Treatment of Extensive Stage Small Cell Lung Cancer

Martin Früh
Oncology und Hematology Cantonal Hospital St. Gallen
Incidence (SEER Data)

- Smoking behaviour?
- New Subtypes (LCNEC)?
Cancer deaths: Rank 6!
Overview

• First line chemotherapy
• Second line chemotherapy
• Radiotherapy in ES-SCLC?
• Future strategies
Treatment algorithm in SCLC

Small-cell lung cancer

- **30%** Curative
  - T1-4 N2,3 M0
  - T1-4 N1-3 M1a,b solitary and not confirmed

- **70%** Palliative
  - T1-4 N1-3 M1a,b multiple or confirmed
  - T1-2 N0,1 M0

- Concomitant chemoradiotherapy
- Concomitant chemoradiotherapy*
- Surgery plus adjuvant chemotherapy**
- Chemotherapy

- Prophylactic cranial irradiation if response***

*If no confirmation of solitary metastasis is obtained, radiotherapy may be added after first response evaluation and is omitted in case of obvious metastatic involvement

** concomitant chemoradiotherapy as an alternative option

*** or stable disease in case of localised disease

Adapted from Früh, Ann Oncol 2013
1L chemotherapy

ORR : 60-80%, (CR%:  0-15)
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
  – > 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

cis./ amrubicin vs. cis./etoposide
11.8 vs. 10.3 m (HR 0.81, P= ns)

Sun BMC 2016
Iriniotecan/Cis versus Etoposide/Cis in Asian Patients

Overall survival (% of patients)

<table>
<thead>
<tr>
<th>Treatment</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 60mg/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

Etoposide 100 mg/m² d 1,2,3
CDDP 80mg/m² d 1
Q3 weeks x 4 cycles

E 120 mg/m² days 1 to 3
P 60 mg/m² day 1
Q 3 weeks x 4 cycles

NO difference!
Reasons for differential results?

- Pharmacogenetic differences?
- Over estimation of therapeutic effect in Noda study?
- Different doses?
Irinotecan/Platinum vs. Etoposide Platinum: Metaanalysis

Overall Survival

<table>
<thead>
<tr>
<th>Study</th>
<th>&quot;HR&quot; (95% CI)</th>
<th>% Weight</th>
</tr>
</thead>
<tbody>
<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
Number of „Abstracts“

AACR 2014:
- NSCLC: 250
- SCLC: 30
- 15%

ASCO 2014:
- NSCLC: 500
- SCLC: 10
- <3%
Anti-Angiogenesis Plus Chemotherapy in SCLC?

OS: 94%, MOS: 14.2 M, PFS24: 41% (n=17)

2 cycles carboplatin/paclitaxel /ASA404
Sunitinib maintenance: CALGB 30504 (Alliance) Phase II

Median survival:
- Sunitinib: 3.7 months
- Placebo: 2.1 months

Stratified χ² test:
- One-sided P = .022
- HR (placebo vs. sunitinib): 1.62
- 95% CI: 1.02 to 2.60

No. at risk:
- Sunitinib: 44 24 7 2 1
- Placebo: 41 13 4 3 1

Ready J Clin Oncol 2015
Italian, Multicenter, Phase III, Randomized Study of Cisplatin Plus Etoposide With or Without Bevacizumab as First-Line Treatment in Extensive-Disease Small-Cell Lung Cancer: The GOIRC-AIFA FARM6PMFJM Trial

No OS benefit (1-y OS: 25% v. 37% (HR 0.78; P = .113))

→ OS benefit in subgroup with maintenance

Tiseo J Clin Oncol 2017
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>Progression</td>
<td>15</td>
<td>47</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

