THE EVOLVING LANDSCAPE OF EXTENSIVE STAGE SMALL CELL LUNG CANCER

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Alma Mater University of Bologna-Italy
SCLC represents 10-15% of all lung cancers

Incidence decreased in the last decade in Europe
- 1-5 / 10 000 people

Highly smoke-related

Increasing prevalence of elderly patients (>70 years)
- 44% in 2010

Most aggressive form of lung cancer
- 5-year overall survival <10%

PATHOLOGY

High-grade neuroendocrine tumour, according to 2015 World Health Organization (WHO)

Tumour cells measuring less than three resting lymphocytes
Scant cytoplasm
Poorly-defined cell borders
A finely dispersed granular nuclear chromatin, absent or inconspicuous nucleoli
Numerous mitoses (average 80/mm²)
Extensive necrosis (crush artifacts in smear/small biopsies)

Immunohistochemistry:
- CD56 (membranous staining)
- Synaptophysin (54%)
- Chromogranin A (37%)

Possibility of combined histology: adenocarcinoma, squamous cell carcinoma, large cell carcinoma, sarcomatoid (spindle or giant cell)

Molecular classification of SCLC*

Novel SCLC classification based on expression profile identifies 4 main SCLC groups:

- **Neuroendocrine**
  - SCLC-A: expressing ASCL1
  - SCLC-N: expressing NeuroD1

- **Non-neuroendocrine**
  - SCLC-Y: expressing YAP1
  - SCLC-P: expressing POU2F3

*For research purpose only.

NE: neuroendocrine; non-NE: non neuroendocrine

TREATMENT OF ES-SCLC

State of the art before immunotherapy: Treatment strategy

Platinum-based first-line chemotherapy (cisplatin 60–75 mg/m² or carboplatin AUC 5 d1 + etoposide 80–120 mg/m² d1–3), x 4-6 cycles q3wks

Consolidation Thoracic Irradiation 40–50 Gy in selected patients

Prophylactic cranial irradiation (PCI), 25 Gy, for patients in CR/PR and good general conditions after CT

Outcome with first-line treatment: RR 50–60%, mOS 9–10 months

Second-line chemotherapy in case of recurrence/progressive disease after first-line (Re-challenge, Topotecan, Taxol)

Outcome with second-line treatment: RR 10–20%, mOS 5–6 months

Lack of significant drug therapy progress over the last 40 years

AUC: area under curve; wks: weeks; ORR: objective response rate; mOS: median overall survival; PCI: prophylactic cranial irradiation; CR: complete response; PR: partial response; ECOG PS: Eastern cooperative oncology group performance status; ChT: chemotherapy.
TREATMENT OF ES-SCLC
State of the art before immunotherapy: The role of platinum

Meta-analysis of published data from 19 trials (4054 patients)

**OR** for response rate 1.35 in favour of cisplatin ($p<0.0001$)

**OR** for 1-year survival 0.80 in favour of cisplatin ($p<0.002$) corresponding to an absolute survival improvement of 4.4%

Odds ratio and 95% confidence interval of mortality at 1 year for patients treated with a CDDP-containing regimen (symbols as in Figure 1; $P=0.002$). Test for heterogeneity: $Q=26.47$; df: 18; $P=0.10$
TREATMENT OF ES-SCLC

State of the art before immunotherapy: The role of platinum

Carboplatin and cisplatin have similar efficacy in terms of either OS or PFS in ES-SCLC

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Pts</th>
<th>Events</th>
<th>Median OS (months)</th>
<th>95% CI</th>
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<tbody>
<tr>
<td>Cisplatin</td>
<td>328</td>
<td>293</td>
<td>9.64</td>
<td>8.72 to 10.7</td>
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<tr>
<td>Carboplatin</td>
<td>335</td>
<td>296</td>
<td>9.41</td>
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<table>
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<tr>
<th>Treatment</th>
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<th>Events</th>
<th>Median PFS (months)</th>
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</tr>
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<tbody>
<tr>
<td>Cisplatin</td>
<td>328</td>
<td>304</td>
<td>5.46</td>
<td>5.03 to 6.18</td>
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<tr>
<td>Carboplatin</td>
<td>335</td>
<td>314</td>
<td>5.33</td>
<td>4.90 to 5.72</td>
</tr>
</tbody>
</table>

Overall survival

Progression-free survival

**TREATMENT OF ES-SCLC**

State of the art before immunotherapy: The role of thoracic radiation

**CREST trial:** thoracic external radiation therapy (with PCI) prolongs OS (primary endpoint) in patients with ES-SCLC who respond to chemotherapy with residual intrathoracic disease


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TREATMENT OF ES-SCLC

State of the art before immunotherapy: The role of PCI

A multicentre EORTC clinical trial randomised N=286 patients with ES-SCLC achieving any response to chemotherapy between PCI or no PCI

Brain imaging at randomisation not mandatory

Median OS increased by 1.3 months (5.4 months in no PCI to 6.7 months in PCI; p=0.003)

OS at 1 year increased from 13.3% to 27.1%

Decreased symptomatic brain metastases 41.3% → 16.8% (p<0.001)

TREATMENT OF ES-SCLC

State of the art before immunotherapy: The role of PCI

A multicentre Japanese clinical trial randomised N=224 patients with ES-SCLC achieving any response to chemotherapy and no brain metastases at MRI between PCI or no PCI

Early termination for futility: median OS (primary endpoint) 11.6 vs. 13.7 months (p=0.094) in the PCI and observation arm, respectively

TREATMENT OF ES-SCLC

State of the art before immunotherapy: Treatment of relapsed/recurrent disease

Relapsed SCLC is a common clinical problem (80–90% of SCLC)
Short life expectancy (4–6 months), highly symptomatic and poor PS
- Clinical classification of relapsed SCLC
  - “Resistant/refractory” to chemotherapy
    - (initially responding) but progressive <3 months after prior chemotherapy regimen
    - progressive or stable during the prior chemotherapy regimen (refractory)
  - “Sensitive” to chemotherapy: progressive >3 months (after having responded to the previous chemotherapy regimen)
Salvage therapy may provide modest QoL improvement and survival prolongation
Only one drug registered: topotecan

