Small Cell Lung Cancer: Novel Approaches

Sukhmani K. Padda
Assistant Professor of Medicine
Stanford University
California Cancer Consortium Conference
Pasadena, CA
August 11, 2018
Disclosures

Relevant financial relationships in the past twelve months by presenter:

Grant/Research support: EpicentRx, Forty Seven Inc, Bayer

Consultant: AstraZeneca, AbbVie

The speaker will directly disclose the use of products for which are not labeled (e.g., off label use) or if the product is still investigational.
Objectives

• The Current State of Affairs

• Novel Targets

• Immunotherapy
Objectives

• The Current State of Affairs
• Novel Targets
• Immunotherapy
SCLC: The Current State of Affairs

- Poorly differentiated neuroendocrine tumor
- Only 30% present with limited stage disease
- Limited role for surgery
- Sensitive to chemotherapy and radiation
- Resistance common and prognosis poor
Timeline of SCLC Therapeutic Advances

First-line setting
- Cisplatin + etoposide 1985
- Carboplatin + etoposide 1999
- Carboplatin + irinotecan 2006
- Cisplatin + irinotecan 2006

Refractory/recurrent setting
- Irinotecan 1992
- Topotecan 1996
- Docetaxel 1994
- Paclitaxel 1998
- Gemcitabine 2001
- Temozolomide 2012
- Nivolumab + ipilimumab 2016

Radiation therapy
- Thoracic radiotherapy (LS-SCLC) 1992
- 45 Gy b.i.d. (LS-SCLC) 1999
- PCI (LS-SCLC) 1999
- PCI (ES-SCLC) 2007
- Thoracic radiotherapy (ES-SCLC) 2015

Objectives

• The Current State of Affairs

• Novel Targets
  – Overview
  – Targeting DLL3: Developmental NOTCH Signaling Pathway
  – Targeting PARP: DNA Damage and Repair
  – Targeting EZH2: Epigenetics
  – Targeting WEE1: Cell Cycle
  – Targeting HGF-MET Axis: Pleiotropic

• Immunotherapy
SCLC Targeted Therapy: results have been disappointing

<table>
<thead>
<tr>
<th>Agent</th>
<th>Target</th>
<th>Clinical trial</th>
<th>Phase/line</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bevacizumab</td>
<td>VEGF</td>
<td>Pujol et al. (67)</td>
<td>II–III/1st</td>
<td>No benefit</td>
</tr>
<tr>
<td>Afilbercept</td>
<td>VEGF</td>
<td>Allen et al. (68)</td>
<td>IV/2nd</td>
<td>No benefit in OS</td>
</tr>
<tr>
<td>Thalidomide</td>
<td>Immunomodulatory/angiogenesis</td>
<td>Lee et al. (69)</td>
<td>III/1st, maintenance</td>
<td>No benefit</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>Multiple kinases, VEGFR</td>
<td>Ready et al. (70)</td>
<td>I/II/maintenance</td>
<td>Benefit in PFS</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>Multiple kinases, VEGFR</td>
<td>Gitlitz et al. (71)</td>
<td>II/2nd</td>
<td>Insufficient efficacy</td>
</tr>
<tr>
<td>Imatinib</td>
<td>C-kit</td>
<td>Schneider et al. (72)</td>
<td>I/II/maintenance</td>
<td>Insufficient efficacy²</td>
</tr>
<tr>
<td>Gefitinib</td>
<td>EGFR</td>
<td>Moore et al. (74)</td>
<td>II/2nd</td>
<td>Insufficient efficacy</td>
</tr>
<tr>
<td>Dasatinib</td>
<td>C-kit, c-Src</td>
<td>Miller et al. (75)</td>
<td>II/2nd</td>
<td>Insufficient efficacy</td>
</tr>
<tr>
<td>Temsirolimus</td>
<td>mTORC1</td>
<td>Pandya et al. (73)</td>
<td>I/II/maintenance</td>
<td>Insufficient efficacy³</td>
</tr>
<tr>
<td>Everolimus</td>
<td>mTORC1</td>
<td>Tarhini et al. (76)</td>
<td>II/2nd</td>
<td>Insufficient efficacy</td>
</tr>
<tr>
<td>Cxutumubum</td>
<td>IGF-1R</td>
<td>Belani et al. (77)</td>
<td>IV/1st</td>
<td>No benefit⁴</td>
</tr>
<tr>
<td>Vismodegib</td>
<td>SMO</td>
<td>Belani et al. (77)</td>
<td>IV/1st</td>
<td>No benefit⁴</td>
</tr>
<tr>
<td>Tipifarnib</td>
<td>Farnesyl transferase</td>
<td>Heymach et al. (78)</td>
<td>II/2nd</td>
<td>Insufficient efficacy</td>
</tr>
<tr>
<td>Marimastat</td>
<td>Matrix metalloproteinase</td>
<td>Shepherd et al. (79)</td>
<td>III/maintenance</td>
<td>No benefit</td>
</tr>
<tr>
<td>Oblimersen</td>
<td>Bcl-2</td>
<td>Rudin et al. (80)</td>
<td>IV/1st</td>
<td>No benefit</td>
</tr>
<tr>
<td>Navitoclax</td>
<td>Bcl-2 and Bcl-x(L)</td>
<td>Rudin et al. (81)</td>
<td>II/2nd</td>
<td>Limited activity, potential biomarker, Insufficient efficacy</td>
</tr>
<tr>
<td>Bortezomib</td>
<td>Proteasome</td>
<td>Lara et al. (82)</td>
<td>IV/2nd</td>
<td>Insufficient efficacy</td>
</tr>
<tr>
<td>Vandetanib</td>
<td>RET, VEGFR, EGFR</td>
<td>Arnold et al. (83)</td>
<td>IV/maintenance</td>
<td>Insufficient efficacy</td>
</tr>
<tr>
<td>Romidepsin</td>
<td>HDAC</td>
<td>Otterson et al. (84)</td>
<td>II/2nd</td>
<td>Insufficient efficacy</td>
</tr>
<tr>
<td>AT-101 (Gossypol)</td>
<td>Small molecules in apoptosis⁵</td>
<td>Baggstrom et al. (85)</td>
<td>II/2nd</td>
<td>Insufficient efficacy</td>
</tr>
<tr>
<td>Pazopanib</td>
<td>VEGFR</td>
<td>Kotsakis et al. (86)</td>
<td>II/2nd</td>
<td>Moderate efficacy⁴⁴</td>
</tr>
</tbody>
</table>

SCLC Comprehensive Genomic Study

Targeting Delta-like Protein 3 (DLL3) of NOTCH Signaling Pathway in SCLC

- An atypical inhibitory Notch ligand
- Induced by the key neuroendocrine transcription factor, ASCL1
- Expressed on both cancer stem and tumor cells, but not normal adult tissues
- Not prognostic of SCLC outcomes on standard therapy
- >85% of SCLC express DLL3
Targeting DLL3 with Antibody Drug Conjugate Rovalpituzumab Tesirine (Rova-T)

TRINITY: A Phase 2, Single-Arm Study of Rova-T in DLL3-Expressing, Relapsed/Refractory SCLC

Key Eligibility Criteria
- DLL3-positive* SCLC
- Relapsed or refractory disease
- ≥ 2 previous regimens
- ≥ 1 platinum-based regimen
- ECOG Performance Status 0-1
- Stable CNS metastases allowed

Primary Endpoints
- Objective response rate (ORR)
- Overall survival (OS)

Secondary Endpoints
- Duration of response (DOR)
- Clinical benefit rate (CBR)
- Progression-free survival (PFS)

N = 339
Rova-T
0.3 mg/kg IV
q6w x 2

- Re-treatment was permitted at progression
- Study was powered to detect a 25% best overall response rate in DLL3-high Pts with a Simon’s two-stage design
- Study size was increased to ensure adequate enrollment of 3L Pts

*Clinical trial mouse antibody-based immunohistochemistry assay.
*Re-treatment with 2 cycles of Rova-T was permitted for patients who tolerated the initial 2 doses, exhibited SD or better, received no other systemic anticancer therapy after Rova-T, and progressed ≥ 12 weeks after the 2nd initial dose.
CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; IHC, immunohistochemistry; IV, intravenous; q6w, every 6 weeks.
Majority (70%) of Patients had DLL3-High Expression