<table>
<thead>
<tr>
<th></th>
<th>AD Arm (n = 28)</th>
<th></th>
<th>FD Arm (n = 67)</th>
<th></th>
<th>Total (N = 95)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
<td>%</td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>Complete remission</td>
<td>—</td>
<td>—</td>
<td>9</td>
<td>13.4</td>
<td>9</td>
<td>9.5</td>
</tr>
<tr>
<td>Partial remission</td>
<td>11</td>
<td>39.3</td>
<td>37</td>
<td>55.2</td>
<td>48</td>
<td>50.5</td>
</tr>
<tr>
<td>Stable disease</td>
<td>11</td>
<td>39.3</td>
<td>6</td>
<td>8.9</td>
<td>17</td>
<td>17.9</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>4</td>
<td>14.3</td>
<td>4</td>
<td>6.0</td>
<td>8</td>
<td>8.4</td>
</tr>
<tr>
<td>Not assessable</td>
<td>2</td>
<td>7.1</td>
<td>8</td>
<td>11.9</td>
<td>10</td>
<td>10.5</td>
</tr>
<tr>
<td>Unknown</td>
<td>—</td>
<td>—</td>
<td>3</td>
<td>4.5</td>
<td>3</td>
<td>3.1</td>
</tr>
<tr>
<td>Overall response rate</td>
<td>11</td>
<td>39.3</td>
<td>46</td>
<td>68.7</td>
<td>57</td>
<td>60.0</td>
</tr>
<tr>
<td>95% CI, %</td>
<td>22.1 to 59.3</td>
<td></td>
<td>56.0 to 79.1</td>
<td></td>
<td>49.4 to 69.8</td>
<td></td>
</tr>
<tr>
<td>Overall survival</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 year, %</td>
<td>18</td>
<td>0</td>
<td>39</td>
<td>12</td>
<td>32</td>
<td>9</td>
</tr>
<tr>
<td>2 year, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median, weeks</td>
<td>31</td>
<td></td>
<td>41</td>
<td></td>
<td>38</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: AD, attenuated-dose; FD, full-dose.

Ardizzoni et al J Clin Oncol 2005
Cisplatin or Carboplatin-based?

Carboplatin/Eto vs Cisplatin/Eto in >70 y or < 70 y + PS3 Phase III Study

<table>
<thead>
<tr>
<th>Therapeutic response (WHO)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CE</strong></td>
</tr>
<tr>
<td>CR</td>
</tr>
<tr>
<td>PR</td>
</tr>
<tr>
<td>NC</td>
</tr>
<tr>
<td>PD</td>
</tr>
<tr>
<td>NE</td>
</tr>
<tr>
<td><strong>Total</strong></td>
</tr>
</tbody>
</table>

Response rate: 73% (CE) vs 73% (SPE)
95% CI: 63–81% (CE) vs 63–81% (SPE)

No difference!

MST

<table>
<thead>
<tr>
<th></th>
<th>1-year</th>
<th>2-year</th>
</tr>
</thead>
<tbody>
<tr>
<td>CE</td>
<td>10.6 months</td>
<td>81%</td>
</tr>
<tr>
<td>SPE</td>
<td>9.9 months</td>
<td>85%</td>
</tr>
</tbody>
</table>

P = 0.54 (one-sided, log-rank test)

Okamoto et al BJC 2007
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>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin arm</td>
<td>Cisplatin 30mg/m² dd 1-3 + Adriamycin 40 mg/m² d 1 + Etoposide 100mg/m² dd 1-3 Followed (usually after 17-21 d) by Cyclophosphamide 1000mg/m² dd 1 + Methotrexate 20mg/m² dd 14, 17 + Vincristine 1.4mg/m² d 1 + Lomustine 40mg/m² dd 1</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>Carboplatin arm</td>
<td>Carboplatin 80mg/m² d 1 + Teniposide 80mg/m² d 1 weekly</td>
<td>Carboplatin 300mg/m² d 1 + Etoposide 100mg/m² dd 1-3</td>
<td>Carboplatin AUC 5 d 1 + Etoposide 80mg/m² dd 1-3</td>
<td>Carboplatin AUC 5 d 1+ Gemcitabine 1200mg/m² d 1</td>
</tr>
</tbody>
</table>