Kaplan-Meier estimates for overall survival in the intent-to-treat population (log-rank p=0.01)

Unadjusted HR for OS 0.64 (95% CI: 0.45, 0.90) for topotecan relative to best supportive care alone. Adjusted for stratification factors, HR 0.61 (95% CI: 0.43, 0.87)

“Sensitive” relapsed/recurrent patients with SCLC may receive platinum-etoposide rechallenge chemotherapy
- Progressive ≥60/90 days from the end of previous chemotherapy after response

A multicentre French clinical trial randomised N=164 patients with SCLC relapsed ≥90 days after initial response to receive either carboplatin plus etoposide (combination therapy) x 6 cycles or oral topotecan x 6 cycles

PFS (primary endpoint) was significantly longer in the combination chemotherapy group than in the topotecan group (4.7 vs. 2.7 months, respectively; p=0.0041)
TREATMENT OF ES-SCLC
Failed anticancer treatment strategies

High-dose ChT
Accelerated ChT
Alternated/Sequential ChT regimens
Adding 3rd/4th drug
More ChT cycles
Maintenance therapy
Biotherapies (TKIs, MMPIs, FTIs, Proteasome inhibitors)

ChT: chemotherapy; TKIs: Tyrosine kinase inhibitors; MMPIs: Metalloproteinase inhibitors; FTIs: farnesyltransferase inhibitors.
THE NEW IMMUNE ONCOLOGY (IO) PARADIGM
THE NEW IO PARADIGM IN ES-SCLC

Old ineffective immune oncology strategies

IFNs and ILs
Adoptive T-cell transfer
MAGE3 vaccination
TOLL-Like receptors-9 agonists
Bec2/BCG vaccination
Dendritic cell-based vaccination
Personalised peptide vaccination

IFNs: Interferons; ILs: interleukins; MAGE3: Melanoma associated antigen; BCG: bacilli Calmette-Guerin.
THE NEW IO PARADIGM IN ES-SCLC

Is SCLC an immune-excluded tumour?

Secretion of inhibitory cytokines (IL-10, TGF-β)

Loss/reduction of MHC expression (LAMP2/7 and TAP1/2 downregulation due to either epigenetic mechanisms or gene mutations)

Advanced disease associated with immunosuppression (decreased circulating lymphocytes and TILs)

Expression of membrane inhibitory ligands such as PD-L1, PD-L2, B7-H3/4 (adaptive resistance)

IL-10: Interleukin 10; TGF-β: Tumour growth factor β; MHC: Major histocompatibility complex; LAMP2/7: Lysosomal Associated Membrane Protein 2/7; TAP1/2: Transporter associated with Antigen Processing 1 and 2; TILs: Tumour infiltrating lymphocytes; PD-L1/2: programmed death ligand 1 and 2.
THE NEW IO PARADIGM IN ES-SCLC

PD-L1 expression in SCLC (KEYNOTE-028)

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 tumour and associated inflammatory cells or positive staining in stroma

SCLC cohort: of 147 evaluable samples, 42 PD-L1 positive (28.6%)

THE NEW IO PARADIGM IN ES-SCLC
Modern immunotherapy in ES-SCLC – immune checkpoint inhibitors

First-line setting
- Anti-PD-L1 monoclonal antibodies combined with chemotherapy

Maintenance after first-line chemotherapy
- Anti-PD-L1 monoclonal antibodies

Second/third-line setting and beyond
- Anti-PD-1 monoclonal antibodies
THE NEW IO PARADIGM IN ES-SCLC
IMpower133 – study design

Randomised placebo-controlled Phase 3 trial
Carboplatin + etoposide + atezolizumab/placebo x 4 cycles → atezolizumab/placebo
Treated brain metastases allowed
Optional PCI in maintenance phase

N=201 (atezolizumab arm) and N=202 (placebo arm)

Co-primary endpoints met: overall survival and progression-free survival

Median OS: 10.3 vs. 12.3 months, HR: 0.70; p=0.007
Median PFS: 5.3 vs. 4.3 months, HR 0.77; p=0.02

THE NEW IO PARADIGM IN ES-SCLC

IMpower133 – safety

No new safety concerns

Good tolerability profile

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<table>
<thead>
<tr>
<th>Event</th>
<th>Atezolizumab Group (N=198)</th>
<th>Placebo Group (N=196)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Grade 1 or 2</td>
<td>Grade 3 or 4</td>
</tr>
<tr>
<td>Any adverse event</td>
<td>73 (36.9)</td>
<td>112 (56.6)</td>
</tr>
<tr>
<td>Adverse events with an incidence of ≥10% in any grade category or events of grade 3 or 4 with an incidence of ≥2% in either group</td>
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<tr>
<td>Neutopenia</td>
<td>26 (13.1)</td>
<td>45 (22.7)</td>
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<tr>
<td>Anemia</td>
<td>49 (24.7)</td>
<td>28 (14.1)</td>
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<td>Alopecia</td>
<td>69 (34.8)</td>
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<tr>
<td>Nausea</td>
<td>62 (31.3)</td>
<td>1 (0.5)</td>
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<tr>
<td>Fatigue</td>
<td>39 (19.7)</td>
<td>3 (1.5)</td>
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<tr>
<td>Decreased neutrophil count</td>
<td>7 (3.5)</td>
<td>28 (14.1)</td>
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<tr>
<td>Decreased appetite</td>
<td>39 (19.7)</td>
<td>2 (1.0)</td>
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<tr>
<td>Thrombocytopenia</td>
<td>12 (6.1)</td>
<td>20 (10.1)</td>
</tr>
<tr>
<td>Decreased platelet count</td>
<td>17 (8.6)</td>
<td>7 (3.5)</td>
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<tr>
<td>Vomiting</td>
<td>25 (12.6)</td>
<td>2 (1.0)</td>
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<tr>
<td>Constipation</td>
<td>19 (9.6)</td>
<td>1 (0.5)</td>
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<td>Leukopenia</td>
<td>15 (7.6)</td>
<td>10 (5.1)</td>
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<tr>
<td>Decreased white-cell count</td>
<td>10 (5.1)</td>
<td>6 (3.0)</td>
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<tr>
<td>Diarrhea</td>
<td>15 (7.6)</td>
<td>4 (2.0)</td>
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<tr>
<td>Fibrile neutropenia</td>
<td>0</td>
<td>6 (3.0)</td>
</tr>
<tr>
<td>Infusion-related reaction</td>
<td>6 (3.0)</td>
<td>4 (2.0)</td>
</tr>
</tbody>
</table>

