)</th>
</tr>
</thead>
<tbody>
<tr>
<td>KN 028</td>
<td>Ib</td>
<td>Pembrolizumab</td>
<td>25 (PD-L1 pos)</td>
<td>20%</td>
<td>5.4m</td>
<td>18m</td>
</tr>
<tr>
<td>JAVELIN</td>
<td>Ib</td>
<td>Avelumab</td>
<td>53</td>
<td>9%</td>
<td>4.1m</td>
<td>10.7m</td>
</tr>
<tr>
<td>Treme (Italy)</td>
<td>II</td>
<td>Tremelimumab</td>
<td>29</td>
<td>14%</td>
<td>6.2m</td>
<td>11.3m</td>
</tr>
<tr>
<td>MERIT</td>
<td>II</td>
<td>Nivolumab</td>
<td>34</td>
<td>29%</td>
<td>6.1m</td>
<td>17.3m</td>
</tr>
<tr>
<td>Pembro (Chicago)</td>
<td>II</td>
<td>Pembrolizumab</td>
<td>64</td>
<td>22%</td>
<td>4.1m</td>
<td>11.5m</td>
</tr>
<tr>
<td>NIBIT-meso1</td>
<td>II</td>
<td>Treme / Durva</td>
<td>40 (30% 1L)</td>
<td>28%</td>
<td>5.7m</td>
<td>16.6m</td>
</tr>
<tr>
<td>INITIATE</td>
<td>II</td>
<td>Nivo / Ipi</td>
<td>34</td>
<td>29%</td>
<td>NR: &gt;6.2m</td>
<td>NR: &gt;12.7m</td>
</tr>
<tr>
<td>MAPS2</td>
<td>II</td>
<td>Nivo or Nivo/Ipi</td>
<td>63 &amp; 62</td>
<td>19% &amp; 28%</td>
<td>4.0m &amp; 5.6m</td>
<td>11.9m &amp; 15.9m</td>
</tr>
<tr>
<td>DETERMINE</td>
<td>IIb</td>
<td>Treme vs placebo</td>
<td>571 (2:1)</td>
<td>4.5%</td>
<td>2.8m</td>
<td>7.7m</td>
</tr>
<tr>
<td>PROMISE-meso</td>
<td>III</td>
<td>Pembro vs Chemo</td>
<td>144</td>
<td>22%</td>
<td>2.5m</td>
<td>10.7m</td>
</tr>
<tr>
<td>CONFIRM</td>
<td>III</td>
<td>Nivo vs placebo</td>
<td>332</td>
<td>10.4%</td>
<td>3.0m</td>
<td>9.2m</td>
</tr>
</tbody>
</table>

What is clinical significance of the CONFIRM study?

- The phase III CONFIRM placebo-controlled study met both PFS and OS endpoints, with 12.6% improvement in 12-month survival rate.

Awaiting results from 1L IO combination studies

Need Biomarkers

Much still needs to be learned

Discussed by Hui at WCLC 2020
Topics

Lung Cancer Screen
Perioperative adjuvant treatment
Target KRAS
Immunotherapy combo for advanced NASCLC
Immunotherapy for mesothelioma

PLATFORM trial
An Open-Label, Multi-Drug, Biomarker-Directed, Phase II Platform Study in Patients with Non-Small Cell Lung Cancer, who Progressed on an anti-PD(L)-1 Therapy

Benjamin Besse
Institut Gustave Roussy, Villejuif and Paris-Sud University, Paris, France
On behalf of the HUDSON study group
HUDSON study design

<table>
<thead>
<tr>
<th>Group A: biomarker matched (n=85)</th>
<th>Group B: biomarker non-matched (n=177)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HRRm STK11</td>
<td>ceralasertib and durvalumab (ATRi)</td>
</tr>
<tr>
<td>ATM</td>
<td>oleclumab and durvalumab (CD73i)</td>
</tr>
<tr>
<td>CD73</td>
<td>trastuzumab deruxtecan and durvalumab (HER2i)</td>
</tr>
<tr>
<td>HER2e</td>
<td>trastuzumab deruxtecan and durvalumab (HER2i)</td>
</tr>
<tr>
<td>HER2m</td>
<td></td>
</tr>
</tbody>
</table>

Primary endpoint:
- Overall response rate

Secondary endpoints:
- Progression-free survival
- Overall survival
- Disease control rate
- Safety and tolerability

- Immunohistochemistry was also performed.
- PD on ICI within 24 weeks (fresh biopsy or archived tissue).
- PD on ICI > 24 weeks (fresh biopsy or archived tissue).
- ATM, ataxia-telangiectasia mutated; ATRi, ataxia-telangiectasia receptor inhibitor; CD73, cluster of differentiation 73; HER2, human epidermal growth factor receptor 2; HRR, homologous recombination repair; NSCLC, non-small-cell lung cancer; PARPi, poly ADP ribose polymerase inhibitor; PD, progression of disease; STAT3i, Signal transducer and activator of transcription 3 inhibitor; STK11, Serine/threonine kinase 11 (also known as LKB1)
**HUDSON – ORR and median PFS**

