Small cell lung cancer

Targeted agents in SCLC

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ESMO-The Christie Preceptorship program on Lung Cancer
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SCLC, where are we?

- Accounts for ~15% of newly diagnosed lung cancer
- Predominately associated with tobacco smoking
- Rapid doubling times and early propensity to metastasize
- Initial sensitivity to CT with 60-80% RR
**SCLC, where are we?**

- 1st-line treatment for both LD and ED: platinum/etoposide x 4-6 cycles
- For patients with LD
  - ✓ Early TRT (<30 days from CT start) should be added to CT
  - ✓ PCI for patients with CR/PR
- 2nd-line: topotecan or re-induction
- No new agents approved in over 20 years
- No targeted agents approved
Targeted agents in SCLC: outline

• Identification of genomic targets
• Targeted agents
• Immunotherapy
Identification of genomic targets
Genomic Analysis of SCLC

- **Hot spot mutations**
  - TP53, RB1, PIK3CA, CDKN2A, PTEN
  - RAS family regulators (RAB37, RASGRF1, RASGRF2)
  - Chromatin modifiers (EP300, DMBX1, MLL2, MED12, etc.)

- **Hot spot mutations PLUS q-score**
  - RUNX1T1, CDYL, RIMS2

- **Gene families and pathways**
  - PI3K pathway, Notch and Hedgehog, glutamate receptor family, DNA repair/checkpoint, SOX family

- **Focal amplifications**
  - MYC, SOX2, SOX4, KIT

- **Recurrent translocations and fusion genes**
  - Recurrent: RLF–MYCL1
  - Kinase fusions

[Circos plot whole genome SCLC]

22 significantly mutated genes

SCLC: comprehensive mutation analysis program at MSKCC

• Prospectively testing of SCLC biopsies genotyping with Sequenom and NGS

• Sequenom (n=32 samples): AKT1E17-mut (n=1) and PIK3CA E542K-mut (n=1)

• NGS (n=25 samples): loss of RB1 (N=18 mutations; N=4 deletions); TP53-mut (N=24), MLL3 (N=9), and EPHA 5 (N=9); and amplifications of CDKN2C (N=5), MYCL1 (N=3), SOX2 (N=2), and FGFR1 (N=1, confirmed by FISH)
NFIB

• Groups studying genetically engineered mouse models have identified NFIB as a key driver of metastasis in SCLC
  – NFIB, transcription factor, promotes metastatic spread
  – Suppression of NFIB expression in SCLC cell lines led to increased apoptosis and suppression of proliferation

• Better understanding of how NFIB expression is induced and regulated, warranted

1. Denny et al. Nfib promotes metastasis through a widespread increase in chromatin accessibility. Cell 16
2. Semenova et al. Transcription factor NFIB is a driver of small cell lung cancer progression in mice and marks metastatic disease in patients. Cell Rep 16
3. Wu et al. NFIB overexpression cooperates with Rb/p53 deletion to promote small cell lung cancer. Oncotarget 16
Chemosensitive Relapse in Small Cell Lung Cancer Proceeds through an EZH2-SLFN11 Axis

Eric E. Gardner,1,2 Benjamin H. Lok,2,3 Valentina E. Schneeberger,2 Patrice Desmeules,4 Linde A. Miles,2 Paige K. Arnold,5 Andy Ni,6 Inna Khodos,7 Elisa de Stanchina,2,7 Thuyen Nguyen,8 Julien Sage,8 John E. Campbell,9 Scott Ribich,9 Natasha Rekhtman,4 Afshin Dowlati,10 Pierre P. Massion,11 Charles M. Rudin,2,12,13,* and John T. Poirier2,13,14,*

SUMMARY

Small cell lung cancer is initially highly responsive to cisplatin and etoposide but in almost every case becomes rapidly chemoresistant, leading to death within 1 year. We modeled acquired chemoresistance in vivo using a series of patient-derived xenografts to generate paired chemo-sensitive and chemo-resistant cancers. Multiple chemoresistant models demonstrated suppression of SLFN11, a factor implicated in DNA-damage repair deficiency. In vivo silencing of SLFN11 was associated with marked deposition of H3K27me3, a histone modification placed by EZH2, within the gene body of SLFN11, inducing local chromatin condensation and gene silencing. Inclusion of an EZH2 inhibitor with standard cytotoxic therapies prevented emergence of acquired resistance and augmented chemotherapeutic efficacy in both chemo-sensitive and chemo-resistant models of small cell lung cancer.
**OA05.07: Prognostic Value of Circulating Tumour Cells in Limited-Disease Small Cell Lung Cancer Patients Treated on the CONVERT Trial**

**Study objective**
- To assess the impact of circulating tumour cell (CTC) count on outcome in a subgroup of patients in the Concurrent ONce-daily VERSus Twice-daily RadioTherapy (CONVERT) trial.