THE NEW IO PARADIGM IN ES-SCLC
CASPIAN – study design

Randomised open-label Phase 3 trial
EP: Carboplatin or Cisplatin + etoposide; D: Durvalumab; T: tremelimumab
Treated brain metastases allowed

- 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)

*EP consists of etoposide 80–100 mg/m2 with either carboplatin AUC 5–6 mg/mL/min or cisplatin 75–80 mg/m2, durvalumab dosed at 1500 mg, tremelimumab dosed at 75 mg;
†patients could receive additional 2 cycles of EP (up to 6 cycles total) and PCI at the investigator’s discretion; ‡Patients received an additional dose of tremelimumab post EP; § By investigator assessment per RECIST 1.1.

N=268 (D+T+EP arm), N=268 (D+EP arm) and N=269 (EP arm)

Primary endpoint: **overall survival** – only met for **D+EP vs. EP**

Median OS **(D+EP vs. EP)**: 12.9 vs. 10.5 months, HR: 0.75; p=0.0032 (threshold p-value <0.0418)

Median PFS **(D+EP vs. EP)**: 5.1 vs. 5.4 months, HR 0.80

THE NEW IO PARADIGM IN ES-SCLC

CASPIAN – safety

No new safety concerns

Good tolerability profile for D+EP

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THE NEW IO PARADIGM IN ES-SCLC

Consistency with other immune checkpoint inhibition strategies

KEYNOTE-604

Co-primary endpoints: PFS and OS
Median PFS: 4.5 vs. 4.3 months, HR: 0.75; p=0.0023
Median OS: 10.8 vs. 9.7 months, HR: 0.80; p=0.0164*

*Formally not statistically significant

ECOG-ACRIN EA5161

X= NIVOLUMAB + EP; Y= EP
Primary endpoint: PFS
Median PFS: 5.5 vs. 4.7 months, HR: 0.68; p=0.047
Median OS: 11.3 vs. 9.3 months, HR: 0.73; p=0.14

1. Rudin CM, et al. ASCO 2020; abstract 9001. With permission from Dr CM Rudin;
## THE NEW IO PARADIGM IN ES-SCLC

Studies with ICIs in ES-SCLC first-line treatment

<table>
<thead>
<tr>
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<th>IMpower-133</th>
<th>CASPIAN</th>
<th>Keynote-604</th>
<th>EA 5161</th>
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<tbody>
<tr>
<td>Patients (n)</td>
<td>403 (2 arms)</td>
<td>789 (3 arms)</td>
<td>446 (2 arms)</td>
<td>160 (2 arms)</td>
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<tr>
<td>ICI</td>
<td>Atezo</td>
<td>Durva</td>
<td>Pembro</td>
<td>Nivo</td>
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<tr>
<td></td>
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<td>Durva +Treme</td>
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<tr>
<td>CT cycles (n)</td>
<td>4 vs. 4</td>
<td>4-6 (ctr) vs. 4</td>
<td>4 vs. 4</td>
<td>4 vs. 4</td>
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<tr>
<td>Platinum</td>
<td>Carbo</td>
<td>Carbo or Cis</td>
<td>Carbo or Cis</td>
<td>Carbo or Cis</td>
</tr>
<tr>
<td>PCI/TRT</td>
<td>Yes/No</td>
<td>Yes (ctr arm)/No</td>
<td>Yes/No</td>
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UPCOMING QUESTIONS
IO biomarker – Any role of PD-L1 in predicting ICPIs added benefit?

**IMpower133**

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Median OS (months)</th>
<th>OS Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITT (N = 403)</td>
<td>12.3</td>
<td>0.76 (0.61, 0.96)</td>
</tr>
<tr>
<td>ITT-BEP (n = 137)</td>
<td>9.9</td>
<td>0.70 (0.48, 1.02)</td>
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<tr>
<td>Non-BEP (n = 266)</td>
<td>14.6</td>
<td>0.81 (0.61, 1.08)</td>
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<tr>
<td>PD-L1 expression 1% TC or IC</td>
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<tr>
<td>&lt; 1% PD-L1 (n = 65)</td>
<td>8.9</td>
<td>0.51 (0.30, 0.89)</td>
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<td>≥ 1% PD-L1 (n = 72)</td>
<td>10.6</td>
<td>0.87 (0.51, 1.49)</td>
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<tr>
<td>PD-L1 expression 5% TC or IC</td>
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<tr>
<td>&lt; 5% PD-L1 (n = 108)</td>
<td>9.2</td>
<td>0.77 (0.51, 1.17)</td>
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<tr>
<td>≥ 5% PD-L1 (n = 29)</td>
<td>9.2</td>
<td>0.80 (0.25, 1.46)</td>
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**CASPIAN**

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>HR (95% CI)</th>
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<tr>
<td>ITT (n=537)</td>
<td>0.73 (0.591–0.910)</td>
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<tr>
<td>PD-L1 evaluable (n=277)</td>
<td>0.65 (0.482–0.864)</td>
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<tr>
<td>IC &lt;1 (n=215)</td>
<td>0.64 (0.462–0.897)</td>
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<tr>
<td>IC ≥ 1 (n=62)</td>
<td>0.69 (0.370–1.283)</td>
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<tr>
<td>TC &lt;1 (n=263)</td>
<td>0.66 (0.491–0.896)</td>
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<tr>
<td>TC ≥ 1 (n=14)</td>
<td>0.46 (0.119–1.793)</td>
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</tbody>
</table>

**VENTANA SP263**

- 34% biomarker evaluable
- **Favours durvalumab + EP**

**VENTANA SP263**

- 51% biomarker evaluable
- **Favours EP**

UPCOMING QUESTIONS

IO biomarker – Any role of TMB in predicting ICPIs added benefit?

