Treatment of Extensive Stage Small Cell Lung Cancer

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## DISCLOSURE OF INTEREST

<table>
<thead>
<tr>
<th>Company</th>
<th>Role/Support</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMS</td>
<td>Research support paid to institution</td>
</tr>
<tr>
<td>AstraZeneca</td>
<td>Research support paid to institution</td>
</tr>
<tr>
<td>AstraZeneca</td>
<td>Advisory role</td>
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<tr>
<td>MSD</td>
<td>Advisory role</td>
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<tr>
<td>Roche</td>
<td>Advisory role</td>
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<tr>
<td>BMS</td>
<td>Advisory role</td>
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<tr>
<td>Boehringer Ingelheim</td>
<td>Advisory role</td>
</tr>
</tbody>
</table>
Overview

• Introduction
• First line chemotherapy
  – Standard chemotherapy
  – Cisplatin vs. Carboplatin
  – Chemotherapy Dose
• Second line chemotherapy
  – Standard chemotherapy
  – Alternative options
• Future strategies
Diagnosis 2018

- Light microscopy
  - cells < 20 µm
  - Scarce cytoplasm
  - Fine gran. nuclei
  - >10 Mit./ 10 HPF

- Immunohistochemistry:
  - TTF1
  - Neuroendocr. markers

SCLC

NSCLC

Courtesy of Prof. Dirnhofer
Future Diagnosis?
Molecular subtypes of SCLC

• High ASCL1 (=ASH1) expression (classic subtype)
  • ASCL1 regulates NOTCH, RET, SOX2, NFIB
• High NEUROD1 (variant subtype)
  • MYC over expression
  • Increased sensitivity to aurora kinase inhibitors and chemotherapy
• Lack of either
Incidence (SEER Data)

- Smoking behaviour?
- New Subtypes (LCNEC)?

Govindan J Clin Oncol 2006
Cancer deaths: Rank 6!
Overview therapy SCLC 2018

- SCLC
  - 30%
  - 70%

- Curative
  - Concomittant chemoradiotherapy

- Palliative
  - Chemotherapy

- Prophylactic cranial irradiation (PCI) if response
  - PCI if response?
  - Thoracic irradiation if response?

Adapted from Früh Ann Oncol 2013

Log-rank P = 0.032 comparing LS 1986-1999 vs. LS 2000-2008
Log-rank P < 0.001 comparing ES 1986-1999 vs. ES 2000-2008

N=1032

Schabat Lung Cancer 2014
Number of „abstracts“

- AACR 2014: 15%
- ASCO 2014: <3%

NSCLC
SCLC
1L chemotherapy

ORR : 60-80%, (CR%: 0-15)
DCR: 85-90%
MOS: 7-11 months
2 Y survival: 1-10 %
Chemotherapy better than BSC?

• Two small RCTs $^{1,2}$
  – 88 men < 70 years with good PS
  – $\Rightarrow$ Ifosfamide improved OS by 2.8 months

• Impact of chemotherapy on
  – quality of life?
  – older or poor PS patients?
  – women?

$^1$Kokron Oesterr Z Onkol 1977, $^2$Kokron Onkol 1982
History of Chemotherapy in SCLC

- Cyclophosphamide combinations (CAV, CAE, CDE, CEV) (80-ies)
- Etoposide/Cisplatin (EP) = CAV but less toxic (90-ies)
- Metaanalysis (36 studies):  
  - EP better than other combinations (Mascaux, Lung Cancer 2000)
- Metaanalysis (19 studies)  
  - Cisplatin 4.4% survival benefit at 1 year (Pujol, Br J Cancer 2000)
History of Chemotherapy in SCLC

- 21 phase III studies 1972-1990
- Median OS in 70-ies: 7 months
- Median OS in 80-ies: 8.9 months

→ Etoposid/cisplatin
Irinotecan/Cis versus Etoposide/Cis in Asian Patients

<table>
<thead>
<tr>
<th></th>
<th>MS mos.</th>
<th>2 yr %</th>
</tr>
</thead>
<tbody>
<tr>
<td>PE</td>
<td>9.4</td>
<td>5.2</td>
</tr>
<tr>
<td>PIr</td>
<td>12.8</td>
<td>19.5</td>
</tr>
</tbody>
</table>

N=154 (Planned:230)

P=0.002

Cis + Irinotecan Randomized Studies in Non-Asians

Lara et al. JCO 2009
- Irinotecan 60 mg/m² d 1,8,15
- CDDP 60 mg/m² d 1
- Q4 weeks x 4 cycles