**Key patient inclusion criteria**
- Limited stage disease (LD)-SCLC
- CTC analysed
- ≥18 years of age
- ECOG PS 0–1 (or 2 at discretion of local investigator)
- FEV$_1$ >1 L or >40% predicted

**Primary endpoint**
- OS

**CTC analysis**
- Blood samples (7.5 mL) were collected at baseline, prior to any treatment.
- CTCs were enumerated prospectively using the Cellsearch platform.

*Starting on D22 of cycle 1 chemotherapy (4 to 6 cycles of cisplatin 25 mg/m$^2$ D1–3 or 75 mg/m$^2$ D1 with etoposide 100 mg/m$^2$ D1–3)*

Fernandez-Gutierrez et al. J Thorac Oncol 2016; 11(suppl): abstr OA05.07
**Key results**

- CTC count was associated with poor OS and PFS regardless of PET staging at all CTC thresholds
- 15 CTCs at baseline was the optimal threshold for prognosis

**Conclusion**

- In LD-SCLC, CTC count is highly prognostic for poor survival and independent of other relevant clinical factors

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<table>
<thead>
<tr>
<th>N</th>
<th>%</th>
<th>Median</th>
<th>95%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;15 CTCs, No PET</td>
<td>36</td>
<td>48</td>
<td>28.75, 95%CI</td>
</tr>
<tr>
<td>&lt;15 CTCs, PET</td>
<td>22</td>
<td>29</td>
<td>25.40, 17.77, 77.97</td>
</tr>
<tr>
<td>≥15 CTCs, No PET</td>
<td>12</td>
<td>16</td>
<td>9.27, 18.37, 39.27</td>
</tr>
<tr>
<td>≥15 CTCs, PET</td>
<td>5</td>
<td>7</td>
<td>4.33, 0.30, 13.17</td>
</tr>
</tbody>
</table>

p<0.001
Targeted agents
Failed biological / targeted agents for SCLC

- Interferons
- MMP-inhibitors
- Anti-idiotypic antibody BEC2
- Neurotensin analogs
- Farnesyl-transferase-inhibitors
- C-KIT TK-inhibitors
- EGFR TK-inhibitors
- Proteosome-inhibitors
- bcl2-inhibitors
- mTOR-inhibitors
CALGB 30504
Sunitinib in Untreated, Extensive Stage SCLC

Untreated ES-SCLC Enrollment → Chemo 4-6 cycles SD, PR, CR PCI Allowed → Stratify Cis vs Carbo 6 Cycles vs <6 Randomize

Sunitinib 37.5 mg/d Until Progression
Placebo Until Progression (Crossover allowed)
CALGB 30504
Sunitinib in Untreated, Extensive Stage SCLC

**Progression Free Survival**

- Median Progression Free Survival –
  - Sunitinib: 3.77 mo
  - Placebo: 2.30 mo
- Stratified Log-Rank Test
  - 1-sided p = 0.037
  - HR = 1.53
  - 90% CI: 1.03 - 2.27

**Overall Survival**

- Median Overall Survival –
  - Sunitinib: 8.95 mo
  - Placebo: 6.89 mo
- Stratified Log-Rank Test
  - 1-sided p = 0.27
  - HR = 1.17
  - 90% CI: 0.77 - 1.78

Ready JCO 15
Aurora kinase inhibitors: alisertib

• Phase II in SCLC, RR 21%, 19% in sensitive relapse and 27% in resistant relapse

• PFS 2.6 mo in the sensitive and 1.4 mo in the resistant relapse

• Phase II trial comparing paclitaxel alone to the combination of paclitaxel/alisertib in SCLC pts who progress after etoposide/platinum (NCT02038647)
Randomized phase 2 study of investigational aurora A kinase (AAK) inhibitor alisertib + paclitaxel (P) vs placebo + P as second line therapy for SCLC