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>mF/U m</th>
<th>ORR n (%)</th>
<th>Median PFS m (80% CI)</th>
<th>PFS rate (%) 6, 9 and 12 m</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olaparib HRR</td>
<td>21</td>
<td>2.8</td>
<td>2 (9.5)</td>
<td>2.79 (1.48 – 5.26)</td>
<td></td>
</tr>
<tr>
<td>Olaparib STK11</td>
<td>21</td>
<td>1.4</td>
<td>1 (4.8)</td>
<td>1.41 (1.38 – 1.81)</td>
<td></td>
</tr>
<tr>
<td>Ceralasertib ATM</td>
<td>18</td>
<td>5.0</td>
<td>2 (11.1)</td>
<td>7.43 (3.45 – 9.46)</td>
<td></td>
</tr>
<tr>
<td>Oleclumab 73H</td>
<td>23</td>
<td>1.5</td>
<td>0 (0)</td>
<td>1.58 (1.41 – 2.76)</td>
<td></td>
</tr>
<tr>
<td>Olaparib</td>
<td>22</td>
<td>2.8</td>
<td>0 (0)</td>
<td>3.38 (2.10 – 4.93)</td>
<td></td>
</tr>
<tr>
<td>Danvatirsen</td>
<td>23</td>
<td>1.7</td>
<td>0 (0)</td>
<td>1.68 (1.64 – 2.99)</td>
<td></td>
</tr>
<tr>
<td>Ceralasertib</td>
<td>20</td>
<td>2.6</td>
<td>2 (10.5)</td>
<td>4.24 (1.94 – 6.77)</td>
<td></td>
</tr>
<tr>
<td>Oleclumab</td>
<td>9</td>
<td>1.4</td>
<td>0 (0)</td>
<td>1.41 (1.35 – 1.81)</td>
<td></td>
</tr>
<tr>
<td>Olaparib</td>
<td>23</td>
<td>4.2</td>
<td>1 (4.3)</td>
<td>4.17 (2.69 – 4.37)</td>
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</tr>
<tr>
<td>Danvatirsen</td>
<td>22</td>
<td>2.8</td>
<td>0 (0)</td>
<td>3.09 (2.83 – 6.14)</td>
<td></td>
</tr>
<tr>
<td>Ceralasertib</td>
<td>24</td>
<td>4.6</td>
<td>2 (8.3)</td>
<td>4.96 (3.55 – 5.98)</td>
<td></td>
</tr>
<tr>
<td>Oleclumab</td>
<td>25</td>
<td>2.6</td>
<td>1 (4.2)</td>
<td>2.63 (1.64 – 2.79)</td>
<td></td>
</tr>
</tbody>
</table>

Data in italics are not yet mature; treatment modules include the biomarker selected, primary resistance and acquired resistance cohorts for each drug combination.

73H, signal transducer and activator of transcription 3-73H; ATM, ataxia-telangiectasia mutated; CI, confidence interval; HRR, homologous recombination repair; m, months; mF/U, median follow-up; NC, not calculated; ORR, objective response rate; PFS, progression-free survival; STK11, Serine/threonine kinase 11 (also known as LKB1).
## HUDSON – median OS

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>mF/U m</th>
<th>Median OS m (80% CI)</th>
<th>OS rate (%) 6, 9 and 12 m</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olaparib HRR</td>
<td>21</td>
<td>9.6</td>
<td>9.63 (5.26 – 15.97)</td>
<td></td>
</tr>
<tr>
<td>Olaparib STK11</td>
<td>21</td>
<td>5.6</td>
<td>5.75 (5.29 – 10.84)</td>
<td></td>
</tr>
<tr>
<td>Ceralasertib ATM</td>
<td>18</td>
<td>10.5</td>
<td>15.80 (11.01 – NC)</td>
<td></td>
</tr>
<tr>
<td>Oleclumab 73H</td>
<td>23</td>
<td>7.6</td>
<td>9.49 (7.49 – NC)</td>
<td></td>
</tr>
<tr>
<td>Olaparib</td>
<td>22</td>
<td>7.2</td>
<td>7.16 (4.93 – 10.28)</td>
<td></td>
</tr>
<tr>
<td>Danvatirsen</td>
<td>23</td>
<td>6.0</td>
<td>6.01 (3.55 – 6.51)</td>
<td></td>
</tr>
<tr>
<td>Ceralasertib</td>
<td>20</td>
<td>6.7</td>
<td>11.60 (10.45 - NC)</td>
<td></td>
</tr>
<tr>
<td>Oleclumab</td>
<td>9</td>
<td>2.8</td>
<td>7.06 (4.90 – 7.06)</td>
<td></td>
</tr>
<tr>
<td>Olaparib</td>
<td>23</td>
<td>11.6</td>
<td>15.51 (8.80 – 19.75)</td>
<td></td>
</tr>
<tr>
<td>Danvatirsen</td>
<td>22</td>
<td>10.8</td>
<td>11.20 (9.72 – 12.55)</td>
<td></td>
</tr>
<tr>
<td>Ceralasertib</td>
<td>24</td>
<td>12.7</td>
<td>17.38 (14.06 – NC)</td>
<td></td>
</tr>
<tr>
<td>Oleclumab</td>
<td>25</td>
<td>6</td>
<td>12.78 (6.14 – 12.78)</td>
<td></td>
</tr>
</tbody>
</table>

**Significance:**
HUDSON demonstrates that molecularly stratified enrolment in the immune therapy failed setting is feasible.
Welcome Message

It is our great pleasure and honor to extend a warm invitation to attend and participate in the 2020 World Conference on Lung Cancer (#WCLC20) of the International Association for the Study of Lung Cancer (IASLC) to be held January 28 - 31, 2020 (WCLC 2020 Virtual).