Hanna et al. JCO 2006
- Irino 65 mg/m² days 1,8
- P 30 mg/m² days 1,8
- Q3 weeks x 4 cycles

RANDOMIZED
N=671
N=331
NO difference!
Irinotecan/Platinum vs. Etoposide Platinum: Metaanalysis

Overall Survival

<table>
<thead>
<tr>
<th>Study</th>
<th>“HR” (95% CI)</th>
<th>% Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hermes (2008)</td>
<td>0.70 (0.53, 0.92)</td>
<td>14.6</td>
</tr>
<tr>
<td>Schmittel (2011)</td>
<td>0.75 (0.54, 1.03)</td>
<td>12.0</td>
</tr>
<tr>
<td>Subtotal</td>
<td>0.72 (0.58, 0.89)</td>
<td>26.6</td>
</tr>
<tr>
<td>DDP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Noda (2002)</td>
<td>0.60 (0.43, 0.83)</td>
<td>11.7</td>
</tr>
<tr>
<td>Hanna (2006)</td>
<td>0.96 (0.76, 1.20)</td>
<td>17.9</td>
</tr>
<tr>
<td>Lara (2009)</td>
<td>0.94 (0.81, 1.09)</td>
<td>25.1</td>
</tr>
<tr>
<td>Zatloukal (2010)</td>
<td>0.81 (0.65, 1.01)</td>
<td>18.6</td>
</tr>
<tr>
<td>Subtotal</td>
<td>0.84 (0.71, 1.00)</td>
<td>73.4</td>
</tr>
<tr>
<td>Overall</td>
<td>0.81 (0.71, 0.93)</td>
<td>100.0</td>
</tr>
</tbody>
</table>

favours irinotecan  favours etoposide

Shao J Thor Oncol 2012
CARBOPLATIN- OR CISPLATIN-BASED CHEMOTHERAPY IN FIRST-LINE TREATMENT OF SMALL-CELL LUNG CANCER: THE COCIS INDIVIDUAL PATIENT DATA META-ANALYSIS

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>Treatment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cisplatin arm</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cisplatin 30mg/m² dd 1-3 +</td>
<td>Cisplatin 50mg/m² dd 1-2+ Etoposide 100mg/m² dd 1-3</td>
<td>Cisplatin 25mg/m² dd 1-3 + Etoposide 80mg/m² dd 1-3</td>
<td>CDDP 60mg/m² d 1 + Etoposide 120mg/m² d 1, 100mg/m² bid pos dd 2+3</td>
</tr>
<tr>
<td></td>
<td>Adriamycin 40 mg/m² d 1 + Etoposide 100mg/m² dd 1-3</td>
<td>Followed (usually after 17-21 d) by</td>
<td>Every 3 weeks up to 6 x</td>
<td>Every 3-4 weeks, up to 4 x</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cyclo- phosphamide 1000mg/m² d 1 + Methotrexate 20mg/m² dd 14, 17 + Vincristine 1.4mg/m² d 1 + Lomustine 40mg/m² d 1</td>
<td>2-3 every 3 weeks, up to 6 x</td>
<td></td>
</tr>
<tr>
<td>Carboplatin arm</td>
<td>Carboplatin 80mg/m² d 1 + Teniposide 80mg/m² d 1 weekly</td>
<td>Carboplatin 300mg/m² d 1 + Etoposide 100mg/m³ dd 1-3</td>
<td>Carboplatin AUC 5 d 1 + Etoposide 80mg/m³ dd 1-3</td>
<td>Carboplatin AUC 5 d 1 + Gemcitabine 1200mg/m³ d 1</td>
</tr>
<tr>
<td></td>
<td>Every 3 weeks up to 6x</td>
<td>every 3-4 weeks, up to 4 x</td>
<td>8 every 3 weeks, up to 6 x</td>
<td></td>
</tr>
</tbody>
</table>

Rossi, Früh et al J Clin Oncol 2012
Overall Survival COCIS Meta-Analysis

Overall Survival

Hazard Ratio (95% CI)

- Skarlos (n=143): 0.91 (0.62 – 1.31)
- Joss (n=59): 2.18 (1.25 – 3.80)
- Okamato (n=220): 1.01 (0.77 - 1.34)
- Lee (n=241): 1.06 (0.81 - 1.38)
- Overall (n=663): 1.08 (0.92 – 1.27)