**Key results**

<table>
<thead>
<tr>
<th>Group</th>
<th>Alisertib</th>
<th>Placebo</th>
<th>HR (95%CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS (resistant/refractory relapse patients), days</td>
<td>87</td>
<td>50</td>
<td>0.659 (0.442, 0.983)</td>
<td>0.0372</td>
</tr>
<tr>
<td>OS, days</td>
<td>186</td>
<td>165</td>
<td>0.93 (0.652, 1.341)</td>
<td>0.714</td>
</tr>
<tr>
<td>ORR, %</td>
<td>22</td>
<td>18</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DCR, %</td>
<td>58</td>
<td>46</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Stratification definition of sensitive was amended after 30% of patients had been enrolled but prior to analysis to better reflect the guidelines*

Randomized phase 2 study of investigational aurora A kinase (AAK) inhibitor alisertib + paclitaxel (P) vs placebo + P as second line therapy for SCLC

• Key results (cont.)
  – Rates of AEs were higher with alisertib

<table>
<thead>
<tr>
<th></th>
<th>Alisertib (n=87)</th>
<th>Placebo (n=89)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade &gt;3 AEs, %</td>
<td>76</td>
<td>51</td>
</tr>
<tr>
<td>Drug-related grade &gt;3 AEs, %</td>
<td>67</td>
<td>25</td>
</tr>
<tr>
<td>Drug-related serious AEs, %</td>
<td>32</td>
<td>7</td>
</tr>
<tr>
<td>AEs leading to discontinuation of study drug, %</td>
<td>15</td>
<td>6</td>
</tr>
</tbody>
</table>

• Conclusions
  – Alisertib + paclitaxel showed favourable PFS vs. paclitaxel alone with a significant difference observed in the protocol redefined subgroup of resistant/refractory tumours
  – The combination did not reach statistical significance for OS, ORR and DCR
  – Greater toxicity was observed with alisertib + paclitaxel vs. paclitaxel alone

PARP inhibitor, temozolamide/veliparib

- SCLC, characterized by frequent aberrant methylation and epigenetic silencing of the MGMT gene

- Temozolamide phase II in 62 p with relapsed SCLC (Pietanza, CCR 12)
  - 20% ORR (23%, sensitive group / 13%, refractory cohort)
  - P with tumor demonstrating MGMT promoter methylation responded better to treatment

- Phase II comparing temozolamide/veliparib vs temozolamide/placebo, ongoing
**Hedgehog pathway inhibitors**

- Hedgehog signaling in preclinical SCLC models
  - May play a significant role in the development and proliferation of SCLC
  - Inhibition of hedgehog pathway decreases cell growth

- A phase I trial of the Hedgehog inhibitor, sonidegib (LDE225), in combination with etoposide/cisplatin for the initial treatment of ED SCLC *(Pietanza Lung Cancer 16)*
  - 15 patients enrolled
  - G≥3 toxicities: anemia (n=5), neutropenia (n=8), CPK elevation (n=2), fatigue (n=2), and nausea (n=2)
  - PR confirmed in 79%
  - One patient with SOX2 amplification remains progression-free on maintenance sonidegib after 27 mo
NOTCH inhibitors

• Notch pathway, central role in embryonic development, the regulation of stem and progenitor cells, and is implicated centrally in many human cancers, including SCLC

• OMP-59R5, a fully human IgG2 antibody, inhibits signaling of Notch2&3 receptors
  – Phase Ib/II study of OMP-59R5 in combination with etoposide/platinum in untreated ED-SCLC showed promise with 13/16 (81%) attaining a PR and 3 achieving SD (Pietanza ASCO 2015)

• Rovalpituzumab tesirine is an antibody drug conjugate (ADC) that targets the atypical Notch ligand delta-like ligand 3 (DLL3) on the cell surface and then delivering the DNA damaging agent pyrrolobenzodiazepine dimer toxin
OA05.03: Single-Agent Rovalpituzumab Tesirine, a Delta-Like Protein 3 (DLL3)-Targeted Antibody-Drug Conjugate (ADC), in SCLC

- **Study objective**
  - First-in-human study to assess safety and efficacy of rovalpituzumab tesirine in SCLC

**Key patient inclusion criteria**
- Progressive SCLC after at least one previous systemic therapy
- Any DLL3 expression (n=74)

**Dosing regimens**
- Rovalpituzumab tesirine, q3w
- 0.05 mg/kg (n=3)
- 0.1 mg/kg (n=25)
- 0.2 mg/kg (n=3)
- 0.4 mg/kg (n=2)
- 0.8 mg/kg (n=2)