Yi-long Wu  
IASLC WCLC 2020  
Conference President

Daniel Tan  
IASLC WCLC 2020  
Conference Co-Chair

Ross Soo  
IASLC WCLC 2020  
Conference Co-Chair

Thank you for your attention
Selected Day 4 Abstracts

Ross Soo, MBBS, PhD, FRACP
Senior Consultant
Department of Hematology-Oncology
National University Cancer Institute, Singapore
Disclosures

Ross Soo, MBBS, PhD, FRACP

› **Advisory Board**: Amgen, Astra-Zeneca, Bayer, BMS, Boehringer Ingelheim, Lilly, Merck, Novartis, Pfizer, Roche, Taiho, Takeda, Yuhan

› **Research grant**: Astra-Zeneca, Boehringer Ingelheim
A phase 1 study of AMG 757, a half-life extended bispecific T-cell engager (BiTE®) immuno-oncology therapy against DLL3, in SCLC


1Emory University School of Medicine, Atlanta, GA, USA; 2Chris O’Brien Lifehouse, Camperdown, NSW, Australia; 3Sarah Cannon Research Institute, Tennessee Oncology, Nashville, TN, USA; 4Washington University Medical School, St. Louis, MO, USA; 5Hospital Universitario 12 de Octubre, Universidad Complutense & Ciberonc, Madrid, Spain; 6The Christie NHS Foundation Trust, University of Manchester, Manchester, UK; 7The Netherlands Cancer Institute, Amsterdam, Netherlands; 8Gustave Roussy, Paris-Saclay University, Villejuif, France; 9Comprehensive Cancer Center Mainfranken, University Hospital Wuerzburg, Wuerzburg, Germany; 10Memorial Sloan Kettering Cancer Center, New York, NY, USA; 11National Cancer Center Hospital East, Kashiwa, Chiba, Japan; 12Yale School of Medicine, New Haven, CT, USA; 13University Hospitals Seidman Cancer Center and Case Western Reserve University, Cleveland, OH, USA; 14Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD, USA; 15City of Hope Hospital, Duarte, CA, USA; 16University of Chicago Medicine and Biological Sciences, Chicago, IL, USA; 17Amgen Inc., Thousand Oaks, CA, USA; 18Fox Chase Cancer Center, Philadelphia, PA, USA
## Key Eligibility Criteria & Baseline Demographics

### Inclusion Criteria
- Histologically/cytologically confirmed SCLC
  - Received ≥ 1 line systemic therapy
  - Progressed/recurred following ≥ 1 platinum-based chemotherapy
- ECOG performance status: 0–2
- ≥ 1 measurable lesion(s)
- Adequate organ function

### Exclusion Criteria
- Untreated or symptomatic brain metastases
- Prior anti-cancer therapy within 28 days
- Immunodeficiency or systemic steroid use
- Interstitial lung disease

### Baseline Characteristic

<table>
<thead>
<tr>
<th>Baseline Characteristic</th>
<th>All Patients (N = 52)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years (range)</td>
<td>64 (32–80)</td>
</tr>
<tr>
<td>Current/former smoker, n (%)</td>
<td>8 (15) / 36 (69)</td>
</tr>
<tr>
<td>ECOG performance status: 0–1, n (%)</td>
<td>51 (98)</td>
</tr>
<tr>
<td>Prior lines of therapy</td>
<td></td>
</tr>
<tr>
<td>1–2, n (%)</td>
<td>39 (75)</td>
</tr>
<tr>
<td>≥ 3, n (%)</td>
<td>13 (25)</td>
</tr>
<tr>
<td>Median (range)</td>
<td>2 (1–6)</td>
</tr>
<tr>
<td>Prior PD-1 or PD-L1 treatment, n (%)</td>
<td>23 (44)</td>
</tr>
<tr>
<td>Extensive stage disease at initial diagnosis, n (%)</td>
<td>50 (96)</td>
</tr>
<tr>
<td>Brain / liver metastases, n (%)</td>
<td>13 (25) / 25 (48)</td>
</tr>
</tbody>
</table>

ECOG, Eastern Cooperative Oncology Group; PD-1, programmed death-1; PD-L1, programmed death-ligand 1; SCLC, small cell lung cancer.
AMG 757 Demonstrates Anti-Tumor Activity in Patients with SCLC

Median duration of response was 6.2 months

<table>
<thead>
<tr>
<th>Modified RECIST 1.1</th>
<th>Patients† (N = 51)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PR, confirmed</td>
<td>7 (14)</td>
</tr>
<tr>
<td>0.3 mg target dose</td>
<td>1/12 (8)</td>
</tr>
<tr>
<td>1 mg target dose</td>
<td>1/8 (13)</td>
</tr>
<tr>
<td>3 mg target dose</td>
<td>3/9 (33)</td>
</tr>
<tr>
<td>10 mg target dose</td>
<td>2/10 (20)</td>
</tr>
<tr>
<td>PR, unconfirmed</td>
<td>1 (2)</td>
</tr>
<tr>
<td>30 mg target dose</td>
<td>1 (2)</td>
</tr>
<tr>
<td>SD</td>
<td>11 (22)</td>
</tr>
</tbody>
</table>

Disease control rate, % 37

PR** indicates the PR is unconfirmed. SD^ indicates patients who had an initial PR, but did not have confirmation of PR on the subsequent scan. NE indicates PD in the post-baseline scan and came off study without further confirmation scan.