Favours Carboplatin  Favour Cisplatin

Rossi, Früh et al J Clin Oncol 2012
Outcome: overall survival

- Treatment: gender interaction p = 0.42
- Treatment: stage interaction p = 0.17
- Treatment: PS interaction p = 0.96
- Treatment: age interaction p = 0.27

Outcome: progression-free survival

- Treatment: gender interaction p = 0.57
- Treatment: stage interaction p = 0.57
- Treatment: PS interaction p = 0.67
- Treatment: age interaction p = 0.005

Rossi J Clin Oncol 2012
## Toxicity COCIS metaanalysis

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Patients with information</th>
<th>Any grade</th>
<th>Severe toxicity (grade ≥ 3)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Cis</td>
<td>Carbo</td>
</tr>
<tr>
<td>Leucopenia</td>
<td>655</td>
<td>74%</td>
<td>77%</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>458</td>
<td>86%</td>
<td>90%</td>
</tr>
<tr>
<td>Anemia</td>
<td>512</td>
<td>84%</td>
<td>89%</td>
</tr>
<tr>
<td>Platelets</td>
<td>512</td>
<td>39%</td>
<td>71%</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>655</td>
<td>72%</td>
<td>63%</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>655</td>
<td>25%</td>
<td>21%</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>458</td>
<td>19%</td>
<td>22%</td>
</tr>
<tr>
<td>Constipation</td>
<td>239</td>
<td>39%</td>
<td>51%</td>
</tr>
<tr>
<td>Neurotoxicity</td>
<td>416</td>
<td>19%</td>
<td>7%</td>
</tr>
<tr>
<td>Renal toxicity</td>
<td>415</td>
<td>25%</td>
<td>10%</td>
</tr>
<tr>
<td>Toxic deaths</td>
<td>655</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Rossi J Clin Oncol 2012
Cis vs. Carbo in SCLC?

- Outcomes are the same, but:
  - Differences in toxicity
  - Relatively few and small studies
  - Limited information on QoL
  - Insufficient information on LD-SCLC/younger pts
Chemotherapy dose

«I am still depressed. Are you sure you gave me the right dose Doc?»
Monotherapy vs. combination

Carboplatin/Etoposide (oral) vs. oral Etoposide [50 mg/day, days 1–14]

<table>
<thead>
<tr>
<th>Best response</th>
<th>Combination therapy (n = 33), %</th>
<th>Oral etoposide (n = 32), %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Partial</td>
<td>37</td>
<td>25</td>
</tr>
<tr>
<td>Stable disease</td>
<td>21</td>
<td>16</td>
</tr>
<tr>
<td><strong>Progression</strong></td>
<td><strong>15</strong></td>
<td><strong>47</strong></td>
</tr>
<tr>
<td>Nonassessable</td>
<td>15</td>
<td>12</td>
</tr>
</tbody>
</table>
Lower doses vs. full dose in > 70-year old, phase II study

Cisplatin 25 d1,2 + Eto 60 d1-3 vs. Cisplatin 40 d1,2 + Eto 100 d1-3 + G CSF

| Objective Tumor Response and Survival | AD Arm (n = 28) | | FD Arm (n = 67) | | Total (N = 95) |
|--------------------------------------|----------------|----------------|----------------|----------------|
|                                      | AD Arm | %     | FD Arm | %    | No. | %    | No. | %    |
| Complete remission                   | —      | —     | 9      | 13.4 | 9   | 9.5  |
| Partial remission                    | 11     | 39.3  | 37     | 55.2 | 48  | 50.5 |
| Stable disease                       | 11     | 39.3  | 6      | 9.9  | 17  | 17.9 |
| Progressive disease                  | 4      | 14.3  | 4      | 6.0  | 8   | 8.4  |
| Not assessable                       | 2      | 7.1   | 8      | 11.9 | 10  | 10.5 |
| Unknown                              | —      | —     | 3      | 4.5  | 3   | 3.1  |
| Overall response rate                | 11     | 39.3  | 46     | 68.7 | 57  | 60.0 |

95% CI, %
22.1 to 59.3
56.0 to 79.1
49.4 to 69.8

Overall survival
1 year, %
18
39
32
0
12
9
Median, weeks
31
41
38

Abbreviations: AD, attenuated-dose; FD, full-dose.
Failed strategies in 1L chemotherapy

- Longer therapies
- Maintenance therapy
- Alternating regimens
- Dose escalation +/- stem cell support
Recommendation 1L chemotherapy

- »4–6 cycles of etoposide plus cisplatin or carboplatin are recommended[I, B]»