*Spigel et al. J Thorac Oncol 2016; 11(suppl): abstr OA05.03
Rudin et al. Lancet Oncol 16*
## Table 3: Activity outcomes in response-assessable patients treated at active doses, assessed by the investigator and by central review

<table>
<thead>
<tr>
<th></th>
<th>Investigator-assessed</th>
<th>Central review</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All patients (n=60)</td>
<td>DLL3 expression 0-49% (n=8)</td>
</tr>
<tr>
<td>Confirmed objective response (complete response and partial response)</td>
<td>11 (18%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Confirmed disease control (complete response, partial response, and stable disease)</td>
<td>41 (68%)</td>
<td>4 (50%)</td>
</tr>
<tr>
<td>Duration of response (months)</td>
<td>5.6 (2.5–8.3)</td>
<td>0</td>
</tr>
<tr>
<td>Progression-free survival (months)</td>
<td>2.8 (2.5–4.0)</td>
<td>2.2 (1.3–2.5)</td>
</tr>
</tbody>
</table>

Data are number of patients (%) or median (95% CI). Responses reflect confirmed responses according to RECIST version 1.1, based on two consecutive assessments at least 4 weeks apart, in patients treated with 0.2 mg/kg or 0.4 mg/kg every 3 weeks or 0.3 mg/kg or 0.4 mg/kg every 6 weeks. RECIST=Response Evaluation Criteria in Solid Tumors.
<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Grade 1-2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute kidney injury</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Alanine aminotransferase increased</td>
<td>2 (3%)</td>
<td>1 (1%)</td>
<td>1 (1%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Amylase increased</td>
<td>2 (3%)</td>
<td>1 (1%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Anaemia</td>
<td>7 (9%)</td>
<td>2 (3%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>8 (11%)</td>
<td>1 (1%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Aspartate aminotransferase increased</td>
<td>5 (7%)</td>
<td>1 (1%)</td>
<td>1 (1%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>1 (1%)</td>
<td>1 (1%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Blood alkaline phosphatase increased</td>
<td>3 (4%)</td>
<td>1 (1%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Cardiac tamponade</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>1 (1%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>0 (0%)</td>
<td>1 (1%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>12 (16%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Dermatitis aciform</td>
<td>3 (4%)</td>
<td>1 (1%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>6 (8%)</td>
<td>2 (3%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Electrocardiogram ST segment elevation</td>
<td>0 (0%)</td>
<td>1 (1%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Erythema</td>
<td>10 (14%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Erythema multiforme</td>
<td>5 (7%)</td>
<td>1 (1%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>23 (31%)</td>
<td>3 (4%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
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<tr>
<td>Hypoalbuminaemia</td>
<td>13 (18%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
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<tr>
<td>Hypotension</td>
<td>1 (1%)</td>
<td>2 (3%)</td>
<td>1 (1%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Hypoxia</td>
<td>0 (0%)</td>
<td>1 (1%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
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<tr>
<td>Infection</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>1 (1%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Lipase increased</td>
<td>1 (1%)</td>
<td>2 (3%)</td>
<td>3 (4%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Liver function test abnormal</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>1 (1%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

(Continued from previous column)

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Grade 1-2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maculopapular rash</td>
<td>10 (14%)</td>
<td>2 (3%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>14 (19%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Neutrophil count decreased</td>
<td>0 (0%)</td>
<td>1 (1%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Palmar-plantar erythrodysaesthesia syndrome</td>
<td>1 (1%)</td>
<td>1 (1%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Pancytopenia</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>1 (1%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Pericardial effusion</td>
<td>7 (9%)</td>
<td>0 (0%)</td>
<td>2 (3%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Peripheral oedema</td>
<td>18 (24%)</td>
<td>2 (3%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Photophobia</td>
<td>0 (0%)</td>
<td>1 (1%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Photosensitivity reaction</td>
<td>7 (9%)</td>
<td>1 (1%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Platelet count decreased</td>
<td>2 (3%)</td>
<td>1 (1%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>17 (23%)</td>
<td>6 (8%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Pulmonary oedema</td>
<td>0 (0%)</td>
<td>1 (1%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>4 (5%)</td>
<td>3 (4%)</td>
<td>5 (7%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Troponin increased</td>
<td>0 (0%)</td>
<td>1 (1%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Tumour haemorrhage</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>10 (14%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>White blood cell count decreased</td>
<td>0 (0%)</td>
<td>1 (1%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

Data are number of patients (%). The table shows grade 1-2 treatment-related adverse events in ≥10% of patients in any treatment cohort and all grade 3-5 adverse events. All-cause adverse events and serious adverse events are shown in the appendix (pp 11-25).