Rossi J Clin Oncol 2012
Overall Survival COCIS Meta-Analysis

Overall Survival

Skarlos (n=143) 0.91 (0.62 – 1.31)
Joss (n=59) 2.18 (1.25 – 3.80)
Okamoto (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)

Hazard Ratio (95% CI)

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

**Gender**
- Males (n=516)
- Females (n=147)

**Stage**
- Limited (n=210)
- Extensive (n=453)

**Performance status**
- PS 0 – 1 (n=476)
- PS 2 – 3 (n=187)

**Age**
- < 70 (n=386)
- > 70 (n=277)

Overall

Favours carboplatin

Hazard Ratio of death

Favours cisplatin

- 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

**Gender**
- Males (n=516)
- Females (n=147)

**Stage**
- Limited (n=210)
- Extensive (n=453)

**Performance status**
- PS 0 – 1 (n=476)
- PS 2 – 3 (n=187)

**Age**
- < 70 (n=386)
- > 70 (n=277)

Overall

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

**Cytopenia!**
Cisplatin vs. Carboplatin in NSCLC

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>&lt;65 yrs.</td>
<td>2037</td>
</tr>
<tr>
<td>≥65 yrs.</td>
<td>930</td>
</tr>
<tr>
<td>Stage</td>
<td></td>
</tr>
<tr>
<td>IIIB</td>
<td>941</td>
</tr>
<tr>
<td>IV</td>
<td>2025</td>
</tr>
<tr>
<td>PS</td>
<td></td>
</tr>
<tr>
<td>0 - 1</td>
<td>2558</td>
</tr>
<tr>
<td>2</td>
<td>401</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
</tr>
<tr>
<td>Squamous</td>
<td>1139</td>
</tr>
<tr>
<td>Non-squamous</td>
<td>1821</td>
</tr>
<tr>
<td>Drugs generation</td>
<td></td>
</tr>
<tr>
<td>Second-</td>
<td>638</td>
</tr>
<tr>
<td>Third-</td>
<td>2330</td>
</tr>
<tr>
<td>Combined</td>
<td></td>
</tr>
</tbody>
</table>

9 trials, ≈ 3000 pts

Ardizzoni J Natl Cancer Inst 2007
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
Failed strategies in 1L chemotherapy

- Longer therapies
- Maintenance therapy
- Alternating regimens
- Dose escalation +/- stem cell support
2L chemotherapy
Drug approval **SCLC** vs. **NSCLC** since 2006

**SCLC**
- **Approved**
  - Oral Topotecan
  - Amrubicin (Japan)

- **Not approved (response in subgroups)**
  - Rovalpituzumab Tesirine

**NSCLC**
- **Approved**
  - Pemetrexed
  - Bevacizumab
  - Gefitinib
  - Erlotinib
  - Afatinib
  - Osimertinib
  - Crizotinib
  - Ceritinib
  - Alectinib
  - Nintedanib
  - Ramucirumab Nivolumab
  - Keytruda
  - Atezolizumab (FDA)

- **Not approved (response in subgroups)**
  - Cabozantinib
  - Foretinib
  - Dabrafenib
  - Vemurafenib
  - Trametinib
  - Dasatinib
  - Neratinib
  - Dacomitinib
  - Trastuzumab
  - Cabozantinib
  - Vandetanib etc....
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

<table>
<thead>
<tr>
<th>141 pts</th>
<th>BSC</th>
<th>oral Topo</th>
</tr>
</thead>
<tbody>
<tr>
<td>OR</td>
<td>7%</td>
<td>~ 50% sensitive</td>
</tr>
<tr>
<td>OS weeks</td>
<td>14</td>
<td>26 p =0.01</td>
</tr>
<tr>
<td>Toxic deaths</td>
<td>6%</td>
<td></td>
</tr>
</tbody>
</table>