- → NO CHANGE
2L chemotherapy

ORR : 7-24%
MOS: 3-9 months
<table>
<thead>
<tr>
<th>Drug approval SCLC vs. NSCLC since 2006</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SCLC</strong></td>
</tr>
<tr>
<td><strong>Approved</strong></td>
</tr>
<tr>
<td>Oral Topotecan</td>
</tr>
<tr>
<td>Amrubicin (Japan)</td>
</tr>
<tr>
<td><strong>Not approved (response in subgroups)</strong></td>
</tr>
<tr>
<td>Cabozantinib</td>
</tr>
<tr>
<td>• Rovalpituzumab Tesirine</td>
</tr>
<tr>
<td><strong>NSCLC</strong></td>
</tr>
<tr>
<td><strong>Approved</strong></td>
</tr>
<tr>
<td>— Chemotherapie</td>
</tr>
<tr>
<td>— Bevacizumab</td>
</tr>
<tr>
<td>— Gefitinib, Erlotinib</td>
</tr>
<tr>
<td>— Afatinib, Osimertinib</td>
</tr>
<tr>
<td>— Crizotinib</td>
</tr>
<tr>
<td>— Ceritinib, Alectinib</td>
</tr>
<tr>
<td>— Dabrafenib/Trametinib</td>
</tr>
<tr>
<td>— Nintedanib (EMEA)</td>
</tr>
<tr>
<td>— Ramucirumab (FDA, EMEA)</td>
</tr>
<tr>
<td>— Nivolumab</td>
</tr>
<tr>
<td>— Pembrolizumab</td>
</tr>
<tr>
<td>— Atezolizumab</td>
</tr>
<tr>
<td><strong>Not approved (response in subgroups)</strong></td>
</tr>
<tr>
<td>Cabozantinib</td>
</tr>
<tr>
<td>• Cabozantinib</td>
</tr>
<tr>
<td>• Foretinib</td>
</tr>
<tr>
<td>• Dabrafenib</td>
</tr>
<tr>
<td>• Vemurafenib</td>
</tr>
<tr>
<td>• Trametinib</td>
</tr>
<tr>
<td>• Dasatinib</td>
</tr>
<tr>
<td>• Neratinib</td>
</tr>
<tr>
<td>• Dasatinib</td>
</tr>
<tr>
<td>• Vandetanib, Sunitinib, etc...</td>
</tr>
</tbody>
</table>
Randomized Studies with Topotecan in 2L

- Topotecan versus CAV for the treatment of recurrent SCLC
  - “Sensitive” >60 days, 211 pts
    von Pawel et al J Clin Oncol 1999

- Phase III trial comparing supportive care alone with supportive care with oral topotecan in patients with relapsed SCLC
  - “Sensitive” >45-90+ days and resistant, 141 pts
    O’Brien et al, J Clin Oncol 2006

- Phase III study of oral compared with IV topotecan as second-line therapy in SCLC
  - “Sensitive” ≥ 90 day, 309 pts
    Eckardt et al J Clin Oncol 2007
Randomized Studies with ORAL Topotecan 2L

- 141 pts BSC oral Topo
  - OR: 7% ~ 50% sensitive
  - OS weeks: 14 ~ 26 p = 0.01
  - Toxic deaths: 6%

- 309 sensitive pts iv Topo oral Topo
  - OR: 22% ~ 18%
  - OS weeks: 35 ~ 33 NS
Sensitive versus refractory relapsed small cell lung cancer: A pooled analysis of topotecan second-line Phase II/III trials (n=631)

Prognostic groups:
- Treatment-free interval < or > 60 days
- Liver
- PS 2
- Low albumin
- Anemia
- Hyponatriema

Ardizzoni Eur J Cancer 2014
Platinum rechallenge (>90 days)

- Retrospective studies (n=142)\(^1,2\):
  - ORR 35-45 %, PFS 5.5 m

- Prospective study \(^3\):
  - Randomized phase II trial of amrubicin vs. re-challenge of platinum doublet (n=60 pts)
  - ORR (1. EP), 67% vs. 43%
  - PFS 5.4 months vs 5.1 months

\(^1\) Garassino Lung Cancer 2011
\(^2\) Gemestreti Clin Lung Cancer 2015
\(^3\) Inoue Lung Cancer 2015

In favour of amrubicin
Chemotherapies with single agent activity (phase II)