DLL3 Screening and Expression in 3L+ SCLC

- 339 eligible, DLL3-positive patients received ≥ 1 dose in TRINITY

Focus on DLL3-high (i.e. ≥ 75% cells DLL3+):
- Pre-specified subgroup analysis
- Companion Dx assay cut-off
Rova-T Clinical Activity in Overall and DLL3-High Populations

DLL3-high (IRC): 14.3% ORR, 72% CBR, mPFS 3.8 mo, mOS 5.7 mo
Enriched Response Rate among 3L Patients with High DLL3 Expression

IRC-Assessed Outcomes by DLL3 Status (%; 95% CI)

- **High** (N=177):
  - ORR*: 6%
  - Best Overall Response Rate: 16%
  - CBR: 57%

- **Non-High** (N=63):
  - ORR*: 16%
  - Best Overall Response Rate: 24%
  - CBR: 72%

nP-value based on two-sample t test; not adjusted for multiple testing.
*Confirmed CR+ PR per RECIST v1.1

Unique Side Effect Profile of Rova-T

**Summary of TEAEs**

<table>
<thead>
<tr>
<th>TEAEs, Any Grade ≥ 15% Patients</th>
<th>All Patients, N = 339</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any n (%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>130 (38%)</td>
</tr>
<tr>
<td>Photosensitivity reaction</td>
<td>123 (36%)</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>109 (32%)</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>104 (31%)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>103 (30%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>88 (26%)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>84 (25%)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>83 (25%)</td>
</tr>
<tr>
<td>Constipation</td>
<td>75 (22%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>59 (17%)</td>
</tr>
<tr>
<td>Anemia</td>
<td>58 (17%)</td>
</tr>
<tr>
<td>Cough</td>
<td>55 (16%)</td>
</tr>
<tr>
<td>Hypoalbuminemia</td>
<td>53 (16%)</td>
</tr>
<tr>
<td>Pericardial effusion</td>
<td>50 (15%)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>49 (15%)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>49 (15%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TEAEs, Grade 3/4 ≥ 10 Patients</th>
<th>All Patients, N = 339</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any n (%)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>38 (11%)</td>
</tr>
<tr>
<td>Photosensitivity reaction</td>
<td>23 (7%)</td>
</tr>
<tr>
<td>Anemia</td>
<td>16 (5%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>15 (4%)</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>15 (4%)</td>
</tr>
</tbody>
</table>

- Serosal effusions were managed primarily through standard drainage procedures; steroids, NSAIDs, and colchicine also used.
- History of effusions may be identified risk factor for Gr3+ Rova-T-related effusions.

Targeting PARP in SCLC (DNA Damage and Repair)

- PARP1 and PARP2 important in repairing DNA single-strand breaks
- PARP1 is highly expressed at the mRNA and protein level in SCLC\(^1\)
- SLFN11 expression is correlated with sensitivity to PARP inhibitors in SCLC\(^2\)
- PARP inhibition may enhance cytotoxicity of DNA damaging agents and ionizing radiation


PARP=poly [ADP-ribose] polymerase (PARP) enzymes
Phase II Randomized Study of Temozolomide with either Veliparib or Placebo in SCLC: Negative

n=104 patients recurrent SCLC after 1 or 2 prior regimens

**Negative primary endpoint: 4 mo-PFS**, veliparib (36%) and placebo (27%), p=0.1
Higher ORR: veliparib (39%) and placebo (14%); p=0.016

SLFN11 (IHC) in exploratory analysis enriches for clinical outcomes with Veliparib.
ECOG-ACRIN 2511: Cisplatin/Etoposide with either Veliparib or Placebo

*64 patients each arm; No difference in response rate; No difference in OS, HR 0.83 (80% CI 0.64-1.07); p=0.17, mOS 10.3 vs. 8.0 mo for CE+V and CE+P respectively
Strata of Male with High LDH Derived Greatest Benefit with Veliparib

PFS analysis by strata

Male/abnormal LDH stratum
Adjusted PFS HR: 0.34
80% CI: 0.22 - 0.51
1-sided p<0.001

Other Strata:
Adjusted PFS HR: 0.81
80% CI: 0.60 - 1.09
1-sided p=0.18
Targeting EZH2 in SCLC (Epigenetics)

- EZH2 is the enzymatic histone-lysine N-methyltransferase subunit and regulates chromatin remodeling

- EZH2 expression higher in SCLC than other tumor type in TCGA
  - RB1 negatively regulates E2F1 transcriptional activity
  - RB1 loss in SCLC results in high levels of E2F1 transcription and consequent high EZH2 expression

- Upregulating EZH2 linked to H3K27me3 SLFN11 gene silencing as acquired chemoresistance in SCLC patient derived xenografts

EZH2 Inhibition in Combination with Standard of Care Chemotherapy in vivo PDX SCLC Models

CHEMOTHERAPY NAIVE

SLFN11<sup>HIGH</sup>

CHEMOTHERAPY RESISTANT

SLFN11<sup>Silenced</sup>

Targeting WEE1 in SCLC (Cell Cycle)

<table>
<thead>
<tr>
<th>Sponsor</th>
<th>Drugs</th>
<th>Line</th>
<th>Primary Endpoint</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Keunchil Park PI</td>
<td>AZD1775 monotherapy</td>
<td>2nd</td>
<td>Safety Efficacy</td>
<td>Fully recruited</td>
</tr>
<tr>
<td>Keunchil Park PI</td>
<td>AZD1775 monotherapy*</td>
<td>2nd</td>
<td>ORR</td>
<td>Open</td>
</tr>
<tr>
<td>AZ</td>
<td>Paclitaxel/carbo + AZD1775**</td>
<td>2nd+</td>
<td>Safety</td>
<td>Open</td>
</tr>
<tr>
<td>AZ</td>
<td>AZD1775 + olaparib</td>
<td>2nd+</td>
<td>Safety</td>
<td>Open</td>
</tr>
</tbody>
</table>

*MYC Family Amplification or CDKN2A Mutation Combined With TP53 Mutation
**multiple tumour types including SCLC

Table courtesy of Frances Shepherd

Targeting HGF-MET axis in SCLC

- **MET** is relevant in SCLC: overexpression (ligand, receptor), amplification, or mutation
  - first MET mutation, noted in juxtamembrane domain, described in early 2003 by Salgia laboratory

MET inhibition in SCLC

Topoisomerase 1 inhibition + MET inhibition

MET inhibition


Objectives

• The Current State of Affairs

• Novel Targets

• Immunotherapy
  – PD-L1 Biomarker
  – Review of Immunotherapy Studies
  – Tumor Mutation Burden Biomarker
PD-L1 Expression in SCLC

• Modest rates of PD-L1 expression in SCLC
  – CheckMate-032 non-randomized cohort (nivolumab + ipilimumab): 18%¹
  – KEYNOTE-028 (pembrolizumab): 31.7% pts screened²
  – KEYNOTE-158 (pembrolizumab): 47%³

• 1.9% with focal amplification of CD274 (chromosome 9p24)⁴

• Prognostic implications vary⁵-⁶

CheckMate-032: Nivolumab + Iplimumab in PD-L1 Unselected SCLC

<table>
<thead>
<tr>
<th>Treatment</th>
<th>ORR</th>
<th>TTR</th>
<th>DOR</th>
<th>3-mo PFS</th>
<th>3-mo OS</th>
<th>1-yr, 2-yr OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab (non-randomized)</td>
<td>11% *</td>
<td>1.4 mo</td>
<td>17.9 mo</td>
<td>27%</td>
<td>59%</td>
<td>27%, 14%</td>
</tr>
<tr>
<td></td>
<td>(6, 19)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nivolumab (randomized)</td>
<td>12%</td>
<td>1.5 mo</td>
<td>---</td>
<td>18%</td>
<td>65%</td>
<td>---</td>
</tr>
<tr>
<td>Nivolumab + ipilimumab (non-randomized)</td>
<td>23% *</td>
<td>2.0 mo</td>
<td>14.2 mo</td>
<td>36%</td>
<td>72%</td>
<td>40%, 26%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nivolumab + ipilimumab (randomized)</td>
<td>21%</td>
<td>1.4 mo</td>
<td>---</td>
<td>30%</td>
<td>64%</td>
<td>---</td>
</tr>
</tbody>
</table>