*Step dosing. †Includes patients who received ≥ 1 dose of AMG 757 and had at least 8 weeks follow-up. NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease.
Adverse Events (AEs) Summary

- Treatment-emergent AEs occurred in 51/52 (98%) patients
  - Grade ≥ 3 occurred in 27 (52%) patients
- Treatment-related AEs occurred in 41 (79%) patients, resulting in discontinuation in 1 (2%) patient
  - The one DLT was grade 5 pneumonitis and occurred in 1 (2%) patient

AMG 757 monotherapy demonstrated a favorable safety profile

<table>
<thead>
<tr>
<th>Treatment-related AEs</th>
<th>Patients (N = 52)</th>
<th></th>
<th>Grade ≥ 3, n (%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades, n (%)</td>
<td>Grade ≥ 3, n (%)*</td>
<td></td>
</tr>
<tr>
<td>Any treatment-related AE</td>
<td>41 (79)</td>
<td>12 (23)</td>
<td></td>
</tr>
<tr>
<td>Treatment-related AEs in ≥ 10% of patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRS</td>
<td>23 (44)</td>
<td>1 (2)†</td>
<td></td>
</tr>
<tr>
<td>Pyrexia</td>
<td>10 (19)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>7 (14)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>5 (10)</td>
<td>1 (2)</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>5 (10)</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

*Includes one patient with grade 5 pneumonitis; † Grade 3 CRS, more detail presented on next slide.

AE, adverse event; CRS, cytokine release syndrome; DLT, dose limiting toxicity.
Conclusions

- The results presented herein support AMG 757 as the first half-life extended BiTE® immuno-oncology therapy with a favorable safety profile and a durable response profile
  - Grade 3 treatment-related AEs occurred in 12 (23%) patients
  - CRS events were primarily grade 1 or 2 with only 1 case (2%) of grade 3 CRS
  - Only 1 discontinuation of treatment due to treatment-related AEs
  - Encouraging efficacy was observed during dose exploration, with confirmed PR in 14% of patients; response was durable, with a median duration of 6.2 months
- Dose optimization for monotherapy is ongoing
EFFICACY AND SAFETY PROFILE OF LURBINECTEDIN-IRINOTECAN IN PATIENTS WITH RELAPSED SCLC

Results from a phase Ib-II trial

Santiago Ponce¹, Gregory M. Coté², Alejandro Falcón³, Elizabeth Jimenez-Aguilar¹, Jessica J Lin², Inmaculada Sánchez Simón³, María José Flor³, Rafael Núñez⁴, Ana M Jiménez⁴, Eva Jiménez⁴, Sonia Extremera⁴, Carmen Kahatt⁴, Ali Zeaiter⁴, Luis Paz-Ares¹

¹Hospital Universitario 12 de Octubre, Madrid, Spain. ²Massachusetts General Hospital, Boston, MA, U.S.A. ³Hospital Universitario Virgen del Rocío, Sevilla, Spain. ⁴Pharma Mar, S.A., Colmenar Viejo, Madrid, Spain.
Study Design

Cohort A (n=39)
- LUR escalation D1
- IRI 75mg/m² D1&D8 q3w

Cohort B (n=23)
- IRI escalation D1&D8
- LUR 3mg/m² D1 q3w

Cohort C (n=3)
- LUR 2.6mg/m² D1
- IRI 50 mg/m² D1 q3w

RD

LUR 2mg/m² D1
IRI 75mg/m² D1&D8 + G-CSF

SCLC (n=21)
- Glioma (n=20)
- Endometrial (n=21)
- Sarcoma (n=9)
- NEN

Phase Ib
3 cohorts

Dose escalation
Ongoing
DL4
G-CSF

Dose escalation
Ongoing
DL1
G-CSF

LUR: Lurbinectedin
IRI: Irinotecan

LUR: Lurbinectedin
IRI: Irinotecan
### SCLC cohort, Baseline characteristics (n=21)

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>n= 21</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age</td>
<td>61 (52-74)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>48%</td>
</tr>
<tr>
<td>Female</td>
<td>52%</td>
</tr>
<tr>
<td>ECOG</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>24%</td>
</tr>
<tr>
<td>1</td>
<td>76%</td>
</tr>
<tr>
<td>LDH</td>
<td></td>
</tr>
<tr>
<td>&gt;ULN</td>
<td>76%</td>
</tr>
<tr>
<td>Stage at diagnosis</td>
<td></td>
</tr>
<tr>
<td>Limited</td>
<td>19%</td>
</tr>
<tr>
<td>Extensive</td>
<td>81%</td>
</tr>
<tr>
<td>Most common sites (no lung)</td>
<td></td>
</tr>
<tr>
<td>Lymph nodes</td>
<td>90%</td>
</tr>
<tr>
<td>Liver</td>
<td>48%</td>
</tr>
<tr>
<td>Adrenal</td>
<td>38%</td>
</tr>
<tr>
<td>Bone</td>
<td>38%</td>
</tr>
<tr>
<td>Bulky disease</td>
<td></td>
</tr>
<tr>
<td>1 lesion &gt; 50mm</td>
<td>29%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>n= 21</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sum longest diameters mm.</td>
<td>86 (19-180)</td>
</tr>
<tr>
<td>CNS metastases</td>
<td></td>
</tr>
<tr>
<td>PCI</td>
<td>24%</td>
</tr>
<tr>
<td>48%</td>
<td></td>
</tr>
<tr>
<td>Prior lines for advanced disease</td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>1 (1-2)</td>
</tr>
<tr>
<td>62%</td>
<td></td>
</tr>
<tr>
<td>2 lines</td>
<td>38%</td>
</tr>
<tr>
<td>Best response to prior platinum</td>
<td></td>
</tr>
<tr>
<td>CR-PR</td>
<td>71%</td>
</tr>
<tr>
<td>SD</td>
<td>5%</td>
</tr>
<tr>
<td>PD</td>
<td>19%</td>
</tr>
<tr>
<td>UNK</td>
<td>5%</td>
</tr>
<tr>
<td>CTFI</td>
<td></td>
</tr>
<tr>
<td>Median (months)</td>
<td></td>
</tr>
<tr>
<td>&lt;90 days</td>
<td>3.2 months</td>
</tr>
<tr>
<td>38%</td>
<td>38%</td>
</tr>
<tr>
<td>≥90 days</td>
<td>62%</td>
</tr>
</tbody>
</table>
## SCLC cohort, Safety (n=21)