- Irinotecan ¹
- Paclitaxel ²,³
- Docetaxel ⁴
- Temozolomide ⁵,⁶
- Vinorelbine ⁷,⁸
- Oral etoposide ⁹,¹⁰
- Gemcitabine ¹¹,¹²
- Bendamustine ¹³

Higher Dose: 2\textsuperscript{nd} Line PEI (Phase III)

**Key patient inclusion criteria**
- SCLC
- Responded to first-line treatment
- Relapse/PD $\geq$ 90 days after treatment
- ECOG PS 0–2 ($n=180$)

**Primary endpoint**
- OS

**Secondary endpoints**
- PFS, response rate and safety

**Arm A**
- 5 cycles of cisplatin (25 mg/m\textsuperscript{2} d1/8) + etoposide (60 mg/m\textsuperscript{2} d1–3) + irinotecan (90 mg/m\textsuperscript{2} d8) ($n=90$)

**Arm B**
- 4 cycles of topotecan (1.0 mg/m\textsuperscript{2} d1–5, q3w) ($n=90$)

**Stratification**
- PS, localised/extensive disease, institution

Goto Lancet Oncol 2016
OS benefit of 2\textsuperscript{nd} Line PEI

- **Proportion of OS**
  - Months after randomisation
  - Topotecan (n=90)
    - Events: 82
    - MST (95\% CI): 12.5 months (10.8, 14.9)
    - One-sided p: 0.0079
    - HR (90\% CI): 0.67 (0.51, 0.88)
  - PEI (n=90)
    - Events: 72
    - MST (95\% CI): 18.2 months (15.7, 20.6)

Goto Lancet Oncol 2016
## Patients characteristics

<table>
<thead>
<tr>
<th></th>
<th>Topotecan (n=90)</th>
<th>Combination chemotherapy (n=90)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>64 (60-70, 44-75)</td>
<td>64 (61-68, 44-75)</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>78 (87%)</td>
<td>77 (86%)</td>
</tr>
<tr>
<td>Female</td>
<td>12 (13%)</td>
<td>13 (14%)</td>
</tr>
<tr>
<td><strong>Disease stage at entry</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Limited</td>
<td>25 (28%)</td>
<td>20 (22%)</td>
</tr>
<tr>
<td>Extensive</td>
<td>65 (72%)</td>
<td>70 (78%)</td>
</tr>
<tr>
<td><strong>ECOG performance status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>40 (44%)</td>
<td>52 (58%)</td>
</tr>
<tr>
<td>1</td>
<td>47 (52%)</td>
<td>36 (40%)</td>
</tr>
<tr>
<td>2</td>
<td>3 (3%)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td><strong>Time from first-line chemotherapy to relapse or progression (days)</strong></td>
<td>148 (113–228; 92–2318)</td>
<td>181 (120–285; 91–1746)</td>
</tr>
<tr>
<td><strong>First line chemotherapy (including patient in more than one category)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cisplatin or carboplatin plus etoposide</td>
<td>49 (54%)</td>
<td>50 (56%)</td>
</tr>
<tr>
<td>Cisplatin or carboplatin plus irinotecan</td>
<td>33 (34%)</td>
<td>32 (36%)</td>
</tr>
<tr>
<td>Cisplatin or carboplatin plus amrubicin</td>
<td>15 (17%)</td>
<td>17 (19%)</td>
</tr>
<tr>
<td><strong>First-line thoracic radiotherapy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>38 (42%)</td>
<td>42 (47%)</td>
</tr>
<tr>
<td>No</td>
<td>52 (58%)</td>
<td>48 (53%)</td>
</tr>
<tr>
<td><strong>Response to first-line treatment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>20 (22%)</td>
<td>23 (26%)</td>
</tr>
<tr>
<td>Partial response</td>
<td>70 (78%)</td>
<td>67 (74%)</td>
</tr>
</tbody>
</table>

Goto Lancet Oncol 2016
PEI: Too much?

- Hematol. grade 3-4 tox.
  - >80% neutropenia/anemia,
  - >40% tc-penia
  - >30% febrile neutropenie (1 pt grade 5)
- 50% dose reduction
- NO QoL
- Comparator arm?
- Western population?