### iMPower133

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<th>Median OS (months)</th>
<th>OS Hazard Ratio (95% CI)</th>
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<tr>
<td>Male (n = 261)</td>
<td>12.2</td>
<td>10.9</td>
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<tr>
<td>Female (n = 142)</td>
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<td>9.5</td>
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<td>&lt; 60 years (n = 217)</td>
<td>12.1</td>
<td>11.5</td>
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<td>≥ 60 years (n = 100)</td>
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<td>ECOG PS 0 (n = 140)</td>
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<td>ECOG PS 1 (n = 263)</td>
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<td>9.3</td>
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<tr>
<td>Bone metastases (n = 305)</td>
<td>8.5</td>
<td>10.7</td>
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<tr>
<td>No bone metastases (n = 205)</td>
<td>12.6</td>
<td>10.1</td>
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<tr>
<td>Liver metastases (n = 140)</td>
<td>9.3</td>
<td>7.8</td>
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<tr>
<td>No liver metastases (n = 254)</td>
<td>10.3</td>
<td>11.2</td>
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<td>STMB = 10 (n = 134)</td>
<td>11.6</td>
<td>9.8</td>
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<td>STMB ≥ 11 (n = 222)</td>
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<td>STMB ≥ 12 (n = 205)</td>
<td>12.5</td>
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<tr>
<td>STMB ≥ 16 (n = 60)</td>
<td>17.1</td>
<td>11.9</td>
</tr>
<tr>
<td>ITT (n = 403)</td>
<td>12.3</td>
<td>10.3</td>
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### CASPIAN

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>n (%)</th>
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<tr>
<td>ITT (n = 537)</td>
<td>100</td>
<td>0.75 (0.62-0.91)</td>
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<tr>
<td>ITTMB evaluable</td>
<td>178 (33.1)</td>
<td>0.71 (0.51-0.99)</td>
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<tr>
<td>ITTMB &lt;8 mut/Mb</td>
<td>68 (38.2)</td>
<td>0.75 (0.45-1.26)</td>
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<tr>
<td>ITTMB ≥8 mut/Mb</td>
<td>110 (61.8)</td>
<td>0.71 (0.47-1.09)</td>
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<tr>
<td>ITTMB &lt;10 mut/Mb</td>
<td>95 (53.4)</td>
<td>0.77 (0.50-1.20)</td>
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<tr>
<td>ITTMB ≥10 mut/Mb</td>
<td>83 (46.6)</td>
<td>0.68 (0.42-1.14)</td>
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<tr>
<td>ITTMB &lt;12 mut/Mb</td>
<td>111 (62.4)</td>
<td>0.80 (0.53-1.20)</td>
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<tr>
<td>ITTMB ≥12 mut/Mb</td>
<td>67 (37.6)</td>
<td>0.65 (0.37-1.15)</td>
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<tr>
<td>ITTMB &lt;14 mut/Mb</td>
<td>137 (77.6)</td>
<td>0.76 (0.53-1.10)</td>
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<tr>
<td>ITTMB ≥14 mut/Mb</td>
<td>41 (22.4)</td>
<td>0.62 (0.30-1.32)</td>
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### CheckMate 032

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Hazard Ratio</th>
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<tbody>
<tr>
<td>Fevours Atezol + CP/ET</td>
<td>0.76 (0.61, 0.94)</td>
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<tr>
<td>Fevours Placebo + CP/ET</td>
<td>2.8</td>
</tr>
</tbody>
</table>

Molecular classes of SCLC might serve as an IO predictive biomarker.

**YAP1-expressing** SCLC (SCLC-Y) are characterised by inflamed T-cell gene expression profile.

### Table: Molecular Subtypes of Small Cell Lung Cancer

<table>
<thead>
<tr>
<th>Classification</th>
<th>NE</th>
<th>Non-NE</th>
</tr>
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<tbody>
<tr>
<td>Carney et al. (1985)</td>
<td>Classic</td>
<td>Variant</td>
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<tr>
<td>Poirier et al. (2013)</td>
<td>ASCL1-high</td>
<td>NeuroD1-high</td>
</tr>
<tr>
<td>Poirier et al. (2015)</td>
<td>SC-E2</td>
<td>SC-E1</td>
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<td>George et al. (2015)</td>
<td>Group II</td>
<td>Group I</td>
</tr>
<tr>
<td>Borromeo et al. (2016)</td>
<td>ASCL1-high</td>
<td>NeuroD1-high</td>
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<tr>
<td>Mollaoglu et al. (2017)</td>
<td>Group A</td>
<td>Group C</td>
</tr>
<tr>
<td>McCell et al. (2017)</td>
<td>INSM1</td>
<td>YAP1</td>
</tr>
<tr>
<td>Huang et al. (2018)</td>
<td>NE</td>
<td>NEv2</td>
</tr>
<tr>
<td>Wooten et al. (2018)</td>
<td>NEv1</td>
<td>Non-NE</td>
</tr>
<tr>
<td>Proposed nomenclature</td>
<td>SCLC-A</td>
<td>SCLC-N</td>
</tr>
</tbody>
</table>

UPCOMING QUESTIONS
IO biomarker – Any role of novel molecular classification?

Further characterisation of the SCLC-Y subgroup identified an increased expression of immune checkpoints and HLA genes in this group of tumours → SCLC-I (Inflamed)

Trend towards increased benefit with the addition of immunotherapy to chemotherapy in patients from the IMpower133 trial

Need for prospective studies

Reprinted from Cancer Cell, 39(3), Gay CM, et al. Patterns of transcription factor programs and immune pathway activation define four major subtypes of SCLC with distinct therapeutic vulnerabilities, 346–60.e7, Copyright (2021), with permission from Elsevier.
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UPCOMING QUESTIONS

IO biomarker – Any role of DNA damage repair?

