Management of extensive small cell lung cancer

G.L. Ceresoli, MD
Disclosure information

The speaker has no conflict of interest to disclose as regards this presentation.
SCLC: 13% of all lung cancer
M to F ratio 1:1
Almost all cases related to smoking

SCLC: historical role of chemotherapy

<table>
<thead>
<tr>
<th>Stage</th>
<th>Median Survival (months)</th>
<th>1 year survival (%)</th>
<th>5 year survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Limited Stage</td>
<td>20</td>
<td>60</td>
<td>20</td>
</tr>
<tr>
<td>Extensive Stage</td>
<td>10</td>
<td>20-30</td>
<td>&lt;5</td>
</tr>
</tbody>
</table>

Sundstrom et al., JCO 2002; Johnson et al., Chest 1999
First-Line treatment of SCLC: cisplatin vs carboplatin

Meta-analysis of 4 randomized trials with 663 patients

Different range of toxicity of the two platinum agents
Significant interaction with age: CIS < 70yr, CARBO > 70yr
Caution in using this information for management of patients with LD

Rossi et al., JCO 2012
SCLC: benchmarks in the relapsed setting

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N</th>
<th>ORR (%)</th>
<th>mPFS</th>
<th>mOS</th>
<th>1-year OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Topotecan ¹</td>
<td>107</td>
<td>24%</td>
<td>2.8 m (13w)</td>
<td>5.6 m (25w)</td>
<td>14%</td>
</tr>
<tr>
<td>CAV ¹</td>
<td>104</td>
<td>24%</td>
<td>2.7 m (12w)</td>
<td>5.6 m (25w)</td>
<td>14%</td>
</tr>
<tr>
<td>Amrubicin ²</td>
<td>424</td>
<td>31%</td>
<td>4.1 m</td>
<td>7.5 m</td>
<td>27%</td>
</tr>
<tr>
<td>Topotecan ²</td>
<td>213</td>
<td>17%</td>
<td>3.5 m</td>
<td>7.8 m</td>
<td>25%</td>
</tr>
</tbody>
</table>

“sensitive relapse”: ≥90 days after stop of 1st line chemotherapy

“resistant/refractory relapse”: <90 days after stop of 1st line chemotherapy

Modified from Vansteenkiste, ESMO 2018

Standard treatment approach for ES-SCLC

Modified from Newson-Davis 2019
Many failed trials in ED-SCLC

Precision medicine has lagged in SCLC compared with NSCLC

Oze et al., PlosOne 2009; modified from Newson-Davis 2019
Absence of targetable driver mutations and high mutational burden are hallmarks of SCLC


- **High mutational burden** (~50% ≥ 1 mut), 8.6 mut/Mb
- Nearly universal loss-of-function mutations in TP53 and RB
- **Very few actionable targetable driver** mutations: KIT, PIK3CA, BRAF
- Amplification of FGFR1, SOX2 and MYC family of oncogenes
# PD1 & PDL1 inhibitors in relapsed SCLC

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>ORR (%)</th>
<th>mPFS</th>
<th>mOS</th>
<th>1-year OS</th>
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<td>213</td>
<td>17%</td>
<td>3.5 m</td>
<td>7.8 m</td>
<td>25%</td>
</tr>
<tr>
<td>Control (IFCT-1603)</td>
<td>24</td>
<td>10%</td>
<td>4.3 m</td>
<td>8.7 m</td>
<td>NR</td>
</tr>
<tr>
<td>Atezolizumab (IFCT-1603)</td>
<td>49</td>
<td>2%</td>
<td>1.4 m</td>
<td>9.5 m</td>
<td>NR</td>
</tr>
<tr>
<td>Nivolumab (CM-032) ³</td>
<td>98</td>
<td>10%</td>
<td>1.4 m</td>
<td>4.1 m</td>
<td>33%</td>
</tr>
<tr>
<td>Pembrolizumab (KN-028) ⁴</td>
<td>24</td>
<td>33% (PDL1+)</td>
<td>1.9 m</td>
<td>9.7 m</td>
<td>38%</td>
</tr>
<tr>
<td>Pembrolizumab (KN-158) ⁵</td>
<td>107</td>
<td>19% (36 vs 6%)</td>
<td>2.0 m</td>
<td>9.1 m</td>
<td>40%</td>
</tr>
<tr>
<td>Atezolizumab (PCD4989) ⁶</td>
<td>17</td>
<td>6%</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Durvalumab ⁷</td>
<td>21</td>
<td>10%</td>
<td>1.5 m</td>
<td>4.8 m</td>
<td>28%</td>
</tr>
</tbody>
</table>