*PD-L1 expression at 1% threshold:  
---ORR 14% (-) and 9% (+) nivo  
---ORR 32% (-) and 10% (+) nivo/mpi

Hellmann MD et al. Journal of Clinical Oncology 35:8503-8503, 2017
KEYNOTE-028 Pembrolizumab in PD-L1 Selected SCLC

- 24 patients
- **ORR**: 33.3% (15.6, 66.4)
- **TTR**: 2.0 mo (1.7, 3.7)
- **DOR**: 19.4 mo (>3.6->20)
- **PFS**: 1.9 mo (1.7, 5.9)
  - 6-mo PFS 28.6%, 12-mo PFS 23.8%
- **OS**: 9.7 mo (4.1, NR)
  - 6 mo OS 66.0%, 1-yr OS 37.7%

KEYNOTE-158: Pembrolizumab in PD-L1 Unselected SCLC

- 107 patients
- **ORR**: 18.7% (11.8, 27.4)
- **DOR**: NR (2.1+-18.7+)
- **PFS**: 2.0 mo (1.9, 2.1)
  - 6-mo PFS 23.7%
  - 1-yr PFS 16.8%
- **OS**: 8.7 mo (5.6, 12.0)
  - 6-mo OS 57.5%
  - 1-yr OS 40.2%

KEYNOTE-158: PD-L1 Expression Enhances Clinical Activity

<table>
<thead>
<tr>
<th>PD-L1 Status</th>
<th>ORR</th>
<th>PFS</th>
<th>1-yr PFS</th>
<th>OS</th>
<th>1-yr OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD-L1 (+)</td>
<td>35.7%</td>
<td>2.1 mo</td>
<td>28.5%</td>
<td>14.9 mo</td>
<td>53.1%</td>
</tr>
<tr>
<td>n=42</td>
<td>(21.6, 52.0)</td>
<td>(2.0, 8.1)</td>
<td></td>
<td>(5.6, NR)</td>
<td></td>
</tr>
<tr>
<td>PD-L1 (-)</td>
<td>6.0%</td>
<td>1.9 mo</td>
<td>8.2%</td>
<td>5.9 mo</td>
<td>30.7%</td>
</tr>
<tr>
<td>n=50</td>
<td>(1.3, 16.5)</td>
<td>(1.6, 2.0)</td>
<td></td>
<td>(3.3, 10.1)</td>
<td></td>
</tr>
</tbody>
</table>

• PD-L1 assessed using PD-L1 IHC 22C3 pharmDx assay (Agilent Technologies) with 22C3 antibody clone
• PD-L1–positive defined as PD-L1 combined positive score ≥1

CheckMate-032: Tumor Mutation Burden Arising as a Predictive Biomarker for Nivolumab ± Ipilimumab

Tumor Mutation Burden Tertiles*:
- low, 0 to <143 mutations
- medium, 143 to 247 mutations
- high ≥248 mutations

*somatic missense mutations as calculated by whole exome sequencing
Tumor Mutation Burden Arising as a Predictive Biomarker for Nivolumab + Ipilimumab (PFS)

Tumor Mutation Burden Arising as a Predictive Biomarker for Nivolumab + Ipilimumumab (OS)

<table>
<thead>
<tr>
<th>Tumor mutational burden tertile</th>
<th>Low</th>
<th>Med</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median overall survival (95% CI), month</td>
<td>3.1 (2.4–6.8)</td>
<td>3.9 (2.4–9.9)</td>
<td>5.4 (2.8–8.0)</td>
</tr>
<tr>
<td>1 year = 35.2%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 year = 26.0%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 year = 22.1%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Tumor mutational burden tertile</th>
<th>Low</th>
<th>Med</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median overall survival (95% CI), month</td>
<td>3.4 (2.8–7.3)</td>
<td>3.6 (1.8–7.7)</td>
<td>22.9 (8.2–NR)</td>
</tr>
<tr>
<td>1 year = 62.4%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 year = 23.4%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 year = 19.6%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---

Conclusions

• Increased understanding of biology of SCLC – science driving field forward

• Could SCLC eventually have biomarker driven therapies?
  – High TMB = Immunotherapy
  – SLFN11 (+) = PARP inhibitors
  – DLL3 (+) = Rova-T
  – Driver Mutation = TKIs
# Diagnostic Criteria for Lung Neuroendocrine Tumors

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Typical carcinoid</th>
<th>Atypical carcinoid</th>
<th>Large cell neuroendocrine tumor</th>
<th>Small cell lung cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade</td>
<td>Low</td>
<td>Intermediate</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Morphology</td>
<td>Well differentiated</td>
<td>Well differentiated</td>
<td>Poorly differentiated</td>
<td>Poorly differentiated</td>
</tr>
<tr>
<td>Mitoses per 10 HPFs</td>
<td>&lt;2</td>
<td>2–10</td>
<td>&gt;10 (median, 70)</td>
<td>&gt;10 (median, 80)</td>
</tr>
<tr>
<td>Necrosis</td>
<td>None</td>
<td>Present (focal punctate)</td>
<td>Present (extensive)</td>
<td>Present (extensive)</td>
</tr>
</tbody>
</table>

Table 1 Diagnostic criteria and grading of lung neuroendocrine tumors (38)
Current Targets SCLC

Targeting Neuroendocrine Pathway

Backup Slides-Genomics SCLC
Rova-T in SCLC

Rovalpituzumab tesirine (Rova-T™): An Antibody-Drug Conjugate (ADC) Targeting DLL3

- A Phase 1 study demonstrated an IRC objective response rate (ORR) of 16% in 56 Pts with recurrent (2L & 3L) SCLC
- Pts with highest DLL3 expression (n = 26) had an ORR of 31% and mOS of 5.8 Mo

IRC, independent review committee; mOS, median overall survival.

1. Rudin et al., Lancet Oncol 2017

Prolonged Time to Response with Rova-T

Change In Target Lesions from Baseline: ~40% of Responses Occur After 10 Weeks

<table>
<thead>
<tr>
<th>DLL3-High, Line of Rx</th>
<th>Duration of Response, Mo (95% CI), N</th>
<th>3L Dll3-High Responders (Investigator); N = 36</th>
</tr>
</thead>
<tbody>
<tr>
<td>Investigator</td>
<td>IRC</td>
<td>% Change from Baseline</td>
</tr>
<tr>
<td>3L</td>
<td>4.3 (3.4, 5.5), N=36</td>
<td>Rova-T</td>
</tr>
<tr>
<td>4L+</td>
<td>2.9 (2.2, 3.4), N=11</td>
<td>3L Dll3-High Responders (Investigator); N = 36</td>
</tr>
<tr>
<td></td>
<td>2.8 (2.0, 3.0), N=6</td>
<td>Censored</td>
</tr>
</tbody>
</table>

Presented By: David P. Carbone

Abstract # 8507

Rova-T: PFS and OS in DLL3-High Patients

IRC-Assessed PFS & OS Among DLL3-High Patients, All Lines

Progression-Free Survival

Overall Survival

mPFS = 3.8 Mo

mOS = 5.7 Mo

Rova-T – Disease Control correlates with improved Overall Survival

Most Patients Achieved Stable Disease or Better, Which is Associated with Longer Survival

Response Groups, mPFS, and mOS in 3L DLL3-High SCLC Patients (per IRC)

- 12% (NE*)
- 16% (PD)
- 72% (CBR)
- 24%
- 16%

<table>
<thead>
<tr>
<th></th>
<th>mPFS Mo, 95% CI</th>
<th>mOS Mo, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>All 3L DLL3-High (n = 177)</td>
<td>3.9 (3.2, 4.1)</td>
<td>5.6 (4.9, 6.8)</td>
</tr>
<tr>
<td>Best Overall Response Rate (IRC)</td>
<td>4.2</td>
<td>7.8</td>
</tr>
<tr>
<td>ORR** (IRC)</td>
<td>5.5</td>
<td>9.8</td>
</tr>
</tbody>
</table>