DNA damage repair (DDR) pathways are often altered in SCLC and their inhibition can be **synthetic lethal** as SCLC cells have significant genomic instability.

Inhibition of proteins of the DDR pathway, such as PARP or CHK1, can enhance immune activation.

UPCOMING QUESTIONS

IO biomarker – Any role of DNA damage repair?

**MEDIOLA** Phase 2 study: durvalumab 1500 mg q4w + olaparib 300 mg bid in pre-treated patients with SCLC (N=20)

60% (n=12) had platinum resistant SCLC

Primary endpoint ORR ≥35% was **not met** (10.5%, n=2/19)

All responding tumours had a pre-treatment **inflamed phenotype**

Reprinted from Journal of Thoracic Oncology, 14(8), Thomas A, et al. Durvalumab in Combination with Olaparib in Patients with Relapsed SCLC: Results from a Phase II Study title of article / title of chapter, 1447-1457, Copyright 2019, with permission from Elsevier.
UPCOMING QUESTIONS

Other IO strategies

EORTC 1417 – REACTION randomised Phase 2 trial: after 2 cycles of EP and CR/PR, the addition of pembrolizumab (anti-PD-1) to EP for 4 cycles followed by maintenance with pembrolizumab (n=58) compared with 4 cycles of EP alone (n=61) did not improve PFS (primary endpoint), but did improve OS (crossover allowed, threshold for p-value <0.10)

UPCOMING QUESTIONS

Other IO strategies

Checkmate-451 randomised Phase 3 trial: after ≤4 cycles of EP and no progression, maintenance with either nivolumab (240 mg) (n=280) or nivolumab (1 mg/kg) + ipilimumab (3 mg/kg) (n=279) compared with placebo (n=275) did not improve OS (primary endpoint)

UPCOMING QUESTIONS
Optimal radiotherapy management of brain metastases

40–60% of patients with SCLC develop brain metastases
SRS is a feasible alternative to WBRT in select patients in NSCLC in terms of:
  - Overall survival
  - Improvement of cognitive outcomes
  - Quality of life

Few data available on the use of SRS as an alternative to WBRT in patients with brain metastases from SCLC

**UPCOMING QUESTIONS**

Management of brain metastases

**FIRE-SCLC study**: multicentre cohort study comparing SRS (n=710) and WBRT (n=219) in SCLC patients with brain metastases

**Shorter time to CNS progression** (9.0 months vs. NR)

**But similar OS** (6.5 vs. 5.2 months)
THE NEW IO PARADIGM IN ES-SCLC

First-line treatment

The new standard for first-line treatment is platinum-etoposide + anti-PD-L1 inhibition (either atezolizumab or durvalumab) x 4 cycles followed by maintenance with anti-PD-L1 inhibitor

Insufficient data about the role and safety of PCI and/or consolidation thoracic RT in combination with immunotherapy

If immunotherapy with immune checkpoint inhibitors can’t be given, the preferred first-line treatment remains platinum plus etoposide for 4–6 cycles
FIRST-LINE TREATMENT OF ES-SCLC: STATE OF THE ART

Extensive-stage SCLC (i.e. stage IV or stage III SCLC not eligible for treatment of curative intent)

- PS 0-1 no contraindication for IO
  - Carboplatin-etoposide-atezolizumab (4 cycles) and maintenance atezolizumab [I, A; MCBS 3]
  - Platinum-etoposide-durvalumab (4 cycles) and maintenance durvalumab [I, A; MCBS 3]

- PS 0-1 in case of contraindications for IO
  - Carboplatin-etoposide (4-6 cycles) [I, A]<sup>c</sup>
  - Carboplatin-oral topotecan [II, C]
  - Cisplatin-irinotecan [II, C]
  - Response PS 0-2
  - Consolidation thoracic RT is an option [II, C]
  - Age <75 years
  - PCI [II, B] or MRI surveillance [II, B]<sup>d</sup>

- PS 0-1 due to SCLC
  - Carboplatin-etoposide (4-6 cycles) [I, A]<sup>c</sup>
  - Carboplatin-gemcitabine (4-6 cycles) [II, C]<sup>a</sup>

- PS ≥2 due to comorbidities
  - BSC
  - Response PS 0-2

---

<sup>a</sup> ESMO-MCBS v1.1 score for new therapy/indication approved by the EMA or FDA. The score has been calculated by the ESMO-MCBS Working Group and validated by the ESMO Guidelines Committee (https://www.esmo.org/guidelines/esmo-mcbs/scale-evaluation-forms-v1.0-v1.1/scale-evaluation-forms-v1.1);
<sup>b</sup> Carboplatin may be replaced by cisplatin in patients <70 years of age or based on the toxicity profile [II, C];
<sup>c</sup> In patients with a PS of ≥2, consider ChT dose reduction and/or G-CSF prophylaxis;
<sup>d</sup> No brain metastasis on MRI before PCI.

Dingemans A-M C, et al. Ann Oncol 2021;32(7):839–53. © 2021 European Society for Medical Oncology. Published by Elsevier Ltd. All rights reserved.
REFRACTORY/RELAPSED ES-SCLC
# REFRACtORY/RELAPSED ES-SCLC

The role of immunotherapy

Clinical trials of immunotherapy agents in pretreated SCLC patients.