*O`Brien et al J Clin Oncol 2006*

<table>
<thead>
<tr>
<th>309 sensitive pts</th>
<th>iv Topo</th>
<th>oral Topo</th>
</tr>
</thead>
<tbody>
<tr>
<td>OR</td>
<td>22%</td>
<td>18%</td>
</tr>
<tr>
<td>OS weeks</td>
<td>35</td>
<td>33 NS</td>
</tr>
</tbody>
</table>

*Eckardt et al J Clin Oncol 2007*
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 < 60 days
- Liver
- PS 2
- Low albumin
- Anemia
- Hyponatriemia
Platinum rechallenge (>90 days)

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

- Prospective study\textsuperscript{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

\textsuperscript{1} Garassino Lung Cancer 2011
\textsuperscript{2} Gemestreti Clin Lung Cancer 2015
\textsuperscript{3} Inoue Lung Cancer 2015
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: 2nd Line PEI (Phase III)

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

**Primary endpoint**
- OS

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

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

**Arm A**
- 5 cycles of cisplatin (25 mg/m² d1/8) + etoposide (60 mg/m² d1–3) + irinotecan (90 mg/m² d8) (n=90)

**Arm B**
- 4 cycles of topotecan (1.0 mg/m² d1–5, q3w) (n=90)

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

- **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
## Patient 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>31 (34%)</td>
<td>32 (36%)</td>
</tr>
<tr>
<td>Cisplatin or carboplatin plus ametantrone</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>
PEI: Too much?

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

Goto Lancet Oncol 2016
Prophylactic Cranial Irradation (PCI) in ES-SCLC

Stratification: - Institution  
- Performance Score

Chemotherapy (4-6 cycles) → Any Response

No Response

Random

PCI
20 – 30 Gy in 5-12 fractions

No PCI

<5 weeks

4 -6 weeks

N=286

PCI in ES-SCLC – Overall survival

Med OS : 6.7 vs. 5.4
1 J : 27.1% vs. 13.3%
HR: 0.68 (0.52-0.88) p=0.003

PCI reduces Risk of BMet , HR 0.27 p<0.0001 (Prim. EP)
Risk reduction of symptom. BMet after 1 Y: 15% vs. 40%

CAVE: Negative effect on QoL (alopecia, fatigue)

Which patients have increased BM risk?

<table>
<thead>
<tr>
<th>Variable</th>
<th>Estimated Coefficient (95% CI)</th>
<th>Odds Ratio (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemotherapy response</td>
<td>1.70 (0.07, 3.33)</td>
<td>5.49 (1.08, 27.91)</td>
<td>0.04a</td>
</tr>
<tr>
<td>Weight loss (kg)</td>
<td>-0.38 (-0.72, -0.03)</td>
<td>0.69 (0.49, 0.97)</td>
<td>0.03a</td>
</tr>
</tbody>
</table>

20.1% symptomatic brain metastases, but:
-older (68 y, including PS3 and 4, SD,PD)

Greenspoon J Thor Oncol 2011
Toxicity of whole brain irradiation (solid tumors):
NCCTG N0574 (Alliance): A phase III randomized trial of whole brain radiation therapy in addition to radiosurgery in patients with 1 to 3 brain metastases –