*Includes non-evaluable, early death, or indeterminate patients who did not have a post-baseline scan.
**Confirmed CR+ PR per RECIST v1.1
# Rova-T Studies SCLC

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRINITY</td>
<td>Relapsed SCLC&lt;br&gt;Single arm; 3rd line and beyond</td>
<td>Rovalpituzumab Tesirine</td>
</tr>
<tr>
<td>NCT02674568</td>
<td>Presented at ASCO 2018</td>
<td></td>
</tr>
<tr>
<td>NCT02819999</td>
<td>Treatment naïve SCLC</td>
<td>Rovalpituzumab Tesirine&lt;br&gt;Cisplatin&lt;br&gt;Etoposide</td>
</tr>
<tr>
<td>TAHOE</td>
<td>Relapsed SCLC&lt;br&gt;Phase III second line study</td>
<td>Rovalpituzumab tesirine&lt;br&gt;vs.&lt;br&gt;Topotecan</td>
</tr>
<tr>
<td>NCT03061812</td>
<td>Maintenance therapy post platinum doublet</td>
<td>Rovalpituzumab tesirine&lt;br&gt;vs.&lt;br&gt;Placebo</td>
</tr>
<tr>
<td>MERU</td>
<td>Relapsed SCLC</td>
<td>Rovalpituzumab tesirine&lt;br&gt;Nivolumab + Iplimumab</td>
</tr>
<tr>
<td>NCT03026166</td>
<td>Maintenance therapy post platinum doublet</td>
<td></td>
</tr>
</tbody>
</table>

*Table courtesy of Taofeek K. Owonikoko*
Comprehensive genomic studies in SCLC

Table 1. Large-scale genomic sequencing results in SCLC

<table>
<thead>
<tr>
<th>Area</th>
<th>Cases</th>
<th>Sequencing</th>
<th>Gene aberrations detected</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Europe</td>
<td>29</td>
<td>WGS, WES, RNA sequencing</td>
<td>Mutations in CREBBP, EP300, and MLL, FGFR1 amplification</td>
<td>Peifer, 2012 (3)</td>
</tr>
<tr>
<td>USA</td>
<td>53</td>
<td>WGS, WES, RNA sequencing</td>
<td>SOX2 amplification</td>
<td>Rudin, 2012 (32)</td>
</tr>
<tr>
<td>Japan</td>
<td>56</td>
<td>RNA sequencing</td>
<td>PD-L1 (CD274) and KIAA1432 amplifications</td>
<td>Iwakawa, 2013 (27)</td>
</tr>
<tr>
<td>Japan</td>
<td>51</td>
<td>WES</td>
<td>Mutations in PI3K/AKT/mTOR pathway</td>
<td>Umemura, 2014 (16)</td>
</tr>
<tr>
<td>Japan</td>
<td>44</td>
<td>WES</td>
<td>Mutations in TP53, RB1, PTEN</td>
<td>Iwakawa, 2015 (30)</td>
</tr>
<tr>
<td>Germany, Japan and 14 other countries</td>
<td>110</td>
<td>WGS</td>
<td>Activating TP73 rearrangements. CREBBP, EP300 and NOTCH1-3 inactivations</td>
<td>George, 2015 (4)</td>
</tr>
<tr>
<td>China</td>
<td>99</td>
<td>WES</td>
<td>Mutations in TMEM132D, NCAM2, and CDH10. SRSFI1 amplification</td>
<td>Jiang, 2016 (17)</td>
</tr>
</tbody>
</table>

SCLC, small cell lung cancer; WGS, whole genome sequencing; WES, whole exome sequencing.
Signaling Pathways Recurrently Affected in SCLC

Genomic Findings in SCLC

- High mutation rate
  - 8.62 non-synonomous mutations per million base pairs

- C:G > A:T transversions found in 28% of all mutations on average (//smoking clinical history)

- Bi-allelic inactivating mutations in TP53 and RB1 essentially universal – loss of these tumor suppressors is obligatory

- Rare “actionable” events such as BRAF, KIT, PIK3CA

- NOTCH family gene inactivating mutations common, act as tumor suppressors and regulators of neuroendocrine differentiation
  - majority SCLC has gene expression pattern of low NOTCH pathway activity (high ASCL1 and DLK1)

Profile of somatic genetic alterations in 883 SCLC patient samples

Ali S. et al. ESMO 2016 Abs #15000; Slide courtesy of Taofeek K. Owonikoko
SCLC: PAX5 direct regulator of MET transcription

Combinatorial Effect PAX5 Knockdown + MET and Topoisomerase-1 inhibitors

Aurora A Kinase Inhibitor

- **Aurora A Kinase Inhibitor Alisertib- C-MYC expression as biomarker**
  - Randomized Phase 2 Study of the Investigational Aurora A Kinase (AAK) Inhibitor Alisertib (MLN8237) + Paclitaxel vs Placebo + Paclitaxel as Second-Line Therapy for Small Cell Lung Cancer (SCLC); Primary Endpoint PFS
  - IVRS Hazard Ratio (95% CI): 0.77 (0.557–1.067) Log rank p-value: 0.113
  - CORRECTED Hazard Ratio (95% CI): 0.71 (0.509–0.985) Log rank p-value: 0.038
  - Median PFS: 101 days (3.32 months) vs 66 days (2.17 months)

- **C-MYC amplification/over-expression as potential biomarker for therapy**
  - C-MYC (+) HR 0.29 (0.12-0.72)
  - C-MYC (-) HR 11.8 (1.52-91.1)

Owonikoko et al. WCLC 2017 (Abstr #4855)
PARP has a variety of functions

- DNA repair: Functions in BER, DSB repair and NHEJ
- Transcriptional regulation: Component of the TLE1/Groucho corepressor complex involved in Wnt signalling implicated in transcriptional regulation of androgen receptor expression
- Chromatin modification: Maintenance of telomere length and chromosomal stability
- Mitosis: Involved in mitotic-spindle formation
- Cell death: Component of pathways mediating apoptosis

PARP1 mRNA expression in SCLC

mRNA expression of PARP1 in SCLC cell lines

mRNA expression of PARP1 in SCLC

PARP1 mRNA expression was higher in SCLC cell lines than in other solid tumor cell lines

PARP1 protein expression in SCLC samples

SLFN11 confers PARP inhibitor sensitivity

## Current PARP inhibitors in development

<table>
<thead>
<tr>
<th>PARP inhibitor</th>
<th>Company</th>
<th>Target PARP</th>
<th>Route of administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olaparib (AZD2281)</td>
<td>AstraZeneca</td>
<td>PARP1/2/3</td>
<td>Oral</td>
</tr>
<tr>
<td>Veliparib (ABT-888)</td>
<td>Abbott Laboratories</td>
<td>PARP1/2</td>
<td>Oral</td>
</tr>
<tr>
<td>Rucaparib (AG-014,699; CO-338)</td>
<td>Clovis Oncology</td>
<td>PARP1/2</td>
<td>Oral or intravenous</td>
</tr>
<tr>
<td>BMN-673</td>
<td>BioMarin Pharmaceutical</td>
<td>PARP1/2</td>
<td>Oral</td>
</tr>
<tr>
<td>CEP-9722</td>
<td>Teva Pharmaceutical Industries</td>
<td>PARP1/2</td>
<td>Oral</td>
</tr>
<tr>
<td>Niraparib (MK4827)</td>
<td>Merck</td>
<td>PARP1/2</td>
<td>Oral</td>
</tr>
</tbody>
</table>

Phase II Randomized Study of Temozolomide with either Veliparib or Placebo in SCLC Negative

Veliparib does not improve OS

Overall survival (OS)

OS HR: 0.83 (80% CI 0.64-1.07); 1-sided p=0.17.