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¹ Von Pawel et al, J Clin Oncol 17: 658-667, 1999
³ Hellmann et al, abstract 8503, ASCO 2017
⁴ Ott et al, J Clin Oncol 35: 3823-3829, 2017
⁵ Chung et al, abstract 8506, ASCO 2018
⁶ Goldman et al, abstract 8518, ASCO 2018
⁷ Sequist et al, abstract 1425PD, ESMO 2017

Modified from Vansteenkiste, ESMO 2018
IFCT 16-03: Phase II R trial of atezolizumab vs CT in relapsed SCLC

Pujol et al., J Thor Oncol 2019
IFCT 16-03: Phase II trial of atezolizumab vs CT in relapsed SCLC

<table>
<thead>
<tr>
<th>Objective response</th>
<th>N (%)</th>
<th>CHEMO</th>
<th>ATEZO</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>[0.0 ; 23.1]</td>
<td>[0.0 ; 6.8]</td>
<td></td>
</tr>
</tbody>
</table>

Among 53 evaluable specimens, only 1 (2%) had positive immunohistochemical PD-L1 staining (SP142 clone).

Pujol et al., J Thor Oncol 2019
Checkmate 331: Phase III trial of nivolumab vs CT in relapsed SCLC

CheckMate 331 Study Design

Key eligibility criteria
- LD- or ED-SCLC at diagnosis
- Relapse after platinum-based 1L chemotherapy\(^a\)
- ECOG PS 0–1

Stratification factors
- Response to prior platinum-based treatment (sensitive vs resistant\(^b\))
- Brain metastases at baseline (yes vs no)

Nivolumab
240 mg Q2W
n = 284

Chemotherapy:
topotecan (IV or oral)\(^d\) or
amrubicin IV\(^e,f\)

n = 285

Treat until disease progression\(^g,h\) or unacceptable toxicity

Primary endpoint: OS
Secondary endpoints: PFS\(^a\) and ORR\(^a\) (investigator assessed)

- Database lock: 28 September 2018; minimum follow-up for OS: 15.8 months
- Median follow-up: 7.0 months (nivolumab), 7.6 months (chemotherapy)

Reck et al., ESMO Immuno-Oncology 2018
Checkmate 331: OS in all patients

Primary Endpoint: OS With Nivolumab vs Chemotherapy

<table>
<thead>
<tr>
<th></th>
<th>Nivolumab (n = 204)</th>
<th>Chemotherapy (n = 205)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of events</td>
<td>225</td>
<td>245</td>
</tr>
<tr>
<td>mOS</td>
<td>7.5 mos</td>
<td>8.4 mos</td>
</tr>
<tr>
<td>95% CI (mo)</td>
<td>(5.6-10.0)</td>
<td>(7.0-10.0)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.86 (0.72-1.04)</td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td>0.11</td>
<td></td>
</tr>
</tbody>
</table>

Nivolumab 7.5 mos
Chemotherapy 8.4 mos

Reck et al., ESMO Immuno-Oncology 2018
Third-line recurrent SCLC: nivolumab

Subgroup analysis of CK032 trial

Table 2. ORRs with Third-or Later-Line Nivolumab Monotherapy

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Third-or Later-Line Nivolumab (n = 109)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR by BICR</td>
<td></td>
</tr>
<tr>
<td>No. of patients</td>
<td>13</td>
</tr>
<tr>
<td>% of patients (95% CI)</td>
<td>11.9 (6.5-19.5)</td>
</tr>
<tr>
<td>Best overall response, n (%)</td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td>Partial response</td>
<td>12 (11.0)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>25 (22.9)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>56 (51.4)</td>
</tr>
<tr>
<td>Unable to determine</td>
<td>14 (12.8)</td>
</tr>
<tr>
<td>Not reported</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td>Median time to response, mo</td>
<td>1.6</td>
</tr>
<tr>
<td>Duration of response</td>
<td></td>
</tr>
<tr>
<td>( \geq 6) mo, n (%)</td>
<td>10 (76.9)</td>
</tr>
<tr>
<td>( \geq 12) mo, n (%)</td>
<td>8 (61.5)</td>
</tr>
<tr>
<td>Median (95% CI), mo</td>
<td>17.9 (7.9-42.0)</td>
</tr>
<tr>
<td>Range, mo</td>
<td>3.0-42.1</td>
</tr>
</tbody>
</table>

*a* Per the Response Evaluation Criteria in Solid Tumors version 1.1.