<table>
<thead>
<tr>
<th>Treatment-related adverse events</th>
<th>Adverse Events and Laboratory abnormalities</th>
<th>Grade 1-2, %</th>
<th>Grade 3-4, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td></td>
<td>66.7</td>
<td>23.8*</td>
</tr>
<tr>
<td>Nausea</td>
<td></td>
<td>57.1</td>
<td>-</td>
</tr>
<tr>
<td>Vomiting</td>
<td></td>
<td>38.1</td>
<td>4.8</td>
</tr>
<tr>
<td>Diarrhea</td>
<td></td>
<td>33.3</td>
<td>28.6**</td>
</tr>
<tr>
<td>Constipation</td>
<td></td>
<td>19</td>
<td>-</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td></td>
<td>4.8</td>
<td>-</td>
</tr>
<tr>
<td>Anorexia</td>
<td></td>
<td>52.4</td>
<td>-</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td></td>
<td>-</td>
<td>9.5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Laboratory abnormalities</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td></td>
<td>81</td>
<td>19</td>
</tr>
<tr>
<td>Neutropenia</td>
<td></td>
<td>33.3</td>
<td>61.9***</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td></td>
<td>66.7</td>
<td>9.5</td>
</tr>
<tr>
<td>ALT increase</td>
<td></td>
<td>57.1</td>
<td>4.8</td>
</tr>
<tr>
<td>AST increase</td>
<td></td>
<td>61.9</td>
<td>4.8</td>
</tr>
</tbody>
</table>

### Related AEs summary / dose modifications / supportive treatment

<table>
<thead>
<tr>
<th>Related AEs summary / dose modifications / supportive treatment</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>21 (100)</td>
</tr>
<tr>
<td>AE ≥ grade 3</td>
<td>16 (76.2)</td>
</tr>
<tr>
<td>SAEs</td>
<td>6 (28.5)</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>0 (0.0)</td>
</tr>
<tr>
<td>Dose delays treatment related</td>
<td>6 (28.6)</td>
</tr>
<tr>
<td>Dose reductions</td>
<td>11 (52.4)</td>
</tr>
<tr>
<td>Transfusions (red blood)</td>
<td>7 (33.3)</td>
</tr>
</tbody>
</table>

**ALT, alanine aminotransferase; AST, aspartate aminotransferase; IRI, irinotecan; LUR, lurbinectedin.**

*1 episode per patient (n=5 pts)  
**All were grade 3. 1 episode per patient, except in 1 patient (2 episodes of 1 day of duration each)  
*** 6/21 pts (28.6 %) neutropenia grade 4
<table>
<thead>
<tr>
<th></th>
<th>All patients (n=21)</th>
<th>CTFI</th>
<th>Setting</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>≥90 days (n=13)</td>
<td>&lt;90 days (n=8)</td>
</tr>
<tr>
<td>Median number of cycles (range)</td>
<td>8+(1-20)</td>
<td>10+ (6-20)</td>
<td>6+ (1-8)</td>
</tr>
<tr>
<td>Objective Response Rate (PR)</td>
<td>62%</td>
<td>69%</td>
<td>50%</td>
</tr>
<tr>
<td>Clinical Benefit Rate (PR+SD&gt;4m)</td>
<td>81%</td>
<td>92.3%</td>
<td>62.5%</td>
</tr>
<tr>
<td>Disease Control Rate (PR+SD)</td>
<td>90%</td>
<td>100%</td>
<td>75%</td>
</tr>
<tr>
<td>Median DOR (m) (95% CI)</td>
<td>6.7+ (3.0-N.R)</td>
<td>7.5+ (3.0-N.R)</td>
<td>3.7+ (2.8-3.7)</td>
</tr>
<tr>
<td>Median PFS (m) (95% CI)</td>
<td>6.2+ (4.3-8.5)</td>
<td>8.1+ (4.3-N.R)</td>
<td>4.8+ (0.7-5.0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N.R not reached</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
The combination of lurbinectedin and irinotecan after failure of first-line therapy, demonstrates remarkable antitumor activity in SCLC.

Noticeable activity is being observed in pts with poor prognosis such as those with resistant disease (CTFI <90 days), in the 3rd line setting and those with brain metastases.

Toxicity is transient and manageable, being mainly hematological abnormalities, fatigue and diarrhea, with no discontinuations due to AE and no toxic deaths.

This cohort of patients with SCLC is being expanded up to 47 patients.