Median OS: 10.3 vs. 8.9 months for CE+V and CE+P respectively
PARPi Studies (Other)

M14-361: Phase I/II study of carbo/etoposide and veliparib +/- maintenance veliparib

- Carbo/Etoposide
  - Veliparib
  - 4 cycles
  - Veliparib maintenance

- Carbo/Etoposide
  - Veliparib
  - 4 cycles
  - Placebo maintenance

- Carbo/Etoposide
  - Placebo
  - 4 cycles
  - Placebo maintenance

Sample size = 138
Randomize 1:1:1

Still recruiting

Table courtesy of Frances Shepherd
STOMP: SCLC Trial of Olaparib as Maintenance Programme
A randomised phase II trial of the PARP inhibitor olaparib as maintenance treatment in patients with chemosensitive SCLC

Penella J Woll & Clive Stubbs
SLFN11 and DNA Damage

Chemo naive

Chemotherapy induced DNA damage

SLFN11 Transcription ON

Deficient DNA damage repair

Cell Death

Chemoresistant

Chemotherapy induced DNA damage

EZH2

H3K27me3

SLFN11 Transcription OFF

Efficient DNA damage repair

Cell Survival

Epigenetic chemo-resensitization

Chemotherapy induced DNA damage

EZH2i

EZH2

SLFN11 Transcription ON

Deficient DNA damage repair

Cell Death

WEE1 inhibition + PARP inhibition in circulating tumor cell patient-derived explants (CDX)

Depth of Response

Duration of Response

Lurbinectedin:
inhibits activated transcription, induces DNA double-strand breaks → apoptosis, and modulates TME

Lurbinectedin Methods

A.- (Lurbinectedin +DOX)
- Phase Ib dose escalation followed by dose expansion at RD in selected diseases, including SCLC.
- Less than 3 prior chemotherapy lines for advanced disease

Treatment Schedule
- Cohort A: doxorubicin 50 mg/m² + L 3-5 mg flat dose (FD) Day 1 q3w and cont. with L 7 mg FD after DOX cumulative dose of 450 mg/m²
- RD doxorubicin 50 mg/m²+ PM1183 2 mg/m² q3w
- Cohort B: doxorubicin 40 mg/m²+ L 2 mg/m² Day 1 q3w and cont. with L 4 mg/m² after DOX cumulative dose of 450 mg/m²

B.- (Lurbinectedin +TAX)
- Phase I dose escalation followed by dose expansion at RD in selected diseases including SCLC.
- Less than 3 prior chemotherapy lines for advanced disease

Treatment Schedule
- L day 1 q3w+ Paclitaxel weekly for 18w continued with PM1183 alone
- RD Paclitaxel 80mg/m² D1 and 8 + L 2.2 mg/m² q3w

C.- (Lurbinectedin single-agent)
- Phase II Multicenter, open-label, exploratory, Basket trial
- Less than 2 prior chemotherapy lines for advanced disease
- Primary objective: Response rate
- Sample size: initially 15 patients to be recruited

Sample Flowchart:
- SCLC Subgroup
- No responses in first 15 patients
- No activity in this indication
- Continue accrual to 100 evaluable patients
- 1 response in first 15 patients
- Continue accrual to 100 evaluable patients

Treatment Schedule
- PM1183 3.2 mg/m², 1h iv infusion, q3wks

Lurbinectedin Results

<table>
<thead>
<tr>
<th>Response Evaluate patients</th>
<th>Lurbinectedin+DOX (q3wk)</th>
<th>Lurbinectedin +TAX (q3wk)</th>
<th>Lurbinectedin single-agent (q3wk)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort A</td>
<td>Cohort B</td>
<td></td>
<td></td>
</tr>
<tr>
<td>L 3-5 mg FD D1 + DOX</td>
<td>L 2 mg/m² D1 + DOX 40 mg/m² D1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>50 mg/m² D1 (n=21)</td>
<td>(n=27)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>2 (10%)</td>
<td>1 (4%)</td>
<td>1 (14%)</td>
</tr>
<tr>
<td>PR</td>
<td>12 (57%)</td>
<td>9 (33%)</td>
<td>4 (57%)</td>
</tr>
<tr>
<td>ORR</td>
<td>14 (67%)</td>
<td>10 (37%)</td>
<td>5 (71%)</td>
</tr>
<tr>
<td>SD</td>
<td>3 (14%)</td>
<td>9 (33%)</td>
<td>-</td>
</tr>
<tr>
<td>PD</td>
<td>4 (19%)</td>
<td>8 (30%)</td>
<td>2 (29%)</td>
</tr>
<tr>
<td>DCR</td>
<td>17 (81%)</td>
<td>19 (70%)</td>
<td>5 (71%)</td>
</tr>
<tr>
<td>DOR (mo)</td>
<td>4.5</td>
<td>5.2</td>
<td>2.3</td>
</tr>
<tr>
<td>PFS (mo) CTFI &gt;30d*</td>
<td>4.7</td>
<td>5.3</td>
<td>3.9</td>
</tr>
<tr>
<td>PFS (mo) Platinum-sensitive</td>
<td>5.8</td>
<td>6.2</td>
<td>3.9</td>
</tr>
</tbody>
</table>

Lurbinectedin Results

Lurbinectedin PM 1183 in Relapsed SCLC

Trigo JM et al. ASCO 2018. Abstr 8570
# Lurbinectedin PM 1183 in Relapsed SCLC

<table>
<thead>
<tr>
<th>Response</th>
<th>CTFI&lt;90d (n=27)</th>
<th>CTFI&gt;=90d (n=34)</th>
<th>Total (N=61)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>PR</td>
<td>9</td>
<td>33.3</td>
<td>15</td>
</tr>
<tr>
<td>PD</td>
<td>10</td>
<td>37.0</td>
<td>6</td>
</tr>
<tr>
<td>ORR (95% CI;% )</td>
<td>33.3 (16.5-54)</td>
<td>44.1 (27.2-62.1)</td>
<td>39.3 (27.1-52.7)</td>
</tr>
<tr>
<td>Clinical Benefit (95% CI;%)</td>
<td>44.4 (25.5-64.7)</td>
<td>55.9 (37.9-72.8)</td>
<td>50.8 (37.7-63.9)</td>
</tr>
<tr>
<td>DCR (95% CI;%</td>
<td>63 (42.4-80.6)</td>
<td>82.4 (65.5-93.2)</td>
<td>73.8 (60.9-84.2)</td>
</tr>
</tbody>
</table>

Chemotherapy Treatment Free Interval

Trigo JM et al. ASCO 2018. Abstr 8570
Lurbinectedin PM 1183 in Relapsed SCLC

**Progression-Free Survival**

- **CTFI <90 days**: median 3.4 mo; PFS@4mo 44.3%, @6mo 28.1%
- **CTFI >=90 days**: median 4.2 mo, PFS@4mo 56.9%, @6mo 42.8%

**Overall Survival**

- **CTFI <90 days**: median 8.1 mo; OS@6mo 61.9%, @12mo 22.9%
- **CTFI >=90 days**: median 15.8 mo; OS@6mo 92.7%, @12mo 59.1%

**ITT**: 12.0 (10.8-15.8)

Trigo JM et al. ASCO 2018. Abstr 8570
Atlantis Study Design

Randomization:
- Doxorubicin 40 mg/m² D1 *
- Lurbinectedin 2 mg/m², D1 q3wk *
- 600 patients
- 1:1 Randomization
  - Stratified:
    - ECOG (0 vs ≥1)
    - CTFI (≥180, 179-90, <90)
    - CNS involvement Y/N
    - Prior PDL1/PD1 Y/N
    - Investigator preference

Treatment period:
- Topotecan 1.5 mg/m² D1-5 q3wk
- OR, CAV combination, D1, q3wk

Follow up period:
- Disease Progression
- Investigator decision
- Unacceptable Toxicity
- Withdrawal of consent
- Other

* Maximum 10 cycles, Lurbinectedin to be continued at 3.2 mg/m²

Screening:
- Up to 28D
- SCLC
- ≤ 1 prior CT lines (additional exclusively biologic lines allowed)
- ECOG PS ≤ 2
- Measurable/ non-measurable per RECIST
Failed targeted therapies SCLC