*b* Computed by using the Kaplan-Meier method.

BICR, blinded independent central review; CI, confidence interval; ORR, objective response rate.
Third-line recurrent SCLC: pembrolizumab

SCLC 3rd-line setting - combined analysis of KEYNOTE-028 and -158

Exploratory pooled analysis of efficacy and safety of subjects who received ≥2 lines of therapy
- 131 patients, 83 received ≥2 L of therapy
- mFU 7.7 months (range 0.5-48 mos)
- ORR 16%
- Duration of Response ≥18 months

Pembrolizumab granted priority review

Chung et al., J Thor Oncol 2019
There is no effective treatment for relapsed ES-SCLC

SECOND LINE

**Topotecan vs CAV**
- mOS: 5.9m
- ORR: 24%

**Cisplatin + etoposide**
- ORR: 40%

**CheckMate 331**
- mOS: 7.5m
- ORR: 13.7%

FURTHER LINES

**Nivolumab**
- CheckMate 032
  - mOS: 4.1m
  - ORR: 11–12%
  - G≥3 TRAEs: 12%

**Pembrolizumab**
- Pooled KEYNOTE-028 and -158
  - mOS: 7.7m
  - ORR: 19%
  - G≥3 TRAEs: 10%

Modified from Newson-Davis 2019
Many patients do not receive subsequent therapies after 1L treatment.

Real-world prospective data from Germany (2010–2016)

Steffens et al., Lung Cancer 2019
Taking advantage of IO & chemotherapy interaction as soon as possible

Modified from: Owonikoko, ASCO 2018; Vasteenkiste, ESMO 2018; Newson Davis 2019
Impower 133: study design

**IMpower133: Global Phase 1/3, double-blind, randomized, placebo-controlled trial evaluated atezolizumab + carboplatin + etoposide in 1L ES-SCLC**

- **Patients with** (N = 403):
  - Measurable ES-SCLC (RECIST v1.1)
  - ECOG PS 0 or 1
  - No prior systemic treatment for ES-SCLC
  - Patients with treated asymptomatic brain metastases were eligible

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

**Induction (4 x 21-day cycles)**

- **Atezolizumab** (1200 mg IV, Day 1)
  - + carboplatin
  - + etoposide

- **Placebo**
  - + carboplatin
  - + etoposide

**Maintenance**

- **Atezolizumab**
- **Placebo**

**Co-primary end points:**
- Overall survival
- Investigator-assessed PFS

**Key secondary end points:**
- Objective response rate
- Duration of response
- Safety

**Survival follow-up**

Horn et al., NEJM 2018
Impower 133: investigator-assessed PFS (co-primary endpoint)

Horn et al., NEJM 2018
Impower 133: OS (co-primary endpoint)
Impower 133: OS (updated follow-up)

12-month OS
51.9%
39.0%

18-month OS
34.0%
21.0%

HR = 0.76

Median follow-up 22.9 months

Reck et al., ESMO 2019
IMpower133: ability to deliver chemotherapy was not compromised by the addition of Atezolizumab

Horn et al., NEJM 2018; Reck et al., ESMO 2019
CASPIAN: study design

- Treatment-naïve ES-SCLC
- WHO PS 0 or 1
- Asymptomatic or treated and stable brain metastases permitted
- Life expectancy ≥12 weeks
- Measurable disease per RECIST v1.1
  N=805 (randomised)

**Primary endpoint**
- OS

**Secondary endpoints**
- PFS
- ORR
- Safety & tolerability
- Health-related QoL

The durvalumab + tremelimumab + EP versus EP comparison continues to final analysis

Paz Ares et al., Lancet 2019
CASPIAN: OS (primary endpoint)