Further development of this combination is warranted in pts with SCLC.
Whole Exome Sequencing Reveals the Potential Role of Hereditary Predisposition in Small Cell Lung Cancer, a Tobacco-Related Cancer

Nobuyuki Takahashi¹, Camille Tlemsani¹, Lorinc Pongor¹, Vinodh N. Rajapakse¹, Manoj Tyagi¹, Xinyu Wen¹, Grace-Ann Fasaye¹, Keith T. Schmidt¹, Chul Kim², Arun Rajan¹, Shannon Swift¹, Linda Sciuto¹, Rasa Vilimas¹, Santhana Webb¹, Samantha Nichols¹, William Douglas Figg¹, Yves Pommier¹, Kathleen Calzone¹, Seth M. Steinberg¹, Jun S. Wei¹, Udayan Guha¹, Clesson E. Turner³, Javed Khan¹, Anish Thomas¹

¹Center for Cancer Research, National Cancer Institute, Bethesda, MD, USA
²Georgetown University, Washington DC, USA
³Walter Reed National Military Medical Center, Bethesda, MD
Germline mutations are highly prevalent in patients with SCLC

- 34/77 (44.2%) of SCLC patients had a P/LP germline mutation
- 9/77 (11.7%) of SCLC patients had a P/LP germline mutation in ACMG genes
- Most genes were involved in DNA repair (66.7%)
- 3/31 cases with available tumor had loss of heterozygosity (*BRCA2, MLH1, SMARCA4*)
Germline genotype is associated with family history of cancer and platinum sensitivity

Recurrence free survival with platinum

Overall survival since diagnosis
Updated efficacy, safety, and dosing management of poziotinib in previously treated EGFR and HER2 exon 20 NSCLC patients

R Cornelissen¹, MC Garassino², X Le³, J Clarke⁴, N Tchekmedyian⁵, J Goldman⁶, F Lebel⁷, G Bhat⁷, MA Socinski⁸

¹Erasmus Medical Center, Netherlands; ²Fondazione IRCCS Istituto Nazionale dei Tumori, Italy; ³The Univ Texas MD Anderson Cancer Center, TX; ⁴Duke Cancer Institute, NC; ⁵Pacific Shores Medical Group, CA; ⁶Univ California Los Angeles, CA; ⁷Spectrum Pharmaceuticals, CA; ⁸AdventHealth Cancer Institute, FL
## Efficacy in patient subgroups

### EGFR
- Responses observed regardless of lines of therapy in EGFR cohorts

### HER2
- Higher responses (38.7%) observed in patients with ≥3 prior lines of therapy than overall
- Clinical activity seen in all 14 patients with baseline CNS metastasis; Responses seen in 4 (28.6%); none had progression in brain lesion resulting in CNS specific DCR of 100%

### Exon 20 mutations Type
- No clear differences between types of Exon 20 mutations in EGFR or HER2 cohorts

<table>
<thead>
<tr>
<th>Lines of Therapy</th>
<th>2L EGFR Exon 20 (N=115) ORR % (n/N)</th>
<th>2L HER2 Exon 20 (N=90) ORR % (n/N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Line</td>
<td>14.3 (7/49)</td>
<td>23.3 (7/30)</td>
</tr>
<tr>
<td>2 Lines</td>
<td>13.8 (4/29)</td>
<td>20.7 (6/29)</td>
</tr>
<tr>
<td>3+ Lines</td>
<td>16.2 (6/37)</td>
<td><strong>38.7 (12/31)</strong></td>
</tr>
<tr>
<td>Chemotherapy only</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TKI</td>
<td>10.3 (3/29)</td>
<td>31.8 (7/22)</td>
</tr>
<tr>
<td>HER2 therapy</td>
<td>6.9 (2/29)</td>
<td>NA</td>
</tr>
<tr>
<td>Immune checkpoint inhibitors</td>
<td></td>
<td>24.0 (6/25)</td>
</tr>
<tr>
<td>Stable brain metastasis at baseline</td>
<td></td>
<td><strong>27.9 (12/43)</strong></td>
</tr>
</tbody>
</table>
Conclusions

- **Successfully met primary endpoint for 2L HER2 exon 20 insertion mutations**
  - ORR was 27.8% in 2L HER2 cohort
  - Higher response rates (38.7%) seen in heavily pre-treated HER2 cohort (≥3 lines of therapy)

- Clinical activity seen in previously-treated NSCLC patients with EGFR and HER2 exon 20 insertions across common mutational profile
  - DCR of 68.7% and 70% respectively

- Clinically meaningful responses (28.6%) observed in 14 HER2 patients with brain metastases at entry with no progression in brain lesion (CNS specific DCR of 100%)
  - Activity in CNS metastatic disease for both EGFR and HER2 cohorts

- Safety profile similar to second generation TKI’s
VISION: Cohort A baseline characteristics

VISION comprises a large population of elderly patients with MET exon 14 skipping NSCLC

- **VISION** is a single-arm, Phase II trial of tepotinib in patients with MET-altered NSCLC (NCT02864992)
  - Cohort A enrolled patients with MET exon 14 skipping NSCLC
- Patients were mostly elderly, half were male, half had smoking history, and most had adenocarcinoma
- Baseline characteristics were similar in the safety population, comprising all patients with MET exon 14 skipping NSCLC who received at least one dose of tepotinib across Cohorts A and C (N=255)