Cognitive function at 3 months

<table>
<thead>
<tr>
<th>Change from baseline&lt;sup&gt;b&lt;/sup&gt;</th>
<th>No. (% of Participants)</th>
<th>Mean Difference, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SRS Alone (n = 63)</td>
<td>SRS Plus WBRT (n = 48)</td>
</tr>
<tr>
<td>HVLTR - Immediate recall</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deterioration</td>
<td>5 (8.2)</td>
<td>14 (30.4)</td>
</tr>
<tr>
<td>No deterioration</td>
<td>56 (91.8)</td>
<td>32 (69.6)</td>
</tr>
<tr>
<td>Delayed recall</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deterioration</td>
<td>12 (19.7)</td>
<td>24 (51.1)</td>
</tr>
<tr>
<td>No deterioration</td>
<td>49 (80.3)</td>
<td>23 (48.9)</td>
</tr>
<tr>
<td>Recognition</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deterioration</td>
<td>14 (22.6)</td>
<td>19 (40.4)</td>
</tr>
<tr>
<td>No deterioration</td>
<td>48 (77.4)</td>
<td>28 (59.6)</td>
</tr>
<tr>
<td>TMT-A time to complete</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deterioration</td>
<td>10 (16.7)</td>
<td>14 (30.4)</td>
</tr>
<tr>
<td>No deterioration</td>
<td>50 (83.3)</td>
<td>32 (69.6)</td>
</tr>
<tr>
<td>TMT-B time to complete</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deterioration</td>
<td>11 (19.0)</td>
<td>16 (37.2)</td>
</tr>
<tr>
<td>No deterioration</td>
<td>47 (81.0)</td>
<td>27 (62.8)</td>
</tr>
<tr>
<td>COWAT total</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deterioration</td>
<td>1 (1.9)</td>
<td>8 (18.6)</td>
</tr>
<tr>
<td>No deterioration</td>
<td>52 (98.1)</td>
<td>35 (81.4)</td>
</tr>
<tr>
<td>GPS total seconds</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deterioration</td>
<td>17 (29.3)</td>
<td>21 (47.7)</td>
</tr>
<tr>
<td>No deterioration</td>
<td>41 (70.7)</td>
<td>23 (52.3)</td>
</tr>
<tr>
<td>Outcome for cognitive progression at 3 mo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stable</td>
<td>23 (36.5)</td>
<td>4 (8.3)</td>
</tr>
<tr>
<td>Progression</td>
<td>40 (63.5)</td>
<td>44 (91.7)</td>
</tr>
</tbody>
</table>
Japanese phase III trial of PCI in ES-SCLC

Key patient inclusion criteria
- Extensive-disease SCLC
- Any response to first-line platinum doublet CT
- No BM by MRI assessment
- ECOG PS 0–2 (n=163)

Arm A: Prophylactic cranial irradiation (n=84)
Arm B: Observation alone (n=79)

Stratification
- Age, ECOG PS, response, institution

Primary endpoint
- OS

• cMRI before start, then every 3 months
Is monitoring better (MRIs?)?

<table>
<thead>
<tr>
<th></th>
<th>Arm A: PCI n=84</th>
<th>Arm B: no PCI n=79</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of OS events</td>
<td>61</td>
<td>50</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>1.38 (0.95, 2.02)</td>
<td></td>
</tr>
<tr>
<td>Median OS (95% CI), mo</td>
<td>10.1 (8.5, 13.2)</td>
<td>15.1 (10.2, 18.7)</td>
</tr>
</tbody>
</table>

Problems: -NOT published
-NO QoL

Stratified log-rank test: p=0.091 (2-sided)
Thoracic irradiation in ES-SCLC?

CREST

ES SCLC without brain metastases or pleural involvement and response to 4-6 x chemotherapy
N=483

1. EP: OS

PCI + TRT (30 Gy)

PCI only
Thoracic Irradiation in ESCLC

Overall survival at:
1 year: 33% vs. 28% (p=0.066)
18 months: 16% vs. 9% (p=0.03)
2 years: 13% vs. 3% (p=0.004)
Post hoc analysis

With residual intrathoracic disease
Overall result 202/215 212/219 0.70 (0.57 – 0.85)
P<0.001

Without residual intrathoracic disease
Overall result 29/32 27/29 1.00 (0.59 – 1.70)
N.S.
Future Strategies
Immunotherapy „Biomarker“

- Smoking 1-3
- Mutational load 4,5
- CD8+ TILs 6
- PD-L1 Expression 1-3,7,8

Mutation rate

Top Genes: P53 und Rb1
Targets? Driver?