Table 2: Treatment-related adverse events in 74 patients with small-cell lung cancer
Immunotherapy
Immuno-oncology in SCLC: background

• Although current strategies successfully induce a response, the response is not long-lasting

• SCLC closely associated with tobacco-smoking; in NSCLC immuno-oncology compounds more active in smokers (higher mutational burden)
Phase III Randomized Trial of Ipilimumab Plus Etoposide and Platinum Versus Placebo Plus Etoposide and Platinum in Extensive-Stage Small-Cell Lung Cancer

Martin Reck, Alexander Luft, Aleksandra Szczesna, Libor Havel, Sang-We Kim, Wallace Akerley, Maria Catherine Pietanza, Yi-long Wu, Christoph Zielinski, Michael Thomas, Enriqueta Felip, Kathryn Gold, Leora Horn, Joachim Aerts, Kazuhiko Nakagawa, Paul Lorigan, Anne Pieters, Teresa Kong Sanchez, Justin Fairchild, and David Spigel

![Graph showing overall survival rates and time since random assignment](image-url)
KEYNOTE-028 (NCT02054806): Phase 1b Multicohort Study of Pembrolizumab for PD-L1+ Advanced Solid Tumors

Patients
- Small cell lung cancer
- Failure of or inability to receive standard therapy
- ECOG PS 0 or 1
- ≥1 measurable lesion
- PD-L1 positivity
- No autoimmune disease or interstitial lung disease

Pembrolizumab 10 mg/kg IV Q2W

Complete or partial response or stable disease

Treat for 24 months or until progression or intolerable toxicity

Confirmed progressive disease or unacceptable toxicity

Discontinue pembrolizumab

Response Assessment*

*Response assessment: Every 8 weeks for the first 6 months; every 12 weeks thereafter

Primary end points: ORR per RECIST v1.1 (investigator-assessed) and safety

Secondary end points: PFS, OS, duration of response

*aIf clinically stable, patients are to remain on pembrolizumab until progressive disease is confirmed on a second scan performed ≥4 weeks later.
Analysis of PD-L1 Expression

• Samples: archival or newly obtained core or excisional biopsy of a nonirradiated lesion
• Immunohistochemistry: performed at a central laboratory using a prototype assay and the 22C3 antibody clone (Merck)
• Positivity: membranous PD-L1 expression in ≥1% of tumor and associated inflammatory cells or positive staining in stroma
• SCLC cohort: of 147 evaluable samples, 42 PD-L1 positive (28.6%)
## Patient and Disease Characteristics

<table>
<thead>
<tr>
<th>Characteristic, n (%)</th>
<th>N = 24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years (range)</td>
<td>60.5 (41–80)</td>
</tr>
<tr>
<td>Male</td>
<td>14 (58.3)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>13 (54.2)</td>
</tr>
<tr>
<td>Asian</td>
<td>3 (12.5)</td>
</tr>
<tr>
<td>Not specified</td>
<td>8 (33.3)</td>
</tr>
<tr>
<td>ECOG performance status</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>7 (29.2)</td>
</tr>
<tr>
<td>1</td>
<td>17 (70.8)</td>
</tr>
<tr>
<td>Stable brain metastases</td>
<td>3 (12.5)</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
</tr>
<tr>
<td>Small cell</td>
<td>23 (95.8)</td>
</tr>
<tr>
<td>Neuroendocrine</td>
<td>1 (4.2)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Characteristic, n (%)</th>
<th>N = 24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of prior therapy(^a)</td>
<td></td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>24 (100)</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>1 (4.2)</td>
</tr>
<tr>
<td>Investigational TKI</td>
<td>1 (4.2)</td>
</tr>
<tr>
<td>Other investigational therapy</td>
<td>1 (4.2)</td>
</tr>
<tr>
<td>Specific prior therapies(^a,b)</td>
<td></td>
</tr>
<tr>
<td>Cisplatin/carboplatin + etoposide</td>
<td>24 (100)</td>
</tr>
<tr>
<td>Irinotecan or topotecan</td>
<td>11 (45.8)</td>
</tr>
<tr>
<td>Taxane</td>
<td>7 (29.2)</td>
</tr>
<tr>
<td>Previous lines of therapy(^c)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>3 (12.5)</td>
</tr>
<tr>
<td>2</td>
<td>12 (50.0)</td>
</tr>
<tr>
<td>≥3</td>
<td>9 (37.5)</td>
</tr>
</tbody>
</table>

\(^a\)Patients could have received ≥1 type of prior therapy. \(^b\)Not all prior therapies are listed. \(^c\)Includes adjuvant and neoadjuvant therapies.