<table>
<thead>
<tr>
<th>Agent</th>
<th>Mechanism of action</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sorafenib</td>
<td>Inhibits intracellular Raf kinases, most notably BRAF, and cell surface kinase receptors most notably, vascular endothelial growth factor (VEGFR)</td>
<td>No benefit</td>
</tr>
<tr>
<td>Thalidomide</td>
<td>Immunomodulatory and antiangiogenic effects vary given targeted cancer</td>
<td>No benefit</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>Monoclonal antibody which binds VEGFR</td>
<td>No benefit</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>Multi receptor tyrosine kinase inhibitor (RTKI) including VEGFR</td>
<td>No benefit in OS</td>
</tr>
<tr>
<td>Affibercept</td>
<td>VEGF trap inhibiting VEGF A and B</td>
<td>No benefit</td>
</tr>
<tr>
<td>Marimastat</td>
<td>Matrix metalloproteinase inhibitor</td>
<td>No benefit</td>
</tr>
<tr>
<td>Vandetanib</td>
<td>Tyrosine kinase inhibitor (TKI) of epidermal growth factor reception (EGFR) and VEGF</td>
<td>No benefit</td>
</tr>
<tr>
<td>Gefitinib</td>
<td>TKI inhibits multiple cell surface receptors including EGFR</td>
<td>No benefit</td>
</tr>
<tr>
<td>Imatinib</td>
<td>Inhibits Bcr-Able tyrosine kinase produced by the Philadelphia chromosome</td>
<td>No benefit</td>
</tr>
<tr>
<td>Bortezomib</td>
<td>Proteasome inhibitor</td>
<td>No benefit</td>
</tr>
<tr>
<td>Oblimersen</td>
<td>Antisense oligodeoxynucleotide directed at blocking production of Bcl-2</td>
<td>No benefit</td>
</tr>
<tr>
<td>Temsirolimus</td>
<td>Mechanistic target of rapamycin (mTOR) inhibitor</td>
<td>No benefit</td>
</tr>
<tr>
<td>AT 101</td>
<td>Inhibitor of the anti-apoptotic Bcl proteins (Bcl-2, Bcl-XL, Bcl-W, and Mcl-1) and an inducer of the pro-apoptotic proteins noxa and puma</td>
<td>No benefit</td>
</tr>
<tr>
<td>Romidepsin</td>
<td>Histone deacetylase inhibitor</td>
<td>No benefit</td>
</tr>
<tr>
<td>Dasatinib</td>
<td>Second generation BCR-ABL TKI</td>
<td>No benefit</td>
</tr>
<tr>
<td>Cediranib</td>
<td>TKI targeting VEGFR-1, 2, and 3, PDGFR-alpha/beta, FGFR-1, and c-kit</td>
<td>No benefit</td>
</tr>
</tbody>
</table>

Backup Slides-Immunotherapy SCLC
1.9% have focal amplification of CD274 (chromosome 9p24)

Gene expression in region of 9p24.1 amplicon; case 9P and S00213 are amplified and have high PD-L1 expression
PD-L1 Expression in Surgically Resected SCLC: Different Antibodies Tested

<table>
<thead>
<tr>
<th>Method</th>
<th>Antibody clone</th>
<th>Cells</th>
<th>E1L3N</th>
<th>28-8</th>
<th>SP142</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allred score</td>
<td></td>
<td>TCs</td>
<td>22.50%</td>
<td>27.50%</td>
<td>35%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ICs</td>
<td>42.50%</td>
<td>42.50%</td>
<td>50%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TCs/ICs</td>
<td>50%</td>
<td>47.50%</td>
<td>60%</td>
</tr>
<tr>
<td>≥1%</td>
<td></td>
<td>TCs</td>
<td>20%</td>
<td>27.50%</td>
<td>32.50%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ICs</td>
<td>40%</td>
<td>42.50%</td>
<td>52.50%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TCs/ICs</td>
<td>45%</td>
<td>47.50%</td>
<td>57.50%</td>
</tr>
<tr>
<td>≥5%</td>
<td></td>
<td>TCs</td>
<td>15%</td>
<td>15%</td>
<td>15%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ICs</td>
<td>37.50%</td>
<td>37.50%</td>
<td>40%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TCs/ICs</td>
<td>42.50%</td>
<td>42.50%</td>
<td>45%</td>
</tr>
</tbody>
</table>

[Images of Placenta, Tumor, and TILs sections with E1L3N, 28-8, and SP142 antibody staining]

### Ongoing immunotherapy studies in SCLC

<table>
<thead>
<tr>
<th>Phase</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Anti-PD-1 antibodies</td>
</tr>
<tr>
<td>1</td>
<td>Pembrolizumab</td>
</tr>
<tr>
<td>1</td>
<td>Pembrolizumab plus chemotherapy/radiation</td>
</tr>
<tr>
<td>1</td>
<td>Pembrolizumab plus itacitinib</td>
</tr>
<tr>
<td>2</td>
<td>Pembrolizumab plus chemotherapy with or without radiation</td>
</tr>
<tr>
<td>2</td>
<td>Pembrolizumab</td>
</tr>
<tr>
<td>2</td>
<td>Pembrolizumab plus paclitaxel</td>
</tr>
<tr>
<td>2</td>
<td>Pembrolizumab plus irinotecan</td>
</tr>
<tr>
<td>3</td>
<td>Pembrolizumab plus etoposide/platinum</td>
</tr>
<tr>
<td>1/2</td>
<td>Nivolumab with or without Iapilimumab</td>
</tr>
<tr>
<td>1/2</td>
<td>Nivolumab plus ulocuplumab</td>
</tr>
<tr>
<td>2</td>
<td>Nivolumab plus Iapilimumab</td>
</tr>
<tr>
<td>2</td>
<td>Nivolumab vs chemotherapy</td>
</tr>
<tr>
<td>3</td>
<td>Nivolumab vs nivolumab plus Iapilimumab as maintenance therapy</td>
</tr>
<tr>
<td></td>
<td>Anti-PD-L1 antibodies</td>
</tr>
<tr>
<td>1</td>
<td>Durvalumab plus tremelimumab with chemotherapy</td>
</tr>
<tr>
<td>1/2</td>
<td>Durvalumab plus olaparib</td>
</tr>
<tr>
<td>2</td>
<td>Durvalumab plus tremelimumab</td>
</tr>
<tr>
<td>2</td>
<td>Durvalumab plus tremelimumab with or without radiation</td>
</tr>
<tr>
<td>2</td>
<td>Atezolizumab, carboplatin, and etoposide with or without trilaciclib</td>
</tr>
<tr>
<td>2</td>
<td>Atezolizumab vs chemotherapy</td>
</tr>
<tr>
<td>3</td>
<td>Carboplatin plus etoposide with or without azezolizumab</td>
</tr>
</tbody>
</table>
## Immunotherapy Studies in SCLC

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMpower133 NCT02763579</td>
<td>Treatment naïve SCLC</td>
<td>Carboplatin/Etoposide With or Without Atezolizumab</td>
</tr>
<tr>
<td>NCT03059667</td>
<td>Relapsed SCLC Phase II</td>
<td>Atezolizumab vs. Topotecan or Carboplatin/Etoposide</td>
</tr>
<tr>
<td>NCT02963090</td>
<td>Relapsed SCLC Phase II</td>
<td>Topotecan vs. Pembrolizumab</td>
</tr>
<tr>
<td>KEYNOTE-604 NCT03066778</td>
<td>Treatment naïve SCLC Phase I/III</td>
<td>Pembrolizumab/Etoposide/Platinum vs. Etoposide/Platinum</td>
</tr>
<tr>
<td>NCT02402920</td>
<td>Treatment naïve SCLC Phase I/II</td>
<td>Pembrolizumab + Etoposide/Platinum (Cisplatin or Carboplatin) + XRT</td>
</tr>
<tr>
<td>CheckMate331 NCT02481830</td>
<td>Relapsed SCLC Phase III</td>
<td>Nivolumab vs. Topotecan vs. Amrubicin</td>
</tr>
<tr>
<td>Checkmate 451 NCT02538666</td>
<td>Treatment Naive SCLC Phase III</td>
<td>Nivolumab vs. Nivolumab + Ipilimumab vs. Placebo</td>
</tr>
<tr>
<td>Caspian Study NCT03043872</td>
<td>Treatment naïve SCLC Phase III</td>
<td>EP vs. Durvalumab + Tremelimumab + EP</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EP vs. Durvalumab + EP</td>
</tr>
<tr>
<td>NCT02701400</td>
<td>Relapsed SCLC Phase II</td>
<td>Tremelimumab + Durvalumab ± Radiation</td>
</tr>
</tbody>
</table>