Pfeifer Nat Genet 2012
Phase III Randomized Trial of **Ipilimumab** Plus Etoposide and Platinum Versus Placebo Plus Etoposide and Platinum in Extensive-Stage Small-Cell Lung Cancer

Anti-CTLA-4 AB plus chemotherapy does NOT work
Pembrolizumab in Patients With Extensive-Stage Small Cell Lung Cancer: Updated Survival Results From KEYNOTE-028

Patrick A. Ott,¹ Enriqueta Felip,² Sandrine Hiret,³ Dong-Wan Kim,⁴ Anne Morosky,⁵ Sanatan Saraf,⁵ Bilal Piperdi,⁵ Janice M. Mehnert⁶

¹Dana-Farber Cancer Institute, Boston, MA, USA; ²Vall d’Hebron Institute of Oncology, Barcelona, Spain; ³ICO site René Gauducheau, Nantes, France; ⁴Seoul National University Hospital, Seoul, Republic of Korea; ⁵Merck & Co., Inc., Kenilworth, NJ, USA; ⁶Rutgers Cancer Institute of New Jersey, New Brunswick, NJ, USA
## Antitumor Activity
(RECIST v1.1, investigator review, confirmed)

<table>
<thead>
<tr>
<th>Best Overall Response</th>
<th>n</th>
<th>%</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>1</td>
<td>4.2</td>
<td>0.1-21.1</td>
</tr>
<tr>
<td>Partial response</td>
<td>7</td>
<td>29.2</td>
<td>12.6-51.1</td>
</tr>
<tr>
<td>Stable disease</td>
<td>1</td>
<td>4.2</td>
<td>0.1-21.1</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>13</td>
<td>54.2</td>
<td>32.8-74.4</td>
</tr>
<tr>
<td>No assessment(^a)</td>
<td>2</td>
<td>8.3</td>
<td>1.0-27.0</td>
</tr>
</tbody>
</table>

**Duration of response, median (range), months\(^b\)**: 19.4 (3.6+ to 20.0+)

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

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

---

\(^a\)For "No Assessment," the patient discontinued before postbaseline assessment.

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

Data cutoff date: June 20, 2018.

---

all PD-L1 positive, 10mg/kg Pembro q2w, 88% >2L!
Treatment Duration and Duration of Response (RECIST v1.1, investigator review)

- Treatment discontinuation
- Progressive disease
- Stable disease
- Partial response
- Complete response
- Treatment ongoing

N=34

MOS 9.7 months

Duration of Treatment, Weeks

The length of each bar corresponds to the duration of treatment. Response symbols represent time to first report and not best overall. Data cutoff date: June 23, 2016.
Pseudoprogression with Atezolizumab

Initial

After 6 weeks

PR for 9 months
Nivolumab +/- Ipilimumab in Recurrent SCLC: CheckMate 032 Study Design

SCLC (N = 216) with progressive disease after ≥1 prior line of therapy, including a first-line platinum-based regimen (unselected by PD-L1 expression)

- Nivolumab 3 mg/kg IV Q2W (n = 98)
- Nivolumab 1 mg/kg + Ipilimumab 3 mg/kg IV Q3W for 4 cycles (n = 61)
- Nivolumab 3 mg/kg + Ipilimumab 1 mg/kg IV Q3W for 4 cycles (n = 54)

Nivolumab 3 mg/kg IV Q2W
### Nivolumab +/- Ipilimumab in Recurrent SCLC: Summary of Response