Goto Lancet Oncol 2016
Recommendation 2 L

• „For refractory patients and resistant patients with early relapse (<6 weeks), participation in a clinical trial or best supportive care is recommended [II, C]“
  • discard „refractory category“, resistant: <60 days
Future Strategies
Novel therapies

PARPi in *SLFN11* expression (Lok CCR 2017)

WEE1: Gatekeeper TKI og G2/M (Dobbelstein Nat Rev Drug Discov 2015)
Aurora Kinase in MYC Ampl. (Mollaoglu Cancer Cell 2017)

Regulates chromatin modelling, associated with suppression of *SLFN11* (Gardner Cancer Cell 2017)
Immunotherapy „Biomarker“

- Smoking \(^1\text{-}^3\)
- Mutational load \(^4,^5\)
- CD8+ TILs \(^6\)
- PD-L1 Expression \(^1\text{-}^3,^7,^8\)
- Low expression of MHC class I antigens \(^9\)

\(^1\)Garon NEJM 2015, \(^2\)Gettinger JCO 2015, \(^3\)Herbst Nature 2014, \(^4\)Rizvi Science 2015, \\
\(^5\)Capesato Oncotarget 2015, \(^6\)Tumeh Nature 2014, \(^7\)Brahmer NEJM 2012, \(^8\)Sharma Science 2015, \\
\(^9\)Blank Science 2016
Mutation rate

Top Genes: P53 und Rb1
Targets? Driver?

Pfeifer Nat Genet 2012
Patients selection in SCLC?
Roalpituzumab Teresin

Confirmed response rate
Overall: 11/60 (18%)
DLL3-high: 10/26 (38%)

Mutational load?

<table>
<thead>
<tr>
<th>TMB Level</th>
<th>Median PFS (95% CI), mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low TMB</td>
<td>1.5 (1.3, 2.7)</td>
</tr>
<tr>
<td>Med TMB</td>
<td>1.3 (1.2, 2.1)</td>
</tr>
<tr>
<td>High TMB</td>
<td>7.8 (1.8, 10.7)</td>
</tr>
</tbody>
</table>

1-y PFS:
- Low TMB: 30.0%
- Med TMB: 8.0%
- High TMB: 6.2%

Rudin Lancet Oncol 2017
Antonia WCLC 2017
MERU Study Treatment Design  Phase III (maintenance)

N=740
(~275 sites, ~41 countries)

Extensive SCLC with clinical benefit following first-line platinum based chemotherapy

Rova-T 0.3 mg/kg IV on D1 q6 wk omitting every 3rd cycle + dexamethasone 8 mg BID, oral, on D-1, 1, 2

Placebo IV on D1 q6 wk omitting every 3rd cycle + placebo BID oral on D-1, 1, 2

1:1 randomization
TAHOE Treatment Design  Phase III (2nd line)
Phase III Studies Nivo and Nivo/Ipi

Checkmate 331 (2nd line)

- Relapsed Small Cell Lung Cancer
  - Prior platinum-based first-line chemotherapy
  - Tumor tissue available and received by the central laboratory

Randomize 1:1
- Stratify by:
  - Response to platinum-based chemotherapy
  - Brain metastases

Arm A
- n=240
- Nivolumab 240 mg IV on Day 1 of a 14-day cycle
- Treat until RECIST 1.1 defined progression or unacceptable toxicity

Arm B
- n=240
- Topotecan (except subjects enrolled in Japan): 1.5 mg/m² administered as 30-minute IV infusion once daily on Days 1 to 5 of a 21-day cycle.
- Anastrozole (only for subjects enrolled in Japan): 40 mg/m² administered as 5-minute IV infusion once daily on Days 1 to 3 of a 21-day cycle.

Follow-up
- Visit 1 and Visit 2
- Survival Follow-up

Checkmate 451 (maintenance)

- Estimated: March 2018
- Estimated: Sep 2018
Phase 3 1 L immunotherapy studies

– KEYNOTE-604
  • pembrolizumab plus etoposide/platinum vs. chemotherapy alone (Jan 2019)

– IMpower133
  • atezolizumab with carboplatin and etoposide to chemotherapy alone (June 2019)

– CASPIAN (3-arms)
  • durvalumab ± tremelimumab plus platinum-based CT followed by durvalumab ± tremelimumab maintenance therapy versus chemotherapy alone (March 2019)
Current Therapies in Metastatic SCLC (2018)

- **Platinum-based combination in 1 L**
  - All similar survival rates (EP preferred)
  - Differences in toxicity
  - Cisplatin or carboplatin
  - Dose matters

- **Topotecan in 2 L**
  - CAV is alternative

- **Immunotherapy/ ROVA-T promising**
  - Ongoing phase III studies

- **Role of Radiotherapy**
  - Symptomatic treatment
  - Prophylactic cranial irradiation/ consolidative chest RT?
Prevention is the best strategy

Thank you for your kind attention!