<table>
<thead>
<tr>
<th>Study</th>
<th>CheckMate-032</th>
<th>CheckMate-032</th>
<th>KEYNOTE-028</th>
<th>KEYNOTE-158</th>
<th>Durvalumab</th>
<th>Balti Study</th>
<th>IFCt-1603</th>
<th>CheckMate 451</th>
<th>CheckMate 451</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase</td>
<td>II</td>
<td>II</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>II</td>
<td>III</td>
<td>III</td>
<td>III</td>
</tr>
<tr>
<td>Nivo</td>
<td>Nivo 3 mg/kg q2w</td>
<td>Nivo 1 mg/kg + lpi 3 mg/kg q3w x 4 → Nivo 3 mg/kg q2w</td>
<td>Pembrolizumab 10 mg/kg q2w x 2 years</td>
<td>Pembrolizumab 200 mg q3w x 2 years</td>
<td>Durvalumab 10 mg/kg q2w x 12 months</td>
<td>Durvalumab 1500 mg + Tremel 75 mg q4w x 4 → Durvalumab 1500 mg q4w</td>
<td>Atezol 1200 mg q3w</td>
<td>Nivo/lipi 3 mg/kg q3w x 4 → Nivo 240 mg q2w x 2 years</td>
<td>Nivo 240 mg q2w x 2 years</td>
</tr>
<tr>
<td>Selection criteria</td>
<td>Biopsy/Tissue available for biomarkers</td>
<td>Biopsy/Tissue available for biomarkers</td>
<td>PD-L1 CPS &gt;1%</td>
<td>Available tissue for PD-L1 determination</td>
<td>ED-SCLC PS 0-1</td>
<td>Pt-refractory</td>
<td>PS 0-2</td>
<td>ED-SCLC Maintenance setting PS 0-1</td>
<td>ED-SCLC Maintenance setting PS 0-1</td>
</tr>
<tr>
<td>Primary Endpoint</td>
<td>ORR</td>
<td>Safety</td>
<td>ORR</td>
<td>Safety</td>
<td>ORR</td>
<td>ORR</td>
<td>ORR</td>
<td>ORR</td>
<td>ORR</td>
</tr>
<tr>
<td>No.</td>
<td>98</td>
<td>61</td>
<td>24</td>
<td>107</td>
<td>21</td>
<td>25</td>
<td>49</td>
<td>279</td>
<td>280</td>
</tr>
<tr>
<td>ORR, % (95%CI)</td>
<td>11%</td>
<td>25%</td>
<td>33%</td>
<td>18.7%</td>
<td>9.5%</td>
<td>9.5%</td>
<td>2.3%</td>
<td>45%</td>
<td>47%</td>
</tr>
<tr>
<td>mOS, months (95%CI)</td>
<td>4.1</td>
<td>7.9</td>
<td>9.7</td>
<td>9.1</td>
<td>4.8</td>
<td>6.0</td>
<td>9.5</td>
<td>9.2</td>
<td>10.4</td>
</tr>
<tr>
<td>OS12, % (95%CI)</td>
<td>30%</td>
<td>42%</td>
<td>37.7%</td>
<td>34%</td>
<td>27.6%</td>
<td>NA</td>
<td>42.5%</td>
<td>41%</td>
<td>44%</td>
</tr>
<tr>
<td>mPFS, months (95%)</td>
<td>1.4</td>
<td>2.6</td>
<td>(1.2–2.6)</td>
<td>1.9</td>
<td>(1.7–2.6)</td>
<td>2.0</td>
<td>(1.8–2.5)</td>
<td>1.7</td>
<td>1.9</td>
</tr>
<tr>
<td>PFS12, % (95%)</td>
<td>11%</td>
<td>19%</td>
<td>(9–32)</td>
<td>23.8%</td>
<td>16.9%</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>G ≥ 3 AE</td>
<td>14%</td>
<td>88%</td>
<td>8.3%</td>
<td>59%</td>
<td>0%</td>
<td>48%</td>
<td>NA</td>
<td>42%</td>
<td>52%</td>
</tr>
<tr>
<td>Predictive biomarker</td>
<td>TMB (ORR, mPFS, mOS)</td>
<td>TMB (ORR, mPFS, mOS)</td>
<td>PD-L1 CPS &gt;1% (ORR, mPFS, mOS)</td>
<td>PD-L1 CPS &gt;1% (ORR, mPFS, mOS)</td>
<td>PD-L1 on tumor and immune cells</td>
<td>PD-L1 on tumor and immune cells</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

ED-SCLC: extensive disease small cell lung cancer; LD-SCLC: limited disease small cell lung cancer; Nivo: Nivolumab; lpi: ipilimumab; Pemb: Pembrolizumab; Durv: Durvalumab; Trem: Tremelimumab; Atez: Atezolizumab; Pt: Platinum; PD-L1: programmed death ligand 1; ORR: objective response rate; NA: not available; NR: not reached; mOS: median overall survival; OS12: 12-month overall survival rate; mPFS: median progression-free survival; PFS12: 12-month progression-free survival rate; 95%CI: 95% confidence interval; G ≥ 3 AE: adverse events highest grade equal to or higher than 3.

# REFRACTORY/RELAPSED ES-SCLC

The role of immunotherapy – pembrolizumab

<table>
<thead>
<tr>
<th>Study</th>
<th>Phase</th>
<th>Regimen</th>
<th>Patients</th>
<th>ORR, %</th>
<th>DOR, mos</th>
<th>PFS, mos</th>
<th>OS, mos</th>
</tr>
</thead>
<tbody>
<tr>
<td>KEYNOTE-028</td>
<td>Ib</td>
<td>10 mg/kg</td>
<td>24 (PD-L1+)</td>
<td>33.3</td>
<td>19.4</td>
<td>1.9</td>
<td>9.7</td>
</tr>
<tr>
<td>KEYNOTE-158</td>
<td>II</td>
<td>200 mg</td>
<td>42 (PD-L1 +ve)</td>
<td>35.7</td>
<td>NR</td>
<td>2.1</td>
<td>14.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>50 (PD-L1 –ve)</td>
<td>6.0</td>
<td>1.9</td>
<td>7.7</td>
<td></td>
</tr>
</tbody>
</table>

REFRACTORY/RELAPSED ES-SCLC

The role of immunotherapy – pembrolizumab

Pooled analysis of patients KEYNOTE-028 (Phase 1b) and KEYNOTE-158 (Phase 2) who received 2 or more lines of previous treatment