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>Treatment-naïve (n=69)</th>
<th>Previously treated (n=83)</th>
<th>Overall (N=152)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years (range)</td>
<td>74.0 (56–94)</td>
<td>72.6 (41–88)</td>
<td>73.1 (41–94)</td>
</tr>
<tr>
<td>Sex, %</td>
<td>Male/Female</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>52.2/47.8</td>
<td>51.8/48.2</td>
<td>52.0/48.0</td>
</tr>
<tr>
<td>Race, † %</td>
<td>White/Asian</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>81.2/17.4</td>
<td>62.7/31.3</td>
<td>71.1/25.0</td>
</tr>
<tr>
<td>ECOG PS, %</td>
<td>0/1</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>36.2/63.8</td>
<td>19.3/80.7</td>
<td>27.0/73.0</td>
</tr>
<tr>
<td>Smoking history, ‡ %</td>
<td>Yes/No</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>62.3/37.7</td>
<td>43.4/47.0</td>
<td>52.0/42.8</td>
</tr>
<tr>
<td>Histology, § %</td>
<td>Adenocarcinoma/Squamous</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>84.1/8.7</td>
<td>88.0/10.8</td>
<td>86.2/9.9</td>
</tr>
<tr>
<td>Brain metastases at baseline, ¶ %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>14.5</td>
<td>15.7</td>
<td>15.1</td>
</tr>
</tbody>
</table>

Best responses to prior therapies

- Any (n=83)
  - 2 CRs (2.4%)
  - 24 PRs (28.9%)
- Platinum-based CT* (n=74)
  - 2 CRs (2.7%)
  - 19 PRs (25.7%)
- IO + platinum-based CT (n=10)
  - 3 PRs (30.0%)

Additional information on tepotinib. *Prior platinum-based CT for metastatic disease. †Race was unknown or missing in four patients, one patient was Black/African American, and one patient was ‘other’. ‡Smoking history was missing in eight patients. §Two patients had adenosquamous histology (one treatment-naïve and one previously treated), three patients had sarcomatoid (all treatment naïve), and one patient had NSCLC-NOS (treatment naïve). ¶Baseline brain metastases identified by IRC or investigator.

VISION: Cohort A overall efficacy

Tepotinib demonstrated clinical activity irrespective of therapy line in this elderly patient population

<table>
<thead>
<tr>
<th>Efficacy according to IRC</th>
<th>Treatment-naïve (n=69)</th>
<th>Previously treated (n=83)</th>
<th>Overall (N=152)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR, % (95% CI)</td>
<td>44.9 (32.9, 57.4)</td>
<td>44.6 (33.7, 55.9)</td>
<td>44.7 (36.7, 53.0)</td>
</tr>
<tr>
<td>BOR, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>PR</td>
<td>31 (44.9)</td>
<td>37 (44.6)</td>
<td>68 (44.7)</td>
</tr>
<tr>
<td>SD</td>
<td>16 (23.2)</td>
<td>23 (27.7)</td>
<td>39 (25.7)</td>
</tr>
<tr>
<td>PD</td>
<td>13 (18.8)</td>
<td>13 (15.7)</td>
<td>26 (17.1)</td>
</tr>
<tr>
<td>NE</td>
<td>9 (13.0)</td>
<td>10 (12.0)</td>
<td>19 (12.5)</td>
</tr>
<tr>
<td>Median DOR, months (95% CI)</td>
<td>10.8 (6.9, ne)</td>
<td>11.1 (9.5, 18.5)</td>
<td>11.1 (8.4, 18.5)</td>
</tr>
<tr>
<td>Median PFS, months (95% CI)</td>
<td>8.5 (6.8, 11.3)</td>
<td>10.9 (8.2, 12.7)</td>
<td>8.9 (8.2, 11.2)</td>
</tr>
</tbody>
</table>

Data cut-off: July 1, 2020.

*Platinum-based CT for metastatic disease; three patients had stage III NSCLC at study entry and are, therefore, not included in this categorization. †One patient received IO as monotherapy and in combination with platinum-based CT and, as such, is included in both subgroups. ‡Patients could have received first-line platinum-based CT followed by second-line single-agent IO, or vice versa.

BOR, best overall response; CI, confidence interval; CR, complete response; CT, chemotherapy; DOR, duration of response; IRC, independent review committee; NE, not evaluable; ne, not estimable; ORR, objective response rate; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.
Methods and Demographics

14 patients with TRK fusion lung cancer

**Patient characteristics**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>52 (25–76)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex, n (%)</strong></td>
<td>8 (57)</td>
</tr>
<tr>
<td>Male</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>6 (43)</td>
</tr>
<tr>
<td><strong>NTRK fusion, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>NTRK1</td>
<td>11 (79)</td>
</tr>
<tr>
<td>NTRK2</td>
<td>0</td>
</tr>
<tr>
<td>NTRK3</td>
<td>3 (21)</td>
</tr>
<tr>
<td><strong>CNS metastases at baseline, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>7 (50)</td>
</tr>
<tr>
<td>No</td>
<td>7 (50)</td>
</tr>
<tr>
<td><strong>Number of prior systemic therapies, median (range)</strong>†</td>
<td>3 (0–5)</td>
</tr>
<tr>
<td><strong>Number of prior systemic therapies, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>1 (7)</td>
</tr>
<tr>
<td>1</td>
<td>4 (29)</td>
</tr>
<tr>
<td>2</td>
<td>2 (14)</td>
</tr>
<tr>
<td>≥3</td>
<td>7 (50)</td>
</tr>
</tbody>
</table>

**Dosing**
- Larotrectinib, 100 mg BID continuously
- 28-day cycles

**Endpoints**
- **Primary**
  - Best ORR per IRC and INV (RECIST v1.1)
- **Secondary**
  - DoR
  - PFS
  - OS
  - Safety

**Data cut-off:** July 15, 2019

Adult phase I trial (NCT02122913)
- Age ≥18 years
- Advanced solid tumors

Adult/adolescent phase II basket trial (NAVIGATE, NCT02576431)
- Age ≥12 years
- Advanced solid tumors
- TRK fusion cancer

† Median prior systemic therapies for CNS metastases patients = 1 (range 0–4). The best overall response to prior therapy was PR in two patients, SD in two patients, and PD in one patient. Responses were unavailable for two patients.