Data cutoff date: June 20, 2016.
## Antitumor Activity
(RECIST v1.1, Investigator Review, confirmed)

<table>
<thead>
<tr>
<th>Best Overall Response</th>
<th>n</th>
<th>%</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>1</td>
<td>4.2</td>
<td>0.1-21.1</td>
</tr>
<tr>
<td>Partial response</td>
<td>7</td>
<td>29.2</td>
<td>12.6-51.1</td>
</tr>
<tr>
<td>Stable disease</td>
<td>1</td>
<td>4.2</td>
<td>0.1-21.1</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>13</td>
<td>54.2</td>
<td>32.8-74.4</td>
</tr>
<tr>
<td>No assessment(^a)</td>
<td>2</td>
<td>8.3</td>
<td>1.0-27.0</td>
</tr>
<tr>
<td>Median duration of response, months (range)(^b)</td>
<td></td>
<td>19.4 (3.6+ to 20.0+)</td>
<td></td>
</tr>
</tbody>
</table>

Objective response rate: 33.3% (95% CI, 15.6–55.3)

Clinical benefit rate (CR + PR + SD ≥6 months): 33.3% (95% CI, 15.6–55.3)

\(^a\)For “No Assessment”, the patient discontinued prior to post-baseline assessment.

\(^b\)Calculated using the Kaplan-Meier method for censored data.

Data cutoff date: June 20, 2016.
Progression-Free Survival (Investigator Review)

<table>
<thead>
<tr>
<th>PFS</th>
<th>N = 24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events, n (%)</td>
<td>20 (83.3)</td>
</tr>
<tr>
<td>Median PFS (95% CI), months</td>
<td>1.9 (1.7–5.9)</td>
</tr>
</tbody>
</table>

**Graph:**
- Time, months: 0, 4, 8, 12, 16, 20, 24
- Progression-Free Survival (%): 100, 80, 60, 40, 20, 0
- Number at risk:
  - 24 at risk
  - 9 at risk
  - 6 at risk
  - 6 at risk
  - 5 at risk
  - 4 at risk
  - 2 at risk
  - 2 at risk
  - 2 at risk
  - 2 at risk
  - 2 at risk
  - 0 at risk

Key points:
- 28.6% at 4 months
- 23.8% at 12 months
Overall Survival

**Overall Survival (OS)**

- **Events, n (%):** 15 (62.5)
- **Median OS (95% CI), months:** 9.7 (4.1-NR)

![Overall Survival Graph](image)

- **Number at risk:**
  - 24 at 0 months
  - 20 at 4 months
  - 17 at 8 months
  - 14 at 12 months
  - 14 at 16 months
  - 9 at 20 months
  - 8 at 24 months

---

**6198 – PA Ott**
Checkmate 032: nivolumab ± ipilimumab
Phase I/II study in ≥2L advanced/metastatic SCLC

N=216

Key Inclusion Criteria
- Progressive disease after ≥1 prior line of therapy, including platinum-based regimen
- Measurable disease
- ECOG PS ≤1

- Primary objective:
  - ORR per RECIST v1.1
- Secondary objectives:
  - TRAEs leading to discontinuation, PFS, OS

Nivolumab

N 3 mg/kg IV q2w
(n=98)\(^a\)

Nivolumab

N 1 mg/kg + ipi 3 mg/kg
Q3W for 4 cycles
(n=61)\(^b\)

Nivolumab

N 3 mg/kg + ipi 1 mg/kg
Q3W for 4 cycles
(n=54)\(^c\)

Nivolumab alone and nivolumab plus ipilimumab in recurrent small-cell lung cancer (CheckMate 032): a multicentre, open-label, phase 1/2 trial