ORR 19.3% (16/83) → median DoR: NR

Median PFS: 2.0 months

Median OS: 7.7 months

Best overall response per response evaluation criteria in solid tumours version 1.1 by independent review

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Evaluable patients$^a$ (N=83)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective response, n (%; 95% CI)</td>
<td>16 (19.3; 11.4, 29.4)</td>
</tr>
<tr>
<td>Best overall response, n (%)</td>
<td>-</td>
</tr>
<tr>
<td>CR</td>
<td>2 (2.4)</td>
</tr>
<tr>
<td>PR</td>
<td>14 (16.9)</td>
</tr>
<tr>
<td>SD</td>
<td>15 (18.1)</td>
</tr>
<tr>
<td>Non-CR/non-PD$^b$</td>
<td>1 (1.2)</td>
</tr>
<tr>
<td>PD</td>
<td>45 (54.2)</td>
</tr>
<tr>
<td>No assessment</td>
<td>6 (7.2)</td>
</tr>
<tr>
<td>Time to response,$^d$ median (range), mo</td>
<td>2.1 (1.7–4.1)</td>
</tr>
<tr>
<td>Duration of response,$^e$ median (range), mo</td>
<td>NR (4.1–35.8+)</td>
</tr>
<tr>
<td>Kaplan-Meier estimate of number of patients with extended duration of response,$^e$ n (%)</td>
<td>-</td>
</tr>
<tr>
<td>≥12 mo</td>
<td>10 (67.7)</td>
</tr>
<tr>
<td>≥18 mo</td>
<td>9 (60.9)</td>
</tr>
</tbody>
</table>

$^a$ Efficacy analyses included patients who received at least one dose of pembrolizumab and who had confirmed responses.

$^b$ Persistence of at least one target lesion.

$^c$ Includes patients without postbaseline assessment.

$^d$ Assessed in patients with a best objective response of confirmed CR or PR.

$^e$ From the product-limit (Kaplan-Meier) method for censored data.

$^f$ "+" indicates no progressive disease at time of last assessment.
FDA approves pembrolizumab for metastatic small cell lung cancer

On June 17, 2019, the Food and Drug Administration granted accelerated approval to pembrolizumab for patients with metastatic small cell lung cancer (SCLC) with disease progression on or after platinum-based chemotherapy and at least one other prior line of therapy.
REFRACTORY/RELAPSED ES-SCLC

The role of immunotherapy – pembrolizumab

In March 2021, Merck (NYSE:MRK), known as MSD outside the United States and Canada, announced in a press release on their website, the voluntary withdrawal of the U.S. indication for pembrolizumab for the treatment of patients with metastatic small cell lung cancer (SCLC) with disease progression on or after platinum-based chemotherapy and at least one other prior line of therapy. Merck stated the withdrawal of this indication was done in consultation with the U.S. Food and Drug Administration (FDA) and Merck is working to complete this process…

REFRACTORY/RELAPSED ES-SCLC
The role of immunotherapy – nivolumab

CheckMate 032 study design

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

Nonrandomised cohort

- Nivolumab 3 mg/kg IV q2w
  - Until disease progression or unacceptable toxicity

Randomised cohort

- Randomise 3:2

- Nivolumab 1 mg/kg + ipilimumab 3 mg/kg IV q3w for 4 cycles
- Nivolumab 3 mg/kg IV q2w until disease progression or unacceptable toxicity
- Nivolumab 3 mg/kg IV q2w
  - Until disease progression or unacceptable toxicity
- Nivolumab 1 mg/kg + ipilimumab 3 mg/kg IV q3w for 4 cycles
- Nivolumab 3 mg/kg IV q2w
  - Until disease progression or unacceptable toxicity

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

REFRACTORY/RELAPSED ES-SCLC

The role of immunotherapy – nivolumab

Randomised, open-label, Phase 3 trial of nivolumab (240 mg q2w) vs. topotecan or amrubicin in relapsed SCLC

OS (primary endpoint) was not improved:

- Nivolumab 7.5 months (5.6–9.2)
- Chemotherapy 8.4 months (7.0–10.0)
- HR: 0.86 (95% CI: 0.72, 1.04), p=0.11

REFRACTORY/RELAPSED ES-SCLC

The role of immunotherapy – nivolumab

Analysis of patients from CheckMate 032 treated with nivolumab monotherapy (3 mg/kg) as third or later line of treatment
ORR 11.9% (13/109) → median DoR: 17.9 months
Median PFS: 1.4 months
Median OS: 5.6 months

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&lt;sup&gt;a&lt;/sup&gt;</td>
<td>No. of patients</td>
</tr>
<tr>
<td></td>
<td>13</td>
</tr>
<tr>
<td>Best overall response, n (%)</td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td>PR</td>
<td>12 (11.0)</td>
</tr>
<tr>
<td>SD</td>
<td>25 (22.9)</td>
</tr>
<tr>
<td>PD</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>≥6 mo, n (%)</td>
<td>10 (76.9)</td>
</tr>
<tr>
<td>≥12 mo, n (%)</td>
<td>8 (61.5)</td>
</tr>
<tr>
<td>Median (95% CI), mo&lt;sup&gt;b&lt;/sup&gt;</td>
<td>17.9 (7.9, 42.0)</td>
</tr>
<tr>
<td>Range, mo</td>
<td>3.0–42.1</td>
</tr>
</tbody>
</table>

<sup>a</sup> Per the Response Evaluation Criteria in Solid Tumors version 1.1.

<sup>b</sup> Computed by using the Kaplan-Meier method.

FDA grants nivolumab accelerated approval for third-line treatment of metastatic small cell lung cancer

On August 16, 2018, the Food and Drug Administration granted accelerated approval to nivolumab for patients with metastatic small cell lung cancer (SCLC) with progression after platinum-based chemotherapy and at least one other line of therapy
REFRACTORY/RELAPSED ES-SCLC

The role of immunotherapy – nivolumab

In December 2020, Bristol Myers Squibb stated in their press release, that, in consultation with the FDA, they had made the decision to withdraw the indication of nivolumab for SCLC from the U.S. market. They had taken this action in accordance with the Agency’s standard procedures for evaluating accelerated approvals that had not met their post-marketing requirements and as part of a broader industry-wide evaluation.