Table courtesy of Taofeek K. Owonikoko
KEYNOTE-068: combination PT-DT chemotherapy +/- pembrolizumab

KEYNOTE 068 (REACTION - EORTC 1416) - B. Besse
A phase II study of etoposide and cis/carboplatin with or without pembrolizumab in untreated extensive SCLC

- Metastatic SCLC (n = 152)
  - First line metastatic
  - Measurable disease
  - ECOG PS 0-1
  - PD-L1 status

- Primary endpoint: Progression-free survival @ 6 months
- Secondary endpoints:
  - Overall response rate (ORR)
  - Immune-Related Disease Control Rate (iDCR)
  - Progression Free Survival (PFS PD-L1 (+))
  - Overall survival
  - Tolerability and safety

* Patients receiving pembrolizumab are allowed to stop after 1 year. Should they progress >3 months after stopping therapy, retreatment will be allowed provided they are meeting all inclusion criteria.
IMpower 133: Phase I/III: 1L Extensive Stage SCLC

Patients with Extensive-Stage SCLC who are Chemotherapy Naïve (n ~ 400)

Stratification by:
- Sex (male vs. female)
- ECOG PS (0 vs. 1)
- Brain Mets (yes vs. no)

R 1:1

Induction: 4 x 21 day Cycles
- Arm A: Atezolizumab + Carboplatin + Etoposide
- Arm B: Placebo + Carboplatin + Etoposide

Maintenance
- Atezolizumab
- PCI
- Placebo

Survival Follow-up
- Treat until PD *

Endpoints:
- PFS / OS co-primary endpoints

* Treatment may be continued beyond PD
PD = disease progression, PCI = prophylactic cranial irradiation

PRESS RELEASE POSITIVE STUDY
Durvalumab + Tremelimumab SCLC

Stratification Factors:
1. Level of Response to 2 cycles of EP (SD or PR/CR)
2. Choice of Platinum Agent at Cycle 3 (cisplatin or carboplatin)

Patients with ED-SCLC Stage IV
EP x 2 cycles
N = 1040

Responders (SD/PR/CR)
Randomized
N = 785 pts

Arm 1
Durva + Treme + EP
N = 265

Arm 2
Durva + EP
N = 265

Arm 3
EP
N = 265

Confirmed Disease Progression

Subsequent Therapies

Follow Up for OS

Dose and final schedule pending
CheckMate 451: Nivolumab +/- ipilimumab maintenance

CheckMate 451: A Randomized, Multicenter, Double-Blind, Phase 3 Study of Nivolumab, Nivolumab With Ipilimumab, or Placebo as Maintenance in Extensive-Stage Small Cell Lung Cancer (ED-SCLC) After Completion of 1st-line Platinum-based Chemotherapy (NCT02538666)

Phase III trial
N=810

After 4 cycles of platinum-based first-line chemotherapy

Nivolumab Flat Dose 240 mg IV Q 2 wks

Nivolumab & Ipi Q 3 wks x 4 Then Ipilimumab 240 mg IV Q 2 wks

Placebo

Primary Outcome Measures
- OS
- PFS

Secondary Outcome Measures
- PFS descriptive analysis: nivolumab vs nivolumab + ipilimumab
- OS descriptive analysis: nivolumab vs nivolumab + ipilimumab

Study Specific Eligibility Criteria
- Histologically or cytologically confirmed extensive-stage disease SCLC
- Ongoing response of stable disease or better following 4 cycles of platinum-based first-line chemotherapy
- No CNS metastases
- All toxicities attributed to prior anti-cancer therapy resolved to ≤Grade 1

Study Start Date: September 2015
Estimated Study Completion Date: June 2019
Estimated Primary Completion Date: April 2018
CheckMate 331: Nivolumab vs. Chemotherapy in Relapsed SCLC

CheckMate 331: Nivolumab or Chemotherapy in Patients With Relapsed SCLC (NCT02481830)

Primary Endpoint
• OS, approximately 12 months

Secondary Endpoints
• PFS, up to 12 months
• ORR, up to 12 months

Study Specific Eligibility Criteria
• Histologically or cytologically confirmed limited or extensive SCLC
• Recurrence or progression after platinum-based first-line chemotherapy or chemoradiation therapy for the treatment of limited or extensive disease stage SCLC
• ECOG PS ≤1
• No untreated or symptomatic CNS metastases
• No prior therapy with anti-CTLA-4, anti-CD137, anti-PD-1, anti-PD-L1, or anti-PD-L2

Phase III trial
N=480
Randomize
Nivolumab IV
Topotecan IV
Amrubicin IV
OS

Study Start Date: August 2015
Estimated Study Completion Date: November 2019
Estimated Primary Completion Date: May 2018

Primary Investigator: Bristol-Myers Squibb
CNS=central nervous system; CTLA-4=cytotoxic T-lymphocyte-associated protein 4; ECOG PS=Eastern Cooperative Oncology Group performance status; IV=intravenous; ORR=objective response rate; OS=overall survival; PD-1=programmed cell death 1; PD-L1/2=programmed death-ligand 1/2; PFS=progression-free survival; SCLC=small cell lung cancer.
**Carbo/paclitaxel + Iplimumumab SCLC**

**PHASED IPI**

- n=42 patients improved irPFS but not PFS or OS compared to control

**HR 0.64**

**CONCURRENT IPI**

- n=43 patients did not improve irPFS, PFS, or OS compared to control

**HR 0.75**

KN-028 Pembrolizumab SCLC

Only 1/3 screened PD-L1 (+)

Table 2. Treatment-Related Adverse Events

<table>
<thead>
<tr>
<th>Adverse Event and Grade</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>16 (66.7)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>3 (12.5)</td>
</tr>
<tr>
<td>2</td>
<td>1 (4.2)</td>
</tr>
<tr>
<td>Asthenia</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>2 (8.3)</td>
</tr>
<tr>
<td>2</td>
<td>1 (4.2)</td>
</tr>
<tr>
<td>3</td>
<td>1 (4.2)</td>
</tr>
<tr>
<td>Rash*</td>
<td>4 (16.7)</td>
</tr>
<tr>
<td>Diarrhea*</td>
<td>3 (12.5)</td>
</tr>
<tr>
<td>Fatigue*</td>
<td>3 (12.5)</td>
</tr>
<tr>
<td>Dry skin*</td>
<td>2 (8.3)</td>
</tr>
<tr>
<td>Insomnia*</td>
<td>2 (8.3)</td>
</tr>
<tr>
<td>Excessive tearing*</td>
<td>2 (8.3)</td>
</tr>
<tr>
<td>Myalgia</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1 (4.2)</td>
</tr>
<tr>
<td>2</td>
<td>1 (4.2)</td>
</tr>
<tr>
<td>Nausea*</td>
<td>2 (8.3)</td>
</tr>
</tbody>
</table>

NOTE. Experienced by ≥ 5% of patients regardless of grade.
*Grade 1 only.
Table 3. Confirmed Efficacy Results (investigator-assessed) in the Total Population