BID, twice daily; CNS, central nervous system; DoR, duration of response; INV, investigator; IRC, independent review committee; NTRK, neurotrophic tyrosine receptor kinase; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; RECIST, response evaluation criteria in solid tumors; SD, stable disease; TRK, tropomyosin receptor kinase.
Best Response to Larotrectinib per IRC†

### Maximum change in tumor size per IRC (%)

- **All patients**
  - IRC: 77% (95% CI: 46–95)
  - INV: 51% (95% CI: 25–75)
- **Patients with CNS metastases**
  - IRC: 71% (95% CI: 29–96)
  - INV: 57% (95% CI: 18–90)

### ORR, %

- **All patients**
  - IRC: 77% (95% CI: 46–95)
  - INV: 71% (95% CI: 42–92)
- **Patients with CNS metastases**
  - IRC: 71% (95% CI: 29–96)
  - INV: 57% (95% CI: 18–90)

### CR, n (%)

- **All patients**
  - IRC: 2 (15)
  - INV: 1 (7)
- **Patients with CNS metastases**
  - IRC: 0
  - INV: 0

### PR, n (%)

- **All patients**
  - IRC: 8 (62)
  - INV: 9 (64)
- **Patients with CNS metastases**
  - IRC: 5 (71)
  - INV: 4 (57)

### SD, n (%)

- **All patients**
  - IRC: 3 (23)
  - INV: 3 (21)
- **Patients with CNS metastases**
  - IRC: 2 (29)
  - INV: 2 (29)

### PD, n (%)

- **All patients**
  - IRC: 0
  - INV: 1 (7)
- **Patients with CNS metastases**
  - IRC: 0
  - INV: 1 (14)

### Treatment Duration

- **Duration of treatment:** 2.1 to 39.6+ months
- **Treatment ongoing in 9 (64%) patients at data cut-off,** including 3 of 7 patients with CNS metastases
- **Median time to response was 1.8 months (range: 1.7–7.3)**
TRIDENT-1 Study Design and Early Interim Phase 2 Data as of August 2020

<table>
<thead>
<tr>
<th>EXP-1</th>
<th>EXP-2</th>
<th>EXP-3</th>
<th>EXP-4</th>
<th>EXP-5</th>
<th>EXP-6</th>
</tr>
</thead>
<tbody>
<tr>
<td>ROS1+ TKI naïve</td>
<td>1 prior ROS1 TKI AND 1 platinum-based chemotherapy (n=60)</td>
<td>2 prior ROS1 TKIs AND No prior chemotherapy (n=40)</td>
<td>1 prior ROS1 TKI AND No prior chemotherapy (n=60)</td>
<td>TRK TKI naïve</td>
<td>TRK TKI pretreated</td>
</tr>
<tr>
<td>ORR 86% (6/7) 95% CI, 42–100</td>
<td>ORR 40% (2/5) 95% CI, 5–85</td>
<td>ORR 40% (2/5) 95% CI, 5–85</td>
<td>ORR 67% (4/6) 95% CI, 22–96</td>
<td>Not Reported</td>
<td>ORR 50% (3/6) 95% CI, 12–88</td>
</tr>
</tbody>
</table>

Today’s presentation will focus on UPDATED Phase 2 EXP-1 data (N=15) utilizing a data cutoff of 31 December 2020:
- Median age 58 (range 30-76); ECOG PS 1 = 60%; Prior Chemotherapy Use = 20%

Previously reported Phase 1 ROS1+ TKI-Naïve results (N=11) based on data cutoff by BICR of 22 July 2019:
- ORR: 91% (10/11) (95% CI: 59 – 100)
  - ORR 86% (6/7) at or above the Phase 2 recommended dose
- Median DOR (95% CI): 23.1 months (5.6 - NR)
- Median PFS (95% CI): 24.6 months (7.2 - NR)
Clinical Activity in \textit{ROS1}+ TKI Naïve Advanced NSCLC Patients

Byoung Chul Cho, Yonsei Cancer Center, Republic of Korea

Overall Response (N=22)

<table>
<thead>
<tr>
<th>Confirmed ORR, % (95% CI)</th>
<th>Phase 2 N=15</th>
<th>Phase 1+2 N=22</th>
</tr>
</thead>
<tbody>
<tr>
<td>93% (68–100)</td>
<td>91% (71–99)</td>
<td></td>
</tr>
</tbody>
</table>

\(N=22\) patients with baseline and at least two post baseline scans
- \(N=15\) Phase 2 patients
- \(N=7\) Phase 1 patients treated at or above the Phase 2 recommended dose

As of 31 December 2020, the 16th patient in Phase 2 has an unconfirmed PR and is on treatment awaiting a second post-baseline confirmatory scan.

\(\text{cORR, confirmed overall response rate; ORR, overall response rate.}\)

\(\text{^A Patient previously a confirmed partial response now in unconfirmed CR on treatment.}\)