REFRACTORY/RELAPSED ES-SCLC

Temozolomide and veliparib

Randomised, double-blind, Phase 2 randomised study of temozolomide (an alkylating agent) + veliparib (a PARPi) (n=55) / placebo (n=49) in patients with relapsed-sensitive or refractory SCLC

PFS at 4 months (primary endpoint) was not improved: TMZ/veliparib (36%) and TMZ/placebo (27%; p=0.19)

Explorative analysis: PFS (5.7 vs. 3.6 months; p=0.009) and OS (12.2 vs. 7.5 months; p=0.014) significantly prolonged in patients with SLFN11-positive tumours treated with TMZ/veliparib

REFRACTORY/RELAPSED ES-SCLC

Lurbinectedin

Single-arm, Phase 2 basket trial of lurbinectedin (3.2 mg/m²) q3w in second-line SCLC patients ECOG PS ≤2 without brain mets, until PD (NCT NCT02454972)

Positive if ORR (primary endpoint) ≥30%

**ORR: 35% (37/105)**

- CFI <90 days: 22% (10/45)
- CFI ≥90 days: 45% (27/60)

Median PFS: 3.5 months

- CFI <90 days: 2.6 months
- CFI ≥90 days: 4.6 months

Median OS: 9.3 months

- CFI <90 days: 5.0 months
- CFI ≥90 days: 11.9 months

ATLANTIS: Randomised controlled Phase 3 trial of lurbinectedin 2.0 mg/m² + doxorubicin vs. investigator’s choice chemotherapy (topotecan or CAV) in second-line SCLC failed to meet its primary endpoint of OS

Screening

- SCLC
- ≤1 prior CT lines (additional biologic lines allowed)
- ECOG PS ≤2
- Measurable/non-measurable per RECIST v1.1

Follow-up period

- Disease progression
- Investigator decision
- Unacceptable toxicity
- Withdrawal of consent
- Other

Follow-up

18 months after last patient randomisation

*Maximum 10 cycles of doxorubicin;
†Lurbinectedin continued as maintenance at 3.2 mg/m² Day 1 q3w.

<table>
<thead>
<tr>
<th>Stratified</th>
<th>N=600</th>
</tr>
</thead>
<tbody>
<tr>
<td>1:1 R</td>
<td></td>
</tr>
<tr>
<td>Doxorubicin 40 mg/m² D1 q3w†</td>
<td>Lurbinectedin 2 mg/m² D1 q3w†</td>
</tr>
<tr>
<td>Topotecan 1.5 mg/m² D1–5 q3w</td>
<td>C 1000 mg/m², A 45 mg/m², V 2 mg fixed dose combination, D1, q3w</td>
</tr>
<tr>
<td>OR (investigator’s choice)</td>
<td></td>
</tr>
</tbody>
</table>

REFRACTORY/RELAPSED ES-SCLC

Lurbinectedin

Phase 1b trial of lurbinectedin 2.0 mg/m² and irinotecan 75 mg/m² in 21 patients with SCLC

Promising activity (ORR 62%) but also high toxicity (grade ≥3 neutropenia 62% and diarrhoea 29%)

REFRACTORY/RELAPSED ES-SCLC
Targeting DLL3 and AMG757

Delta-like ligand 3 protein (DLL3)
- Expressed in about 80% of SCLC, but at very low levels in normal tissues
- Suppresses NOTCH signal, drives neuroendocrine tumourigenesis
- Rovalpituzumab Tesirine (Rova-T) is an antibody-drug conjugate against DLL3
- Rova-T failed to improve survival in two Phase 3 trials (NCT03061812, NCT03033511)

AMG757: half-life extended bispecific T-cell engager (BiTE) against DLL3

REFRACTORY/RELAPSED ES-SCLC

AMG757

First-in-human dose exploration Phase 1 trial of AMG757 (bispecific T-cell engager molecule targeting DLL3)

N=52 refractory/relapsed SCLC

Acceptable safety profile

- Grade ≥3 treatment-emergent AEs in 98% (n=51)
- Treatment-related AEs in 79% (n=41)
  - Most common: CRS 44% (n=23)
  - DLT: 2% (n=1) grade 5 pneumonitis

Signal of activity in SCLC

- ORR: 14% (n=7/51)
- Median DoR: 6.2 months

Recurrence SCLC (i.e. second-line therapy and beyond)

- Platinum-resistant relapse (<3 months TFI)
  - Refractory and/or PS >2:
    - BSC [II, C]
    - Lurbinectedin [III, C; MCBS 1]
  - PS 0-2:
    - Oral or i.v. topotecan [I, A]
    - Cyclofosfamide–doxorubicin–vincristine [II, B]
    - Lurbinectedin [III, C; MCBS 1]

- Platinum-sensitive relapse (≥3 months TFI)
  - Rechallenge with platinum-etoposide [II, B]
  - Oral or i.v. topotecan [I, A]
  - Cyclofosfamide–doxorubicin–vincristine [II, B]
FUTURE DIRECTIONS
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The identification of biomarkers to predict response from IO is of paramount importance in patients with SCLC.

The role of PCI and thoracic radiation therapy with immunotherapy needs to be carefully investigated.

SRS for the treatment of brain metastases could be useful to reduce toxicity of WBRT.

Integration of DDR inhibition into treatment strategies could prove useful, especially for potential synergism with IO.

Targeting DLL3 with Rova-T did not prove effective, but DLL3 remains an appealing target in SCLC (e.g. AMG757).

Future study designs could consider different treatment strategies depending on molecular SCLC groups.
FUTURE DIRECTIONS
The potential for personalised medical treatment of SCLC?

Modern molecular classification of SCLC may serve as a potential biomarker for targeted treatment in SCLC

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THANK YOU!