Scott J Antonia, José A López-Martin, Johanna Bendell, Patrick A Ott, Matthew Taylor, Joseph Paul Eder, Dirk Jäger, M Catherine Pietanza, Dung T Le, Filippo de Braud, Michael A Morse, Paolo A Ascierto, Leora Horn, Asim Amin, Rathi N Pillai, Jeffry Evans, Ian Chau, Petri Bono, Akin Atmaca, Padmanee Sharma, Christopher T Harbison, Chen-Sheng Lin, Olaf Christensen, Emiliano Calvo
<table>
<thead>
<tr>
<th></th>
<th>Nivolumab 3 mg/kg (n=98)</th>
<th>Nivolumab 1 mg/kg plus ipilimumab 3 mg/kg (n=61)</th>
<th>Nivolumab 3 mg/kg plus ipilimumab 1 mg/kg (n=54)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Objective response; 95% CI</strong></td>
<td>10 (10%; 5–18)</td>
<td>14 (23%; 13–36)</td>
<td>10 (19%; 9–31)</td>
</tr>
<tr>
<td><strong>Best overall response</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>0</td>
<td>1 (2%)</td>
<td>0</td>
</tr>
<tr>
<td>Partial response</td>
<td>10 (10%)</td>
<td>13 (21%)</td>
<td>10 (19%)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>22 (22%)</td>
<td>13 (21%)</td>
<td>9 (17%)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>52 (53%)</td>
<td>23 (38%)</td>
<td>29 (54%)</td>
</tr>
<tr>
<td>Unable to determine</td>
<td>12 (12%)</td>
<td>8 (13%)</td>
<td>6 (11%)</td>
</tr>
<tr>
<td>Not reported</td>
<td>2 (2%)</td>
<td>3 (5%)</td>
<td>0</td>
</tr>
<tr>
<td>Time to objective response (IQR), months</td>
<td>2.0 (1.3–2.8)</td>
<td>2.1 (1.4–2.8)</td>
<td>1.4 (1.3–2.7)</td>
</tr>
</tbody>
</table>

Antonia et al. Lancet 2016
Checkmate 032: objective response

- 69% were evaluable for PD-L1 expression at baseline; 16% had ≥1% tumor PD-L1 expression
- Responses were seen regardless of PD-L1 expression
Checkmate 032: overall survival

Events/Number at Risk | mOS, months | 1-year OS Rate, % | Median Follow-up, mo
--- | --- | --- | ---
Nivolumab-3 | 60/98 | 4.4 | 33 | 11.1
Nivolumab-1/ipilimumab-3 | 36/61 | 7.7 | 43 | 16.5
Nivolumab-3/ipilimumab-1 | 35/55 | 6.0 | 35 | 13.1

*Defined as time from first dose to date of database lock; follow-up was shorter for patients who died prior to database lock.
mo=months; mOS=median overall survival; OS=overall survival.
Antonia SJ et al. Oral presentation at ASCO 2016. 100.
Checkmate 032: safety summary

<table>
<thead>
<tr>
<th></th>
<th>Nivolumab-3 (n=98)</th>
<th>Nivolumab-1 + Ipilimumab-3 (n=61)</th>
<th>Nivolumab-3 + Ipilimumab-1 (n=54)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any Grade, %</td>
<td>Grade 3–4, %</td>
<td>Any Grade, %</td>
</tr>
<tr>
<td>Total treatment-related AEs</td>
<td>53</td>
<td>13</td>
<td>79</td>
</tr>
<tr>
<td>Treatment-related AEs leading</td>
<td>6</td>
<td></td>
<td>11</td>
</tr>
<tr>
<td>to discontinuation</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Two treatment-related deaths occurred in the nivolumab-1 + ipilimumab-3 arm: one due to myasthenia gravis and one due to worsening of renal failure. One treatment-related death due to pneumonitis occurred in the nivolumab-3 + ipilimumab-1 arm
- Treatment-related limbic encephalitis was reported in 2 (1%) patients; 1 case resolved, and outcome for 1 case was not reported
- Treatment-related pneumonitis occurred in 8 (4%) patients; 6 cases resolved, outcome for 1 case is unknown, and 1 case was fatal

Antonia SJ et al. Oral presentation at ASCO 2016. 100.
# Phase IA study of atezolizumab in ED SCLC

The ED-SCLC cohort was part of the larger phase Ia clinical trial NCT01375842, which evaluated atezolizumab in patients with locally advanced or metastatic solid tumors.