<table>
<thead>
<tr>
<th></th>
<th>Nivolumab-3 (n = 98)</th>
<th>Nivolumab-1 + Ipilimumab-3 (n = 61)</th>
<th>Nivolumab-3 + Ipilimumab-1 (n = 54)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Objective response rate, % (n/N)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>10 (10/98)</td>
<td>23 (14/61)</td>
<td>19 (10/54)</td>
</tr>
<tr>
<td>Platinum-sensitive(^a)</td>
<td>11 (6/55)</td>
<td>28 (7/25)</td>
<td>19 (4/21)</td>
</tr>
<tr>
<td>Platinum-resistant(^a)</td>
<td>10 (3/30)</td>
<td>17 (4/23)</td>
<td>10 (2/21)</td>
</tr>
<tr>
<td><strong>Best overall response, %</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>0</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Partial response</td>
<td>10</td>
<td>21</td>
<td>19</td>
</tr>
<tr>
<td>Stable disease</td>
<td>22</td>
<td>21</td>
<td>17</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>53</td>
<td>38</td>
<td>54</td>
</tr>
<tr>
<td>Unable to determine</td>
<td>12</td>
<td>13</td>
<td>11</td>
</tr>
<tr>
<td>Not evaluable (no tumor assessment follow-up)</td>
<td>2</td>
<td>5</td>
<td>0</td>
</tr>
</tbody>
</table>

\(^a\)Platinum sensitivity was unknown for 29 patients as follows: nivo-3, n = 10; nivo-1/ipi-3, n = 11; nivo-3/ipi-1, n = 8. 3 pts in the nivo-3 arm, 2 pts in the nivo-1/ipi-3 arm, and 4 pts in the nivo-3/ipi-1 arm did not receive first-line platinum therapy and did not meet eligibility criteria, although they were treated and included in the analysis.
Nivolumab +/- Ipilimumab in Recurrent SCLC: Overall Survival

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Events/Number at risk</th>
<th>mOS, months</th>
<th>1-year OS rate, %</th>
<th>Median* follow-up, mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab-3</td>
<td>60/98</td>
<td>4.4</td>
<td>33</td>
<td>11.1</td>
</tr>
<tr>
<td>Nivolumab-1/ipilimumab-3</td>
<td>36/61</td>
<td>7.7</td>
<td>43</td>
<td>16.5</td>
</tr>
<tr>
<td>Nivolumab-3/ipilimumab-1</td>
<td>35/55</td>
<td>6.0</td>
<td>35</td>
<td>13.1</td>
</tr>
</tbody>
</table>

\*Defined as time from first dose to date of DBL; follow-up was shorter for patients who died prior to DBL

Antonia Lancet Oncol 2016
Phase III Studies

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

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.
- Anabulin (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.

Treat until RECIST 1.1 defined progression* or unacceptable toxicity

* Pts assigned to Arm A may be treated beyond progression under protocol-defined circumstances

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

Checkmate 451 (maintenance)

Screening

- Cycle 3 & 2 (Two 42 day Cycles)
- Cycle 3+ (14 day Cycles)
- Follow-up

ARM A
- Nivolumab Monotherapy
- Nivolumab 240 mg q2 weeks

ARM B
- Nivolumab and Iplilumab Combination Therapy
- Nivolumab 1 mg/kg + iplilumab 3 mg/kg q3 weeks
- Nivolumab Monotherapy
- Nivolumab 240 mg q2 weeks

ARM C
- Placebo
- Placebo

Stratification Factors:
- ECOG 0 vs. 1
- Gender
- Prior PD: Yes or No

Co-Primary Endpoint: Overall Survival / Progression Free Survival
Secondary Endpoint: To compare OS and PFS of iplilumab combined with nivolumab vs. nivolumab monotherapy

Double-blind dosing scheme described in Tables 4.5.1 and 4.5.2

Treatment continues until PD or unacceptable toxicity.
Post treatment follow-up includes 2 visits for safety, PK / immunogenicity and PD (if not previously confirmed).
Subjects will then be followed q3 months for survival and subsequent therapy.
Current Therapies in Metastatic SCLC (2017)

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

- Topotecan in 2 L
  - CAV is alternative

- TRT? Option in selected patients

- PCI? If not: Follow with imaging

- Immunotherapy in studies
Thank you!