Paz Ares et al., Lancet 2019
CASPIAN: investigator-assessed PFS

<table>
<thead>
<tr>
<th></th>
<th>Durvalumab + EP</th>
<th>EP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events, n/N (%)</td>
<td>226/268 (84.3)</td>
<td>233/269 (86.6)</td>
</tr>
<tr>
<td>mPFS*, months (95% CI)</td>
<td>6.1 (4.7–6.2)</td>
<td>6.4 (4.8–6.2)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.78 (0.64–0.936)</td>
<td></td>
</tr>
</tbody>
</table>

- PFS was not formally tested for statistical significance
- 56.8% of patients in the control arm received 6 cycles of EP

Paz Ares et al., Lancet 2019
### IMpower 133 vs CASPIAN: Patient Characteristics

#### Table 1. Baseline Characteristics of All Enrolled Patients (Intention-to-Treat Population). \(^*\)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Atezolizumab Group (N = 203)</th>
<th>Placebo Group (N = 202)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (range) — yr</td>
<td>64 (28-90)</td>
<td>64 (26-87)</td>
</tr>
<tr>
<td>Age group — no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65 yr</td>
<td>111 (55.2)</td>
<td>106 (52.5)</td>
</tr>
<tr>
<td>≥65 yr</td>
<td>90 (44.8)</td>
<td>96 (47.5)</td>
</tr>
<tr>
<td>Male sex — no. (%)†</td>
<td>129 (64.2)</td>
<td>132 (65.3)</td>
</tr>
<tr>
<td>ECOG performance-status score — no. (%)†‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>73 (36.3)</td>
<td>67 (33.2)</td>
</tr>
<tr>
<td>1</td>
<td>128 (63.7)</td>
<td>135 (66.8)</td>
</tr>
<tr>
<td>Smoking status — no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never smoked</td>
<td>9 (4.5)</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>74 (36.4)</td>
<td>75 (37.1)</td>
</tr>
<tr>
<td>Former smoker</td>
<td>120 (59.1)</td>
<td>124 (61.4)</td>
</tr>
<tr>
<td>Brain metastasis at enrollment — no. (%)†</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>37 (18.3)</td>
<td>18 (8.8)</td>
</tr>
</tbody>
</table>

#### Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Durvalumab + EP (n=268)</th>
<th>Placebo (n=269)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (range), years</td>
<td>62 (28-82)</td>
<td>63 (35-82)</td>
</tr>
<tr>
<td>Male, %</td>
<td>70.9</td>
<td>68.4</td>
</tr>
<tr>
<td>White / Asian / Other, %</td>
<td>85.4 / 13.4 / 1.1</td>
<td>82.2 / 15.6 / 2.2</td>
</tr>
<tr>
<td>WHO PS 0 / 1, %</td>
<td>36.9 / 63.1</td>
<td>33.5 / 66.5</td>
</tr>
<tr>
<td>Disease stage III / IV, %</td>
<td>10.4 / 89.6</td>
<td>8.9 / 91.1</td>
</tr>
<tr>
<td>Current / Former / Never smoker, %</td>
<td>44.8 / 47.0 / 8.2</td>
<td>46.8 / 47.6 / 5.6</td>
</tr>
<tr>
<td>Brain or CNS metastases, %</td>
<td>10.4</td>
<td>10.0</td>
</tr>
</tbody>
</table>

\(^*\) All patients were confirmed as having ES-SCLC.

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**Horn et al., NEJM 2018; Paz Ares et al., Lancet 2019**
### Impower 133 vs CASPIAN: outcomes

<table>
<thead>
<tr>
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<th>IMpower 133</th>
<th>CASPIAN</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Atezolizumab (pts n 201)</td>
<td>Placebo (pts n 202)</td>
</tr>
<tr>
<td>OS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR</td>
<td>0.76</td>
<td>0.73</td>
</tr>
<tr>
<td>median</td>
<td>12.3</td>
<td>10.3</td>
</tr>
<tr>
<td>12 mos</td>
<td>52%</td>
<td>39%</td>
</tr>
<tr>
<td>PFS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR</td>
<td>0.77</td>
<td>0.78</td>
</tr>
<tr>
<td>median</td>
<td>5.2</td>
<td>4.3</td>
</tr>
<tr>
<td>12 mos</td>
<td>12.6%</td>
<td>5.4%</td>
</tr>
<tr>
<td>RESPONSE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ORR</td>
<td>60.2%</td>
<td>64.4%</td>
</tr>
<tr>
<td>DoR mos</td>
<td>4.2</td>
<td>3.9</td>
</tr>
<tr>
<td>AE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>G3- G4</td>
<td>67.7%</td>
<td>63.3%</td>
</tr>
<tr>
<td>Ir AE</td>
<td>39.9%</td>
<td>23.5%</td>
</tr>
<tr>
<td>Discontinuation</td>
<td>12.1%</td>
<td>3.1%</td>
</tr>
</tbody>
</table>