<table>
<thead>
<tr>
<th>Efficacy</th>
<th>Value of Patient Population (n = 24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR*, No. (%) [95% CI]</td>
<td>8 (33.3 [15.6-55.3])</td>
</tr>
<tr>
<td>CR, No. (%)</td>
<td>1 (4.2)</td>
</tr>
<tr>
<td>PR, No. (%)</td>
<td>7 (29.2)</td>
</tr>
<tr>
<td>SD, No. (%)</td>
<td>1 (4.2)</td>
</tr>
<tr>
<td>Median DOR, months† (range)</td>
<td>19.4 (≥ 3.6 to ≥ 20.0)</td>
</tr>
<tr>
<td>Median TTR, months (95% CI)</td>
<td>2.0 (1.7–3.7)</td>
</tr>
<tr>
<td>DCR‡, No. (%) [95% CI]</td>
<td>8 (33.3 [15.6-55.3])</td>
</tr>
<tr>
<td>Progressive disease, No. (%)</td>
<td>13 (54.2)</td>
</tr>
<tr>
<td>Not evaluable, No. (%)</td>
<td>2 (8.3)</td>
</tr>
<tr>
<td>PFS</td>
<td></td>
</tr>
<tr>
<td>Events, No. (%)</td>
<td>20 (83.3)</td>
</tr>
<tr>
<td>Median, months (95% CI)</td>
<td>1.9 (1.7-5.9)</td>
</tr>
<tr>
<td>Six-month rate, % (95% CI)</td>
<td>28.6 (12.4-47.2)</td>
</tr>
<tr>
<td>Twelve-month rate, % (95% CI)</td>
<td>23.8 (9.1-42.3)</td>
</tr>
<tr>
<td>OS</td>
<td></td>
</tr>
<tr>
<td>Events, No. (%)</td>
<td>15 (62.5)</td>
</tr>
<tr>
<td>Median, months (95% CI)</td>
<td>9.7 (4.1-NR)</td>
</tr>
<tr>
<td>Six-month rate, % (95% CI)</td>
<td>66.0 (43.3-81.3)</td>
</tr>
<tr>
<td>Twelve-month rate, % (95% CI)</td>
<td>37.7 (18.4-57.0)</td>
</tr>
</tbody>
</table>
KN-028 Pembrolizumab SCLC

KN-028 Pembrolizumab SCLC

A

Progression-Free Survival (%)

Time (months)

28.6% 23.8%

No. at risk: 24 9 8 6 6 5 4 2 2 2 2 0

B

Overall Survival (%)

Time (months)

66.0% 37.7%

No. at risk: 24 20 17 14 14 9 8 6 4 4 4 4 0

KN-158 Slides

• Other slides downloaded from ASCO 2018 presentation
CM-032 Study Design

Patients with SCLC
≥1 prior platinum-containing regimen (1 or 2 prior therapies for randomized cohort)
PD-L1 unselected

Non-randomized cohort

Nivolumab 3 mg/kg IV Q2W
(n = 98)a

Until disease progression or unacceptable toxicity

Nivolumab 1 mg/kg + ipilimumab 3 mg/kg IV Q3W for 4 cycles
(n = 61)b

Nivolumab 3 mg/kg IV Q2W
Until disease progression or unacceptable toxicity

Randomized cohort

Patients (ITT, N = 401)e received either nivolumab monotherapy (n = 245) or nivolumab + ipilimumab (n = 156)

Primary objective: ORR per RECIST v1.1
Secondary objectives: safety, OS, PFS, DOR
Prespecified exploratory objectives: biomarker analysis; health status using the EQ-5D instrument

Nivolumab 3 mg/kg IV Q2W
(n = 147)c

Until disease progression or unacceptable toxicity

Nivolumab 1 mg/kg + ipilimumab 3 mg/kg IV Q3W for 4 cycles
(n = 95)d

Until disease progression or unacceptable toxicity

DOR = duration of response; EQ-5D = EuroQoL-5 Dimensions; ORR = objective response rate; OS = overall survival; PD-L1 = programmed death ligand 1; PFS = progression-free survival

aMedian follow-up 23.3 months; bMedian follow-up 28.6 months; cMedian follow-up 10.8 months; dMedian follow-up 11.2 months; eBased on data

Hellmann MD et al. Journal of Clinical Oncology 35:8503-8503, 2017
CM-032 Nivolumab + Ipilimumab OS

Hellmann MD et al. Journal of Clinical Oncology 35:8503-8503, 2017
Responses irrespective of PD-L1 expression for nivo + ipi

CheckMate 032:
Tumor PD-L1 expression in non-randomized cohort (n = 159)$^{1a}$

- 18% ≥1%
- 82% <1%

CheckMate 032
Nivolumab Monotherapy$^{2}$

CheckMate 032
Nivolumab-1 + Ipilimumab-3

Best change from baseline in target lesion volume (%)

<1% PD-L1 ≥1% PD-L1 PD-L1 not evaluable/missing Confirmed responders Truncated to 100%

Hellmann MD et al. Journal of Clinical Oncology 35:8503-8503, 2017
Tumor Mutation Burden arising as a predictive biomarker for nivolumab + ipilimumab (ORR)
Phase 3 Studies with Nivolumab + Ipilimumumab

CheckMate 451: study design

- Currently enrolling patients

Key eligibility criteria
- ED-SCLC
- Ongoing SD/PR/CR after 4 cycles of 1L PLT-CT
- No symptomatic CNS metastases
- Toxicities from prior therapy resolved to grade ≤1
- ECOG PS ≤1

Randomize 1:1:1

N = 810

Nivolumab

Nivolumab + Ipilimumab

Placebo

Primary outcome measures:
- OS, PFS

Secondary outcome measures:
- OS and PFS descriptive analyses: nivolumab vs nivolumab + ipilimumab

CheckMate 331: study design

Key eligibility criteria
- SCLC
- Recurrence/PD after 1L PLT-CT or CRT (≥4 cycles)
- ECOG PS ≤1
- No symptomatic CNS metastases
- No prior therapy with anti-CTLA-4, anti-CD137, anti-PD-1/ PD-L1/PD-L2

Randomize 1:1

N = 480

Nivolumab

Topotecan or Amrubicina

Primary outcome measures:
- OS

Secondary outcome measures:
- PFS, ORR

1L = first-line; CT = chemotherapy; CRT = chemoradiation therapy; CTLA-4 = cytotoxic T lymphocyte antigen-4; PD-1 = programmed-death 1; PD-L2 = PD ligand 2; PLT = platinum-based; aWhere locally approved
## Durvalumab +/- Tremelimumab Studies in PD-L1 Unselected SCLC

<table>
<thead>
<tr>
<th>Study</th>
<th>ORR</th>
<th>TTR</th>
<th>DOR</th>
<th>1 yr PFS</th>
<th>OS</th>
<th>1 yr OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Durvalumab/Tremelimumab (n=30)</td>
<td>13.3%</td>
<td>1.9 mo</td>
<td>18.9 mo</td>
<td>16.3%</td>
<td>7.9 mo</td>
<td>41.7%</td>
</tr>
<tr>
<td></td>
<td>(3.8, 30.7)</td>
<td>(12.7-18.9)</td>
<td>(5.4, 32.6)</td>
<td>(3.2, 15.8)</td>
<td>(23.3, 59.2)</td>
<td></td>
</tr>
<tr>
<td>Durvalumab (n=21)</td>
<td>9.5%</td>
<td>3.4 mo</td>
<td>NR (14.6 &amp; 29.5+)</td>
<td>14.3%</td>
<td>4.8 mo</td>
<td>27.6%</td>
</tr>
<tr>
<td></td>
<td>(3.6, 32.1)</td>
<td>(1.3, 10.4)</td>
<td>(10.2, 48.4)</td>
<td>(23.3, 59.2)</td>
<td>(23.3, 59.2)</td>
<td></td>
</tr>
</tbody>
</table>

Cho DC. J Clin Oncol 36, 2018 (suppl; abstr 8517), 2018; Goldman JW. J Clin Oncol 36, 2018 (suppl; abstr 8518), 2018
Summary of Immunotherapy in SCLC

- Subset of pre-treated patients with SCLC have prolonged responses with anti-PD-1 axis immunotherapy
- Emerging biomarkers include PD-L1 IHC (KN studies with pembrolizumab) and Tumor Mutation Burden (CM studies with nivolumab ± ipilimumab)
- Immunotherapy may be useful in certain strategies
  - Maintenance pembrolizumab study negative\(^1\)
  - IMpower133 of atezolizumab (PD-L1 inhibitor) in combination with carboplatin and etoposide versus carboplatin plus etoposide (chemotherapy) alone in chemotherapy-naïve patients with ES-SCLC: **POSITIVE STUDY (results pending)**

\(^1\)=Gadgeel SM. ASCO 2017