## Dose-Escalation Phase

<table>
<thead>
<tr>
<th>Dose Escalation</th>
<th>DLT window C1 D1-21</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.01 mg/kg</td>
<td>0.03 mg/kg</td>
</tr>
<tr>
<td>0.1 mg/kg</td>
<td>0.3 mg/kg</td>
</tr>
<tr>
<td>1 mg/kg</td>
<td>3 mg/kg</td>
</tr>
<tr>
<td>10 mg/kg</td>
<td>20 mg/kg</td>
</tr>
</tbody>
</table>

### Standard phase I DLT criteria used

- Standard 3+3 at doses ≥0.3 mg/kg

## Dose-Expansion Phase, SCLC cohort (ongoing)

- 1. PD-L1 selected
- 2. All comers

## Treatment-Related All-Grade AEs, ≥10% Incidence

### Per RECIST v1.1

<table>
<thead>
<tr>
<th>All Patients</th>
<th>N=17</th>
<th>Per RECIST v1.1</th>
<th>n (%)</th>
<th>(95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>1 (5.9%)</td>
<td>(0.2%, 28.7%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PR</td>
<td>1 (5.9%)</td>
<td>(0.2%, 28.7%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>2 (11.7%)</td>
<td>(1.5%, 36.4%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DCR(^a)</td>
<td>3 (17.6%)</td>
<td>(3.8%, 43.4%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### SCLC

<table>
<thead>
<tr>
<th>AEs</th>
<th>N=17</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>4 (24%)</td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>2 (12%)</td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>2 (12%)</td>
<td></td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>2 (12%)</td>
<td></td>
</tr>
<tr>
<td>Pruritus</td>
<td>2 (12%)</td>
<td></td>
</tr>
</tbody>
</table>

---

*Sequist LV et al. Presentation at ESMO 2016. Abstract 1425PD.*

\(^a\) DCR: Disease Control Rate
Ongoing I-O monotherapy or targeted therapy trials in SCLC

### Eligibility Criteria
- **Checkmate 451**
  - ED SCLC, ongoing 1L Pt-CT
  - Nivolumab ± ipilimumab
  - Placebo
  - PFS, OS

- **SCRX001-007**
  - ED SCLC, no prior therapy with corticosteroids, available for DLL3 IHC testing
  - Rovalpituzumab tesirine
  - Safety

- **Checkmate 331**
  - SCLC, tumor progression after Pt-CT or RT, no prior I-O therapies
  - Nivolumab
  - Topotecan
  - Amrubicin
  - OS

- **Checkmate 032**
  - LA or metastatic SCLC, no prior I-O therapies
  - Nivolumab ± ipilimumab
  - ORR

- **KEYNOTE-028**
  - LA or metastatic SCLC, tumor progression ≥1 systemic therapy, no prior I-O therapies
  - Pembrolizumab
  - BOR

- **KEYNOTE-158**
  - Advanced solid tumor, tumor progression ≥1 systemic therapy, no prior I-O therapies
  - Pembrolizumab
  - ORR

- **TRINITY**
  - DLL3+ SCLC, tumor progression ≥2 systemic therapies (≥1 Pt-based therapy)
  - Rovalpituzumab tesirine
  - ORR, OS

- **Ph I8 (N=74)**
  - SCLC, tumor progression ≥1 systemic therapy
  - Rovalpituzumab tesirine
  - ORR

**Clinicaltrials.gov**
Shining light on novel targets and therapies

Charles M. Rudin and John T. Poirier

In 2016, the pace of biological insights into small-cell lung cancer (SCLC) was reflected in new treatment approaches that have suggested meaningful clinical benefit to patients. We focus on three highlights of 2016: preclinical studies defining NFIB as a putative driver of metastasis, and two clinical studies; one that assessed the efficacy of an agent targeting the Notch ligand DLL3, and the other that explored T-cell checkpoint-blockade therapies targeting PD-1 and CTLA-4.

Key advances

- Multiple groups studying genetically engineered mouse models have identified NFIB as a key driver of metastasis in small-cell lung cancer (SCLC)\textsuperscript{1–3}
- Rovalpituzumab tesirine, an antibody-drug conjugate directed at the inhibitory Notch ligand DLL3, showed clinical activity in SCLC, with DLL3 protein expression being a potential predictive biomarker\textsuperscript{4,8}
- T-cell checkpoint blockade using nivolumab, with or without ipilimumab, has demonstrated clinical activity in SCLC, regardless of PD-L1 expression on tumour cells\textsuperscript{5}
Targeted agents in SCLC: conclusions

- Molecular evaluation, feasible in SCLC specimens with NGS technics
- A number of potentially druggable molecular pathways identified
- Too many genetic alterations/pathways (mostly tumor suppressor genes)
- GENOMICS and IMMUNOTHERAPY investigation also in SCLC!!
Thanks!!

efelip@vhebron.net