Horn et al., NEJM 2018; Paz Ares et al., Lancet 2019
Impower 133 vs CASPIAN: survival curves

Horn et al., NEJM 2018; Paz Ares et al., Lancet 2019
Checkmate 451: Maintenance IO in ED SCLC

Nivolumab Plus Ipilimumab, Nivolumab, or Placebo as Maintenance Therapy in Patients With Extensive Disease Small Cell Lung Cancer After First-Line Platinum-Based Chemotherapy: Results From the Double-Blind, Randomized Phase 3 CheckMate 451 Study

Key eligibility criteria
- ED-SCLC at diagnosis
- No symptomatic CNS metastases
- ECOG PS 0 or 1
- Ongoing response of CR, PR, or SD following 4 cycles of platinum-based 1L chemotherapy

Stratified by ECOG PS (0 vs 1), prior PCI (yes vs no), sex

Nivolumab 1 mg/kg Q3W + Ipi1mumab 3 mg/kg Q3W (max 4 doses) n = 279
Nivolumab 240 mg Q2W n = 290
Nivolumab 240 mg Q2W
Placebo n = 275

Treat until disease progression or unacceptable toxicity, for a maximum of 2 years

Owonikoko et al., ELCC 2019

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Checkmate 451: Maintenance IO in ED SCLC

OS for Nivolumab Plus Ipilimumab Versus Placebo
(Primary Endpoint)

<table>
<thead>
<tr>
<th></th>
<th>NIVO + IPI (n = 279)</th>
<th>Placebo (n = 275)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events, n (%)</td>
<td>189 (68)</td>
<td>211 (77)</td>
</tr>
<tr>
<td>Median OS, mo (95% CI)</td>
<td>9.2 (8.2–10.2)</td>
<td>9.6 (8.2–11.0)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.92 (0.9–1.1)</td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td>0.37</td>
<td></td>
</tr>
</tbody>
</table>

1-y OS = 41%

Owonikoko et al., ELCC 2019
**KeyNote-604: pembrolizumab (ongoing)**

**Press Release (06 JAN 2020):**
Only one of the coprimary endpoint was met: PFS HR 0.75 (95%CI 0.61-0.91).
OS endpoint not met: OS HR 0.80 (95%CI 0.64-0.98)
Biomarkers in SCLC

- Low prevalence of TC PD-L1 expression in SCLC
- No clear correlation of benefit from anti-PDL1 therapy by PD-L1 expression or TMB in SCLC

- Additional concerns about SCLC tissue sample evaluable:
  - Crush artifact
  - Higher FNA rate

- Blood-based biomarkers (e.g. bTMB) could overcome these limitations

- SCLC requires rapid treatment initiation
- Turnaround time for biomarker testing may be too long to inform upfront treatment decisions in SCLC

Modified from Liu 2019
PD-L1 expression in IMpower133 was assessed using the SP263 IHC PD-L1 assay. Only 34% of samples were evaluable. Only 6% PD-L1 ≥1% based on tumour cell expression. 50% PD-L1 ≥ 1% based on immune cell expression.
Biomarkers in CASPIAN

**OVERALL SURVIVAL BASED ON PD-L1 EXPRESSION**

(PD-L1 on 52% of the ITT pts)

<table>
<thead>
<tr>
<th>Description</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITT (n=537)</td>
<td>0.73 (0.591–0.910)</td>
</tr>
<tr>
<td>PD-L1 evaluable (n=277)</td>
<td>0.65 (0.482–0.864)</td>
</tr>
<tr>
<td>IC &lt;1 (n=215)</td>
<td>0.64 (0.462–0.897)</td>
</tr>
<tr>
<td>IC ≥1 (n=62)</td>
<td>0.69 (0.370–1.283)</td>
</tr>
<tr>
<td>TC &lt;1 (n=283)</td>
<td>0.66 (0.491–0.896)</td>
</tr>
<tr>
<td>TC ≥1 (n=14)</td>
<td>0.46 (0.119–1.793)</td>
</tr>
</tbody>
</table>

- Durvalumab + EP was associated with improved OS vs EP, regardless of PD-L1 expression with a 1% cut-off.
- No significant interaction was observed with OS based on PD-L1 expression as a continuous variable (TC, p=0.54; IC, p=0.23); similar results were observed with PFS and ORR.

Paz Ares et al., Lancet 2019
# Targeted therapy in relapsed SCLC

<table>
<thead>
<tr>
<th>Drug</th>
<th>Study</th>
<th>Author</th>
<th>PFS (mo)</th>
<th>OS (mo)</th>
<th>ORR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemotherapy</td>
<td><strong>Lurbinectedin</strong></td>
<td>NCT02454972</td>
<td>Paz-Ares ASCO 2019</td>
<td>4.1</td>
<td>9.3</td>
</tr>
<tr>
<td>DLL3-targeting</td>
<td><strong>Rova-T</strong></td>
<td>TRINITY</td>
<td>Morgensztern CCR 2019</td>
<td>3.8</td>
<td>5.7</td>
</tr>
<tr>
<td>DDR-targeting + Chemo or IO</td>
<td><strong>Veliparib+ Temozolomide</strong></td>
<td>NCT01638546</td>
<td>Pietanza JCO 2018</td>
<td>3.8</td>
<td>8.2</td>
</tr>
<tr>
<td></td>
<td><strong>Olaparib+ Durvalumab</strong></td>
<td>NCT02484404</td>
<td>Thomas JTO 2019</td>
<td>1.8</td>
<td>4.1</td>
</tr>
<tr>
<td></td>
<td><strong>Olaparib+ Temozolomide</strong></td>
<td>NCT02446704</td>
<td>Farago Cancer Discov 2019</td>
<td>4.2</td>
<td>8.5</td>
</tr>
<tr>
<td>New TKI (VEGFR,FGFR,PDGFR,cKIT)</td>
<td><strong>Anlotinib</strong></td>
<td>ALTER 1202</td>
<td>Cheng ESMO 2019</td>
<td>4.1</td>
<td>7.3</td>
</tr>
</tbody>
</table>
Lurbinectedin: mechanism of action

- DNA binding
- Cell cycle block
- DNA repair
- Inhibition of TF

- Mono-TAM apoptosis
- Inhibition of CCL2, CXCL8, IL-6
- Inhibition of angiogenesis

Germano et al., Cancer Cell 2013; D’Incalci et al., Oncotarget 2013; Belgiovine et al., Br J Cancer 2017
Lurbinectedin single agent in pretreated SCLC

**Primary Objective:** ORR by RECIST V.1.1

- Investigator assessed

**SCLC Patients**

- PS 0-2
  - One prior chemotherapy line
  - Prior immunotherapy was allowed
  - Adequate organ function
  - CNS mets excluded

- Lurbinectedin 3.2 mg/m², 1h iv, q3wk

- ≥ 2 responses in first 15 patients

- Enroll up to 100 patients

**Statistical Assumptions for SCLC Cohort**

- Null hypothesis: ≤15% get a response (p ≤ 0.15)
- Alternative hypothesis: ≤20% get a response (p ≤ 0.20)
- Statistical power: 95%
- ≥ 23% of confirmed responses needed to reject the null hypothesis

**ORR 35%**

**Decrease in tumor size in 65% patients**

**OS according to sensitive or resistant population**

- mOS 9.3 mo
  - RES 5.0 mo
  - SENS 11.9 mo

**ORR 35%**

- (95% CI) 26.2-45.2

- Best response
  - n (%)
    - PR (confirmed) 27 (35.2) * 
    - SD 15 (19.3)
    - PD 21 (26.7)
    - NE* (non-evaluable) 5 (4.8)

- Disease Control Rate, %
  - 68.6 (95% CI) 58.8-77.3

- *5 of 8 patients who failed prior immunotherapy had confirmed response

- *Treatment discontinuation without any tumor assessment performed

**mPFS 4.1 mo**

**Data cut-off: January 13th, 2019**

Paz-Ares et al., ASCO 2019
Lurbinectedin: ATLANTIS study (Phase III, second-line)

PHASE I: RR in 91% in sensitive relapsed SCLC, 33% in resistant disease, 20% in 3rd line.

*Calvo et al., Ann Oncol 2017; Farago et al, Future Oncol 2019
Rovalpituzumab: TRINITY trial (third-line Tx)

Delta-like Protein 3 (DLL3) in >85% of SCLC; Rovalpituzumab (Ab-drug conjugate) targeting DLL3

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

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

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

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

- 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

**ORR**
- 12.4% (all pts);
- 14.3% (high DLL3 expressors)

**mOS 5.7 mos**

**MPFS 3.8 mos**

Most common AEs: fatigue, photosensitivity reaction, and pleural effusion. **Grade 3–5 AEs were seen in 213 (63%) patients.**

Morgensztern et al., Clin Cancer Res 2019
Rovalpituzumab: MERU trial (Phase III maintenance)

AbbVie PRESS RELEASE (29/08/19): No survival benefit at an interim pre-planned analysis. The MERU trial is being closed, and the Rova-T research and development program has been terminated.
Olaparib+temozolomide (phase I-II trial)

**Phase I**
- Assessed for Eligibility (n=13)
  - Enrolled (n=13)
  - Treated (n=13)

**Phase II**
- Assessed for Eligibility (n=45)
  - Excluded (n=8)
    - Screen fail (n=6)
    - Withdrew consent (n=2)
  - Enrolled (n=37)
  - Treated (n=37)

<table>
<thead>
<tr>
<th>Dose level</th>
<th>Olaparib tablets (d1-7 PO BID)</th>
<th>Temozolomide (d1-7 PO QPM)</th>
<th>Patients (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>100 mg</td>
<td>50 mg/m²</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>100 mg</td>
<td>75 mg/m²</td>
<td>3</td>
</tr>
<tr>
<td>3</td>
<td>200 mg</td>
<td>75 mg/m²</td>
<td>4</td>
</tr>
<tr>
<td>4</td>
<td>200 mg</td>
<td>100 mg/m²</td>
<td>3</td>
</tr>
</tbody>
</table>

BD2: dose level 3; Olaparib tablets (d1-7)
- 200 mg PO BID, Temozolomide (d1-7) 75 mg/m² PO QPM
- n=17 treated in first expansion
- n=20 treated in second expansion

Lost to follow-up (n=0)

- Analyzed (n=13)
  - DLT evaluable (n=12)
  - Excluded from DLT evaluation (n=1)
    - Discontinued treatment during cycle 1 due to disease-related symptoms
    - Response evaluable (n=13)
    - PFS/OS evaluable (n=13)

- Analyzed (n=37)
  - Response evaluable (n=35)
  - Response not evaluable (n=2)
    - No restaging scan performed (n=1)
    - Died before first restaging scan (n=1)
  - PFS/OS evaluable (n=37)
Olaparib+temozolomide (phase I-II trial)

Farago et al, Cancer Discov 2019

<table>
<thead>
<tr>
<th>Best confirmed response, RECIST 1.1</th>
<th>Platinum Sensitive (n=34)</th>
<th>Platinum Resistant (n=14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>PR</td>
<td>16 (47.1)</td>
<td>4 (28.6)</td>
</tr>
<tr>
<td>SD</td>
<td>13 (38.2)</td>
<td>5 (35.7)</td>
</tr>
<tr>
<td>PD</td>
<td>5 (14.7)</td>
<td>5 (35.7)</td>
</tr>
</tbody>
</table>

mPFS: 4.2 mo (95% CI 2.8-5.7)
mOS: 8.5 mo (95% CI 5.1-11.3)

D, E

Farago et al, Cancer Discov 2019
1. SCLC is a very aggressive disease with a generally poor outcome. Relapse is the rule, especially in extensive disease.

1. First-line setting: Immunotherapy (IO) with immune checkpoint inhibitors in combination with standard chemo improved survival in two randomized trials: NEW STANDARD OF CARE. No biomarkers so far.

2. There are limited options for recurrent SCLC, including topotecan, CAV and platinum/etoposide re-challenge. IO has limited activity in this setting.

3. Targeted therapies have failed so far in improving patient outcome. Most promising new agents under evaluation are lurbinectedin and the combination of PARP-inhibitors with temozolomide.